Respiratory Diseases and the Fire Service

U.S. Fire Administration | FEMA

FEMA

U.S. Fire Administration
Mission Statement

As an entity of the Department of Homeland Security's Federal Emergency Management Agency, the mission of the USFA is to reduce life and economic losses due to fire and related emergencies, through leadership, advocacy, coordination and support. We serve the Nation independently, in coordination with other Federal agencies, and in partnership with fire protection and emergency service communities. With a commitment to excellence, we provide public education, training, technology, and data initiatives.

This project was developed through a Cooperative Agreement (Developing Materials on the Long-Term Health Effects of Occupational Respiratory Exposures on Fire Fighters' Respiratory Health and the Ability of Exposure Reduction and Post-Exposure Mitigation Strategies to Improve Outcomes - EME-2003-CA-0342) between the Department of Homeland Security, United States Fire Administration and the International Association of Fire Fighters.

International Standard Book Number: 0-942920-51-1

PREFACE

The United States Fire Administration (USFA) is committed to using all means possible for reducing the incidence of occupational diseases, injuries and deaths to fire fighters. One of these means is to partner with fire service organizations who share this same admirable goal. One such organization is the International Association of Fire Fighters (IAFF). As a labor union, the IAFF has been deeply committed to improving the safety of their members and all fire fighters as a whole. This is why the USFA was pleased to work with the IAFF through a cooperative agreement to research and develop materials addressing the long-term effects from occupational respiratory exposures on fire fighter's health and the ability of exposure reduction and post-exposure mitigation strategies to improve health outcomes. The USFA gratefully acknowledges the following leaders of the IAFF for their willingness to partner on this project.

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Introduction

By Richard M. Duffy, MSc

International Association of Fire Fighters

Respiratory diseases remain a significant health issue for fire fighters and emergency responders, as well as civilians. Respiratory disease is the number three killer in North America, exceeded only by heart disease and cancer, and is responsible for one in six deaths. The American Respiratory Association estimates that more than 35 million Americans are living with chronic respiratory diseases such as asthma or chronic obstructive pulmonary diseases (COPD) including emphysema and chronic bronchitis.

Fire fighters work hard each and every day, proudly protecting and serving our citizens by answering the call for help -- a call to save lives. That call may be to suppress fire and save lives jeopardized by smoke and flame. It may be a response to a hazardous materials incident, a structural collapse or other special operations event. The response may be for emergency medical assistance and transport to the hospital, with potential exposures to a host of infectious disease. Fire fighters have little idea about the identity of many of the materials they are exposed to or the health hazards of such exposures -- whether they are chemical, biological or particulates. Nevertheless, fire fighters and emergency medical responders continue to respond to the scene and work immediately to save lives and reduce property damage without regard to the potential health hazards that may exist. A fire emergency has no engineering controls or occupational safety and health standards to reduce the effect of irritating, asphyxiating or toxic gases, aerosols, chemicals or particulates. It is an uncontrollable environment that is fought by fire fighters using heavy, bulky and often times inadequate personal protective equipment and clothing.

An occupational disease takes years to develop. It is the result of a career of responding to fires and hazardous materials incidents; it is caused by breathing toxic smoke, fumes, biological agents, and particulate matter on the job; and it is the response to continuous medical runs or extricating victims at accidents. Some health effects are immediate while others may take years and even decades to develop and because some respiratory diseases develop over time, it's impossible to say, "This specific emergency response caused my disease," yet fire fighters continue to get sick and die from occupationally-caused respiratory diseases.

Variability in exposures among fire fighters can be great; however, a number of exposures are commonly found in many fire scenarios. The common combustion products encountered by fire fighters that present respiratory disease hazards include but are not limited to: acrylonitrile, asbestos, arsenic, benzene, benzo(a)pyrene and other polycyclic hydrocarbons (PAHs), cadmium, chlorophenols, chromium, diesel fumes, carbon monoxide, dioxins, ethylene oxide, formaldehyde, orthotoluide, polychlorinated biphenyls and vinyl chloride. Also, findings from fire fighters monitored during the overhaul

phase (fire is extinguished, clean-up begins and where respiratory protection is not usually available) of structural fires indicates that short-term exposure levels are exceeded for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide and sulfur dioxide as well as soots and particulates. They are often exposed in their fire stations to significant levels of diesel particulate from the operation of the diesel fueled fire apparatus. Fire fighters are routinely exposed to respirable particulate matter consisting of liquids, hydrocarbons, soots, diesel fumes, dusts, acids from aerosols, and smoke. Health effects are known to be produced not just by the particulates themselves, but also by certain chemicals adsorbed onto the particulates. Further, the mixture of hazardous chemicals is different at every fire and the synergistic effects of these substances are largely unknown.

FIRE FIGHTER STUDIES

Although fire fighters have been shown in some studies to suffer chronic respiratory morbidity from their occupational exposures, fire fighters are probably at increased risk for dying from non-malignant respiratory diseases.

Such studies that address and link fire fighting with respiratory diseases fall into three main groups—laboratory studies, field studies and epidemiological studies. The first, involving animal laboratory experiments, have identified exposure to certain chemicals, biological agents and particulate substances and their contribution to the respiratory disease process. Such studies are invaluable to the understanding of the effect such substances can have on humans and they play a significant role in hazard identification for further risk assessment.

The second group, field studies, documents the exposure of fire fighters to these agents through industrial hygiene or biological and physiological monitoring. Industrial hygiene data indicates that the fire environment contains a number of potentially dangerous toxins. Due to the highly unpredictable nature of the fire fighters' environment, it is almost impossible to predict with any certainty all of the exposures that could be encountered at any given fire. However, these studies are important since they identify and characterize fire fighter exposures during suppression and overhaul at fires as well as at hazardous materials incidents or other special operations responses.

The third group, epidemiologic studies of fire fighters and other occupational groups, is performed to determine if exposures actually result in elevated rates of disease. For example, epidemiological studies have consistently shown excesses of nonmalignant respiratory disease in fire fighters; acute and chronic respiratory function impairment, acute increase in airway reactivity and inflammatory changes in the lower airways of fire fighters. However, there have also been a number of other epidemiologic studies that have not found an increased morbidity or mortality or they provided conflicting information on the health effects of fire fighting on the respiratory system. This is due to a number of factors:

- Statistical constraints — the number of individuals studied may not be sufficient to detect a difference.
- The studies rely on mortality, measuring only deaths from respiratory disease. Differences in survivorship between an occupational group

and the general population resulting from disparities in the quality and accessibility of medical care or other factors may result in misleading conclusions about disease prevalence.

- Mortality studies rely on death certificates that are frequently inaccurate and may erode the ability of the study to detect real differences.
- Due to the physical and medical requirements, fire fighters tend to be healthier than the general population with disease incidence significantly less than the general population. An increase in the prevalence of a medical condition arising from workplace exposures may therefore be missed with comparison to the general population. This "healthy worker effect" is accentuated with fire fighters who are extremely healthy, and has been termed the "super healthy worker effect."
- When studying an occupational group, certain sub-populations may be at greater risk for a disease due to differences in exposures, administrative policies, or other reasons. The ability of a study to identify and establish the increased rates in these sub-groups may be limited due to statistical and study design constraints.
- Any of these factors could result in an otherwise well-designed epidemiologic study failing to find an increase in the prevalence of an illness even if one existed (i.e. a "false negative" result).

WORKER COMPENSATION AND BENEFITS

For more than fifty years, the International Association of Fire Fighters has been addressing the issues of fire fighters and respiratory diseases. The IAFF has protected its members by pursuing enactment of legislation that provides protection and compensation for those fire fighters whose health has deteriorated through the performance of their fire fighting occupation. Such IAFF-sponsored benefit laws have ranged from federal legislation to provide compensation for the families of those fire fighters who die or are severely disabled in the line of duty to federal, state and provincial legislation extending retirement and/or worker compensation benefits to those who become disabled from occupationally-contracted diseases.

Some are confused on the issue of paying for treatment of a fire fighter injured at work, in this case through an exposure to a toxic material, carcinogen or an infectious disease. Some also state that fire fighters are entitled to worker's compensation for injuries and illnesses and that their bills are routinely paid for and the fire fighter is compensated for lost productivity. Well, that is exactly what fire fighter "presumptive" legislation does. It provides for a rebuttable presumption -- that is, the employer may tangibly demonstrate that the exposure did not occur in the line of duty -- to compensate a fire fighter if an exposure leads to a disease. Just as a fire fighter would be compensated for injuries that occurred after falling through the roof of a burning structure, a fire fighter who develops a respiratory disease from job exposure would and should be compensated. The worker's compensation system was designed decades ago to handle injuries easily linked to the workplace, such as a broken leg or a cut hand. As medical science has improved, we've learned that respiratory diseases as well as heart diseases, infectious diseases and cancer are directly related to the work environment, including toxic chemicals in smoke or particulates.

In recognition of the causal relationship of the fire fighting occupation and respiratory disease, 41 states and 7 provinces have adopted some type of presumptive disease law to afford protection to fire fighters with these conditions. The states and provinces that have occupational disease presumptive laws are identified in Table 1. Similar legislation is currently being addressed in the US Congress to provide the same protection for federal fire fighters.

State and Provincial Presumptive Disability Laws

The following states and provinces have presumptive disability laws which recognize that fire fighters are at increased risk for certain illnesses. The laws create a presumption that the specified diseases are job related. Because the laws vary greatly from state to state and province to province and new legislation continually enacted, please refer to the IAFF's Presumptive Legislation website at http://www.iaff.org/hs/phi/ to review the specific state/provincial laws.

State	Heart Disease	Lung Disease	Cancer	Infectious Diseases	Code Part
Alabama	✓	✓	✓	✓	GP
Alaska	✓	✓	✓		WC
Arizona			✓	✓	WC
Arkansas					
California	✓		✓	✓	WC/RS
Colorado			✓	✓	WC
Connecticut	✓				GP
District of Columbia					
Delaware					
Florida	✓			✓	GP
Georgia	✓	✓			RS
Hawaii	✓	✓			RS
Idaho	✓	✓		✓	WC
Illinois	✓	✓	✓	✓	RS
Indiana	✓	✓	✓		GP
Iowa	✓	✓	✓	✓	RS
Kansas	✓	✓	✓		RS
Kentucky					
Louisiana	✓	✓	✓	✓	GP
Maine	✓	✓		✓	WC
Maryland	✓	✓	✓		WC
Massachusetts	✓	✓	✓		RS
Michigan	✓	✓			WC
Minnesota	✓		✓	✓	WC
Mississippi					
Missouri	✓	✓	✓		RS
Montana					
Nebraska			✓		GP
Nevada	✓	✓	✓	✓	GP
New Hampshire	✓	✓	✓		WC
New Jersey					
New Mexico	✓		✓	✓	WC
New York	✓**	✓**	✓	✓	RS
North Carolina					
North Dakota	✓	✓	✓	✓	GP
Ohio	✓	✓			WC
Oklahoma	✓	✓	✓	✓	RS
Oregon	✓	✓	✓		WC
Pennsylvania				✓	WC
Rhode Island		✓	✓	✓	GP
South Carolina	✓	✓			WC
South Dakota	✓	✓	✓		RS
Tennessee	✓	✓	✓		GP
Texas	✓	✓	✓	✓	GP
Utah	✓	✓		✓	WC
Vermont	✓		✓		WC
Virginia	✓	✓	✓	✓	WC
Washington	✓	✓	✓	✓	WC
West Virginia	✓	✓			WC
Wisconsin	✓	✓	✓	✓	GP
Wyoming					

Canadian Province	Heart Disease	Lung Disease	Cancer	Infectious Diseases	Code Part
Alberta	✓		✓		WC
British Columbia		✓	✓	✓	WC
Manitoba	✓		✓		WC
New Brunswick	✓		✓		WC
Newfoundland					
Northwest Territory					
Nova Scotia			✓		WC
Ontario	✓		✓		GP
Prince Edward Island					
Quebec					
Saskatchewan	✓		✓		WC
Yukon					

*Code Part: WC = Workman's Comp, RS = Retirement / Pension System, GP = General Provisions of Law or other systems.

Table 1: State and Provincial Presumptive Disability Laws

All of these laws presume, in the case of fire fighters, that heart, respiratory, and infectious diseases, as well as cancer are occupationally related. Consequently, their provisions rightfully place the burden of proof to deny worker compensation and/or retirement benefits on the fire fighter's employer.

Additionally, many pension and workers' compensation boards in the United States and Canada have established a history of identifying heart, respiratory and infectious diseases and cancer in fire fighters as employment-

related. While all these state and provincial laws recognize these diseases as occupationally related, some have exclusions and prerequisites for obtaining benefits (see Table 2).

Alabama	Heart disease; hypertension; respiratory disease; disabling cancer which is reasonably linked to a know carcinogen; AIDS and Hepatitis.
Alaska	Cardiovascular events within 72 hours; respiratory disease; brain, malignant melanoma, leukemia, non-Hodgkin's lymphoma, bladder, ureter, kidney
Arizona	Brain, bladder, rectal, colon, lymphoma, leukemia, adenocarcinoma or mesothelioma; occupational disease
California	Heart trouble; exposed to a known carcinogen as defined by the IARC; blood-borne infectious disease, MRSA
Colorado	Brain, skin, digestive system, hematological system, or genitourinary system; Hepatitis C
Connecticut	Hypertension or heart disease
Florida	Heart disease or hypertension; hepatitis, meningococcal meningitis, or tuberculosis
Georgia	Heart disease; respiratory disease
Hawaii	Heart, lungs or respiratory system
Illinois	Heart disease, stroke or any disease of the lungs or respiratory tract; cancer which may be caused by exposure to heat, radiation or a known carcinogen as defined by the IARC; Tuberculosis
Indiana	Disease or impairment of the cardiovascular or respiratory system; cancer that is caused by a known carcinogen to which an individual is at risk for occupational exposure
Iowa	Heart disease or any disease of the lungs or respiratory tract; prostate cancer, primary brain cancer, breast cancer, ovarian cancer, cervical cancer, uterine cancer, malignant melanoma, leukemia, non-Hodgkin's lymphoma, bladder cancer, colorectal cancer, multiple myeloma, testicular cancer, and kidney cancer; HIV or AIDS, hepatitis, meningococcal meningitis, and mycobacterium tuberculosis
Kansas	Heart disease or disease of the lung or respiratory tract; type of cancer which may, in general, result from exposure to heat, radiation or a known carcinogen
Louisiana	Disease or infirmity of the heart or lungs; bladder, brain, colon, liver, pancreas, skin, kidney, gastrointestinal tract, leukemia, lymphoma, multiple myeloma; Hepatitis B or Hepatitis C; hearing loss
Maine	Cardiovascular injury, cardiovascular disease or pulmonary disease; hepatitis, meningococcal meningitis or luberculosis; cancers of the kidney, prostate, breast, non-Hodgkin's lymphoma, testicular, colon, brain, bladder, leukemia or multiply myeloma
Maryland	Heart disease, hypertension, or lung disease; leukemia or pancreatic, prostate, rectal, or throat cancer that is caused by contact with a toxic substance
Massachusetts	Hypertension or heart disease; disease of the lungs or respiratory tract; cancer affecting the skin or the central nervous, lymphatic, digestive, hematalogical, urinary, skeletal, oral or prostate systems, lung or respiratory tract
Michigan	Respiratory and heart diseases or illnesses
Minnesota	Myocarditis, coronary sclerosis, pneumonia; cancer of a type caused by exposure to heat, radiation, or a known or suspected carcinogen, as defined by the IARC; infectious of communicable disease
Missouri	Lungs or respiratory tract, hypertension, or disease of the heart; cancer affecting the skin or the central nervous, lymphatic, digestive, hematological, urinary, skeletal, oral, breast, testicular, genitourinary, liver or prostate systems, as well as any condition of cancer which may result from exposure to heat or radiation or to a known or suspected carcinogen as determined by the IARC
Nebraska	Hypertension or heart or respiratory defect or disease; Cancer affecting the skin or the central nervous, lymphatic, digestive, hematological, urinary, skeletal, oral, or prostate systems; blood-borne infectious disease, tuberculosis, meningococcal meningitis, or MRSA
Nevada	Diseases of the heart; diseases of the lungs; exposed to a known carcinogen as defined by the IARC; contagious disease
New Hampshire	Heart or lung disease; cancer involved must be a type which may be caused by exposure to heat, radiation, or a known or suspected carcinogen as defined by the IARC (legislation never funded)
New Mexico	Heart injury or stroke suffered within 24 hours; brain, bladder, kidney, colorectal, non-Hodgkin's lymphoma, leukemia, ureter, testicular, breast, esophageal, multiple myeloma; hepatitis, tuberculosis, diphtheria, meningococcal disease and MRSA
New York	Heart and lung (NYC only); cancer affecting the lymphatic, digestive, hematological, urinary, neurological, breast, reproductive, or prostate systems; HIV, tuberculosis or hepatitis
North Dakota	Hypertension, heart disease; lung or respiratory disease; cancer is one which arises due to exposure to smoke, fumes, or carcinogenic, poisonous, toxic, or chemical substances; bloodborne pathogen
Ohio	Cardiovascular, pulmonary, or respiratory diseases
Oklahoma	Heart disease, injury to the respiratory system; existence of any cancer which was not revealed by the physical examination passed by the member upon entry into the department; hepatitis, human immunodeficiency virus, meningitis and tuberculosis
Oregon	Disease of the lungs or respiratory tract, hypertension or cardiovascular-renal disease; brain cancer, colon cancer, stomach cancer, testicular cancer, prostate cancer, multiple myeloma, non-Hodgkin's lymphoma, cancer of the throat or mouth, rectal cancer, breast cancer or leukemia
Pennsylvania	Hepatitis C
Rhode Island	Lungs or respiratory tract; disabling occupational cancer which develops as a result of the inhalation of noxious fumes or poisonous gases; infectious disease
South Carolina	Heart disease or respiratory disease
South Dakota	Hypertension, heart disease, or respiratory disease; impairment of health caused by cancer
Tennessee	Disease of the lungs, hypertension or heart disease; cancer resulting in hospitalization, medical treatment or any disability.
Texas	Myocardial infarction or stroke; disease or illness of the lungs or respiratory tract; cancer that may be caused by exposure to heat, smoke, radiation, or a known or suspected carcinogen as determined by the IARC; tuberculosis
Utah	Heart disease, lung disease, or respiratory tract condition; infectious disease as a result of exposure in the performance of duties
Vermont	Heart injury or heart disease; leukemia, lymphoma, or multiple myeloma, and cancers originating in the bladder, brain, colon, gastrointestinal tract, kidney, liver, pancreas, skin, or testicles
Virginia	Hypertension or heart disease; Respiratory diseases, Leukemia or pancreatic, prostate, rectal, throat, ovarian or breast; Hepatitis, meningococcal meningitis, tuberculosis or HIV
Washington	Heart problems, experienced within 72 hours; Respiratory disease; brain cancer, malignant melanoma, leukemia, non-Hodgkin's lymphoma, bladder cancer, ureter cancer, and kidney cancer; HIV/AIDS, all strains of hepatitis, meningococcal meningitis, or mycobacterium tuberculosis
West Virginia	Cardiovascular or pulmonary disease or sustained a cardiovascular injury
Wisconsin	Heart or respiratory impairment or disease; skin, breast, central nervous system or lymphatic, digestive, hematological, urinary, skeletal, oral or reproductive systems; infectious diseases includes the HIV, AIDS, tuberculosis, hepatitis A, hepatitis B, hepatitis C, hepatitis D, diphtheria, meningococcal meningitis, MRSA, and SARS.
Alberta	Myocardial infarction within 24 hours; Leukemia, brain, bladder, lung, ureter, kidney, colorectal, non-Hodgkins Lymphoma
British Columbia	Athsma, Extrinsic allergic alveolitis, Acute upper respiratory inflammation, acute pharyngitis, acute laryngitis, acute tracheitis, acute bronchitis, acute pneumonitis, or acute pulmonary edema; Leukemia, bladder, lung, skin, liver; Staphylococcus aureus, Salmonella organisms, Hepatitis B, Tubercle bacillus
Manitoba	Injury to the heart within 24 hours; Leukemia, brain, bladder, lung, ureter, kidney, colorectal, non-Hodgkins Lymphoma, testicular, esophageal
Nova Scotia	cancer or other disease that is prescribed by the Governor in Council by regulation
New Brunswick	IAFF is working to obtain specific language
Ontario	Heart injury while, or within 24 hours; Leukemia, brain, bladder, ureter, kidney, colorectal, non-Hodgkins Lymphoma, esophageal
Saskatchewan	Injury to the heart that manifests within 24 hours; Leukemia, brain, bladder, lung, ureter, kidney, colorectal, non-Hodgkins Lymphoma, testicular

Table 2: Presumptive Disability Laws Inclusions and Prerequisites

In a recent study, Dr. Tee Guidotti, from the George Washington University Medical Center, addressed the fire fighter occupational disease issues relevant to worker compensation issues and reasonableness of adopting a policy of presumption for those diseases associated with the occupation of fire fighting. Guidotti states that these "presumptions" are based on the weight of evidence, as required by adjudication, not on scientific certainty, but reflect a legitimate and necessary interpretation of the data for the intended purpose of compensating a worker for an injury (in this case an exposure that led to a disease outcome). Guidotti made it clear that the assessments are for medicolegal

and adjudicatory purposes and are not intended to replace the standards of scientific certainty that are the foundation of etiologic investigation for the causation of disease. They are social constructs required to resolve disputes in the absence of scientific certainty. Understanding this is why most states and provinces have adopted legislation or revised compensation regulations that provide a rebuttable presumption when a fire fighter develops occupational diseases. Further, based on actual experience in those states and provinces, the cost per claim is substantially less than the unsubstantiated figures asserted by others. The reason for this, unlike benefits for other occupations, is the higher mortality rate and significantly shorter life expectancy associated with fire fighting and emergency response occupations. These individuals are dying too quickly from occupational diseases, unfortunately producing a significant savings in worker compensation costs and pension annuities for states, provinces and municipalities.

The IAFF maintains full copies of all state laws or regulations and a number of worker compensation awards from the United States and Canada that address these diseases. The IAFF also maintains an up-to-date website that contains an information database of the current presumptive disability provisions in the United States and Canada. This website provides the full legislation from each state and province where a presumptive disease law was enacted. Additionally, the site provides information on how presumptive laws benefit fire fighters and EMS personnel; the limitations of presumptive disability laws; how to bring or maintain such federal, state or provincial legislation; a history of fire fighter disability laws; and presumptive legislation updates and stories. The IAFF is committed to maintain this as a dynamic site which is accessible at: http://www.iaff.org/hs/phi/. The IAFF also continues to provide direct assistance and information to its affiliates to obtain or maintain presumptive legislation and regulations.

IMPLEMENTING RESPIRATORY DISEASE PROGRAMS

The IAFF and the International Association of Fire Chiefs (IAFC) created the Fire Service Joint Labor Management Wellness-Fitness Initiative (WFI) in 1996 to improve the health and fitness of fire fighters and paramedics across North America. Medical, wellness and fitness programs that are developed and implemented in accordance with the WFI will help secure the highest possible level of health to fire response personnel. These programs have also been shown to provide the additional benefit of being cost effective, typically by reducing the number of work-related injuries and lost workdays due to injury or illness.

This was an unprecedented endeavor to join together labor and management to evaluate and improve the health, wellness and fitness of fire fighters and EMS providers. It has been supported by the IAFF, as well as by the IAFC, the individual fire departments participating in the initiative and with additional funding provided by the Federal Emergency Management Agency's Fire Prevention and Safety grant program. The following are the fire departments and IAFF locals participating in this project (See Table 3).

WFI Task Force Jurisdictions

- Austin, Texas Fire Department / IAFF Local 975
- Calgary, Alberta Fire Department / IAFF Local 255
- Charlotte, North Carolina Fire Department /IAFF Local 660
- Fairfax County, Virginia Fire and Rescue Department / IAFF Local 2068
- Indianapolis, Indiana Fire Department / IAFF Local 416
- Los Angeles County, California Fire Department / IAFF Local 1014
- Miami Dade County, Florida Fire Rescue Department / IAFF Local 1403
- Fire Department, City of New York / IAFF Locals 94 and 854
- Phoenix, Arizona Fire Department / IAFF Local 493
- Seattle, Washington Fire Department / IAFF Local 27 and 2898

Table 3: WFI Task Force Jurisdictions

Each of these departments formally agreed to assist in the development of the program and to adopt it for their members. Further the IAFF has provided the program to thousands of fire departments in the United States and Canada.

Specifically, fire departments must offer medical exams, fitness evaluations and individual program design, rehabilitation following injuries and illnesses, and behavioral health services. The program also specifies protocols for physical exams, laboratory testing, and other objective tests (pulmonary function testing, electrocardiograms, audiometry, chest x-rays). All must assess aerobic capacity, strength, endurance, and flexibility using the specified protocols. The WFI also provides tools to collect data from these evaluations as well as the methods to transfer the data to the IAFF.

The medical component was specifically designed to provide a cost-effective investment in early detection, disease prevention, and health promotion for fire fighters. It provides for the initial creation of a baseline from which to monitor future effects of exposure to specific biological, physical, or chemical agents. The baseline and then subsequent annual evaluations provide the ability to detect changes in an individual's health that may be related to their work environment. It allows for the physician to provide the fire fighter with information about their occupational hazards and current health status. Clearly, it provides the jurisdiction the ability to limit out-of-service time through prevention and early intervention of health problems.

The largest success of the WFI was demonstrated immediately after September 11, 2001. The fall of the twin towers and the collapse and destruction of other buildings at the World Trade Center (WTC) site created a dust cloud composed of large and small particulate matter coated with combustion by-products. For three days, Ground Zero was enveloped in that dust cloud. The fires that continued to burn at the site until mid-December created additional exposures and resulted in repeated dust aerosolization. Nearly 2,000 FDNY

rescue workers responded on the morning of 9/11, as did nearly 10,000 during the next 36 hours. And in the weeks and months following 9/11, virtually all of FDNY first responders worked at the WTC site – amid the debris and dust. As a group, FDNY fire fighters experienced more exposure to the physical and emotional hazards at the disaster site than any other group of workers. FDNY, as a participant in the WFI, had implemented the baseline and annual medical component four years prior to 9/11. The adoption of the WFI provided the vehicle to intervene with early diagnosis and aggressive treatment of all affected fire fighters, which clearly improved medical outcomes. FDNY's WFI program had over a 95 percent participation rate, which enabled its Medical Division to analyze and publish data providing critical and unique insights about WTC health effects. While the tragedy of 9/11 brought the medical issues of fire fighters and respiratory diseases to the frontline, the medical successes through the FDNY-IAFF WFI and medical evaluation program must be used as the driving force for all fire departments for adopting this program. There are no longer any excuses.

The IAFF also worked directly with the National Fire Protection Association (NFPA) and their Technical Committee responsible for NFPA 1582, *Standard on Comprehensive Occupational Medical Program for Fire Departments* to ensure that IAFF and NFPA documents were consistent with each other. We provided our copyrighted materials to NFPA, with the provision that the incumbent evaluations mirror the WFI.

The current 2007 edition of NFPA 1582, includes a stringent standard for candidate fire fighters, as well as a more flexible guidance for medical determinations for incumbent fire fighters based upon the specific nature of their condition and the duties and functions of their job. The standard addresses job tasks, where it is explained that those medical conditions that potentially interfere with a member's ability to safely perform essential job tasks are listed by organ system. Most importantly, possession of one or more of the conditions listed within the standard for incumbent fire fighters does not indicate a blanket prohibition from continuing to perform the essential job tasks, nor does it require automatic retirement or separation from the fire department.

The standard gives the fire department physicians guidance for determining a member's ability to medically and physically function using the individual medical assessment.

Foremost, this standard was fundamentally developed for, and primarily intended, as guidance for physicians, to provide them with advice for an association or relationship between essential job functions of a fire fighter as an individual and the fire fighter's medical condition(s).

The federal government, through the National Institute for Occupational Safety and Health (NIOSH) also recognized that hiring and maintaining medically and physically-fit fire fighters is an important step in reducing fire fighter's occupational disease. They are now in full support of the WFI and NIOSH further recommends that all jurisdictions adopt this program for their fire departments.

Fire department wellness programs do make economic sense. Adopting and implementing an occupational wellness program, such as the WFI, can reduce occupational claims and costs while simultaneously improving the quality and longevity of a fire fighter's life.

SUMMARY

This manual is written for fire fighters and emergency medical responders, a group of individuals who face special occupational risks of respiratory diseases due to fire ground exposures and their direct interaction and contact with the public. Respiratory diseases in fire fighters have been an area of concern and focus for the International Association of Fire Fighters and others for several decades.

Although medical progress has led to improvements in the diagnosis and treatment of respiratory diseases, prevention remains the best method of decreasing the number of such diseases and related deaths. Understanding diseases of the respiratory system, identifying respiratory disease-causing agents, and avoiding exposure to these agents are key in preventing respiratory diseases.

The IAFF knows that you will find this manual both informative and useful.

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Chapter 1-1
Anatomy

By Dr. Carrie Dorsey, MD, MPH

The main function of the lungs is to provide oxygen to the body and remove the carbon dioxide that is formed during metabolism. It is important to have an understanding of the normal structure and function of the lungs prior to discussing the diseases and injuries that can occur in the lungs.

LUNG COMPONENTS

The lungs are made up from a series of components all working together to support the respiratory effort.

Bronchial Tree

The lungs can be thought of as branching trees. The main airways into the lungs are the right and left main stem bronchi which branch off of the trachea. Each of these branch to form the bronchi which lead into the main lobes of the lungs. The right lung has three lobes and the left has two lobes. The airways continue to divide separating the lung into smaller and smaller units. The airways terminate at the air sacks known as alveoli. This is the primary site of gas exchange with the blood. As the airways divide they can be grouped into several distinct categories based on structure. The bronchi are the larger airways and are distinguished by the presence of cartilage in the wall and glands just below the mucosal surface. As the branches become smaller they no longer contain cartilage or glands. These are the bronchioles. The bronchioles continue to branch at last forming the terminal bronchioles. Distal to the terminal bronchiole is the respiratory unit of the lung or acinus, the site of gas exchange. It is composed of alveoli and the respiratory bronchioles. The airway walls of the respiratory unit are very thin, the width of a single cell, to facilitate the transfer of gases. The airways to the level of the terminal bronchiole are surrounded by a layer of smooth muscle that is able to control the diameter of the airways by contracting and relaxing. The smooth muscle cells are controlled by the autonomic nervous system and also by chemical signals released from near by cells.

Alveoli

The alveoli and respiratory bronchioles warrant further discussion given the essential role they play in supplying the body with oxygen. As discussed above the walls of the alveoli are thin and designed to allow for efficient transfer of gas with the blood. In addition they are an important site of defense against infection.

The wall of the alveoli is primarily made up of two types of cells, the type I pneumocytes and type II pneumocytes. There are also alveolar macrophages (involved with defense) found in the alveoli or attached to the wall. The cells are described in detail below. Because the alveoli are designed to easily expand when we breathe in and collapse when breathing out there is a risk that the thin walls would stick together. To prevent this there is a layer of a protein called surfactant coating the alveolar membranes. Surrounding the alveoli is a complex network of capillaries that carry the blood and red blood cells through the lungs to pick up oxygen and discard the carbon dioxide. Between the capillaries and the alveoli cells is a layer of protein called the basement membrane and the pulmonary interstitium. The latter contains a variety of cells, collagen and elastic fibers that facilitate the expanse of the lungs.

Parenchyma

The definition of parenchyma is: *The tissue characteristic of an organ, as distinguished from associated connective or supporting tissues.* The majority of the lung tissue consists of the airways and gas exchange membranes as discussed above. There is some interstitial tissue between the alveolar cells and the capillary wall.

Cell Morphology and Function

There are many different types of cells found in the airways of the lung. A variety of functions are performed by these different cells. For example some cells are present for physical support, some produce secretions and others defend the body against infection. Approximately 50 distinct cells have been identified in the airways.[1] Below you will find a brief description of some of the important cell types.

Type I pneumocyte: These are the flat epithelial cells of the alveolar wall that have the appearance of a fried egg with long processes extending out when seen under a microscope. They account for 95% of the alveolar surface .[2]

Type II pneumocyte: These are the cells responsible for the production of surfactant; the protein material that keeps the alveoli from closing off during exhalation. They are rounded in appearance. The surfactant is stored in small sacks called lamellar bodies. They are also involved with the regulation of fluid in the lungs.[1]

Alveolar macrophages: These are cells that clear the lung of particles such as bacteria and dust. They enter the alveoli from the blood through small holes in the wall called the pores of Kohn.

Smooth muscle cells: As discussed above the airways down through the level of the terminal bronchioles contain bands of smooth muscle. The muscle cells are controlled by the autonomic nervous system and chemical or hormones released from other cells such as mast or neuroendocrine cells.[1] The contraction of the muscle cells leads to a narrowing of the airways.

Ciliated epithelia cells: The lining of the majority of the airways is composed of pseudostratified, tall, columnar, ciliated epithelial cells. The cilia are hair-like projections on the surface of these cells that beat in rhythmic waves, allowing the movement of mucus and particles out of the lungs. This mechanism is also a defense mechanism against infection.

Low cuboidal epithelial cells: The terminal airways are lined by this type of epithelia cell. They are only partially ciliated.

Goblet cells: This cell type is found interspersed with the ciliated epithelial cells. There are no goblet cells below the level of the terminal bronchioles. These cells produce mucus, the main component of the respiratory secretions.

Basal cells: These are small epithelia cells that are found along the basement membrane of the epithelium. They give rise to the epithelial cells discussed above.

Lymphocytes and mast cells: These cells are part of the immune defense of the body. They can be found dispersed within the epithelia lining of the airways.

Clara cells: These domed cells are interspersed with the epithelial cells. They make, store and secrete a variety of substances including lipids and proteins. They can also develop into other cell types as needed to replace the loss of cells.

NORMAL PHYSIOLOGY

As discussed above the primary function of the lungs is to provide oxygen to the body and remove carbon dioxide. This is accomplished by the exchange of air in the lungs with the ambient air through the process of pulmonary ventilation. The first phase of ventilation is inspiration. This is initiated when the diaphragm contracts causing it to descend into the abdomen. When this occurs the volume of the lungs increases and by the laws of physics the pressure within the lungs decreases leading to a rush of air into the lungs. The opposite occurs during expiration. When the diaphragm relaxes and the lung tissues naturally recoil, the pressure in the lungs increases pushing air out of the lungs. Respiration is controlled by a number of factors including the autonomic nervous system, the voluntary muscles of respiration, the levels of carbon dioxide and oxygen in the blood, and the level of acid in the blood.

During normal respiration between 400 and 1000 ml of air is moved into and out of the lungs; however, all of this volume is not available for gas exchange. Gases are exchanged across the respiratory bronchioles and the alveoli. The airways proximal to these are referred to as the conducting airways or anatomic dead space. This volume on average is between 130 and 180 ml. Ventilatory function is often expressed as minute ventilation. This is the amount or volume of air breathed each minute and is a function of the tidal volume (see table of lung volume definitions) and the breathing rate. Under normal resting conditions the minute ventilation is approximately 6 L. During exercise this can increased as a result of increasing the rate breathing and volume of each breath to as much as 150 L.[3] There are a variety of different lung volumes that have been defined. These are useful for the diagnosis and discussion of disease processes affecting the lungs. A brief description of the lung volumes which can be measured or calculated using pulmonary function tests is presented in Figure 1-1.1. A more detailed review is discussed in a later chapter.

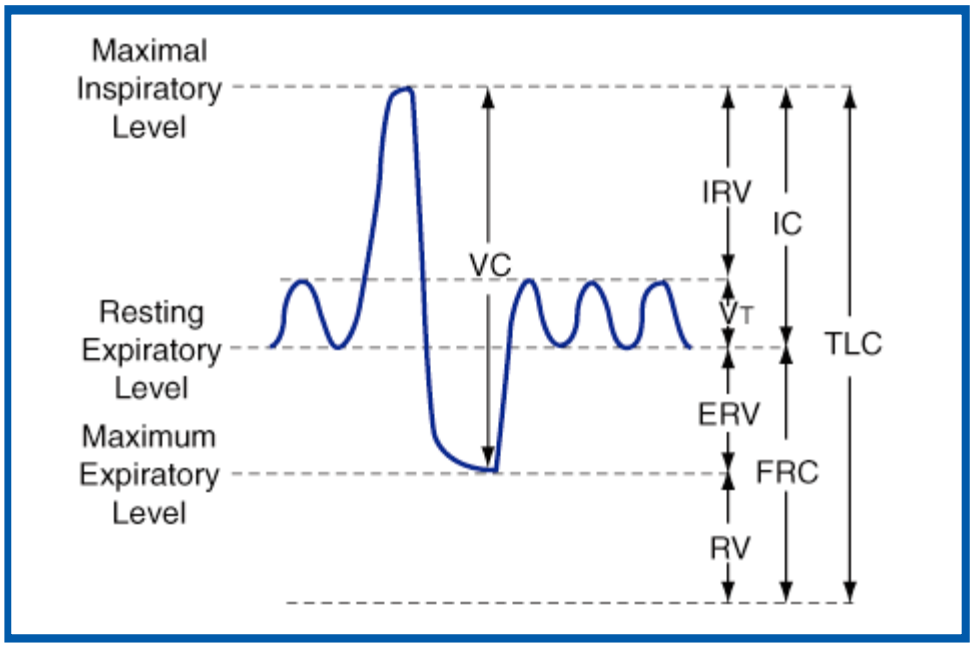

Figure 1-1.1 Lung Volumes Measured in a Pulmonary Function Test

Where:

V_T = Tidal Volume: volume of air normally inhaled or exhaled (0.4-1.0 L).

IRV = Inspiratory Reserve Volume: the additional volume of air inhaled (after the tidal volume) by taking a full deep breath (2.5-3.5 L).

ERV = Expiratory Reserve Volume: the additional volume of air exhaled (after the tidal volume) by forcing out a full deep breath (2.5-3.5 L).

RV = Residual Volume: the volume of air that remains in the lungs following a maximal exhalation (0.9-1.4 L for men; 0.8-1.2 L for woman).

VC = Vital Capacity: maximal volume of air that can be forced out after a maximal inspiration, down to the residual volume (4-5 L in men, 3-4 L in woman). This equals IRV + TV + ERV.

TLC = Total Lung Capacity: the amount of gas contained in the lungs at maximal inspiration (4-6 L). This equals VC + RV.

FRC = Functional Residual Capacity: the amount of air in the lungs at the end of a normal breath; i.e., after the tidal volume is exhaled. This equals ERV + RV.

Ventilation is also dependent on airflow. Through the upper airways and to the level of the terminal bronchioles, airflow occurs by bulk movement or convection. Because of the vast increase in cross-sectional area after the terminal bronchioles airflow slows and the gas molecules move by diffusion. The velocity of airflow is dependent on both airway resistance related to the size of the airway and lung compliance (stiffness) that results from the mechanical constraints of the chest wall.

All areas of the lungs do not receive equal ventilation. The base of the lung receives more ventilation per volume of lung than does the top or apex. This distribution varies with position of the body. For example when lying on the

back the portions of the lungs closest to the ground (dependent portion) receive the bulk of the ventilation.[1] In order to ensure adequate and efficient gas exchange the body adjusts blood flow through the lungs so that the majority of blood flows through capillaries in the areas of the lung with the most ventilation. In other words ventilation and perfusion are matched.

An understanding of normal lung function and physiology provides important clues to the mechanisms underlying diseases of the lung. For example, the abrupt change in flow from convective to diffusion at the level of the terminal bronchioles causes some inhaled particulates to get deposited here, making this area susceptible to damage.[1] Another example relates to the differential ventilation of lung tissue. Diseases which primarily affect the apex of the lung will impact breathing differently than those diseases that affect the base. In the following chapters, specific diseases of the pulmonary system will be discussed; a basic understanding of the normal structure and function of the lungs will allow for a more complete understanding.

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Chapter 1-2
Occupational Risks of Chest Disease in Fire Fighters

By Dr. Carrie Dorsey, MD, MPH

INHALATION OF COMBUSTION PRODUCTS

Fire smoke is a complex mixture of chemicals that result from the combustion (complete burning) and pyrolysis (incomplete burning) of materials. The products of combustion formed during any given fire are dependent on the materials consumed within the fire, the amount of oxygen present and the temperature at which the fire burns.[1] Because of the various factors that influence combustion it is difficult to predict what a fire fighter is exposed to at a specific fire. There are however a number of chemicals that are routinely found in fire smoke. For example, carbon monoxide is produced during all combustion reactions and carbon dioxide, nitrogen dioxide, hydrogen chloride, cyanide, and sulfur dioxide are also commonly detected.

When considering the risk of chest disease in fire fighters exposed to the products of combustion it is helpful to break these down into acute effects (those happening at or shortly following exposure and which tend to resolve), and chronic effects (those changes in health that occur following multiple or long-term exposures). The following is a discussion of each of these with respect to the respiratory system.

Acute Effects

Within fire smoke there are gases and particles that can be irritating and or toxic to the respiratory system. Injury can result from thermal exposure, asphyxiation, and response to irritants and toxicants. Symptoms and signs of inhalation that indicate damage to the respiratory system include tachypnea (rapid breathing), cough, hoarseness, stridor (loud breathing on inhalation and exhalation), shortness of breath, retractions (contraction of the abdominal and neck muscles), wheezing, sooty sputum, chest pain and rales/rhonchi (abnormal breath sounds heard with a stethoscope) .[2]

Because of the respiratory system's ability to rapidly cool inhaled air, thermal injury is isolated to the upper airways (nose, mouth and pharynx). Asphyxiation (lack of oxygen) can result from the replacement of oxygen by another chemical in the environment known as a simple asphyxiant or by the interference of the body's ability to transport and deliver oxygen to the tissues (chemical asphyxiant). Simple asphixiants include carbon dioxide, methane,

helium, nitrogen and nitrogen oxide. Examples of chemical asphyxiants are carbon monoxide, cyanide, hydrogen sulfide and arsine gas.[3] The symptoms and signs of hypoxemia and anoxia (low oxygen in the blood) can include lightheadedness, shortness of breath, chest pain, coma or death.

The effects of exposure to irritants such as hydrogen chloride, sulfur dioxide, phosgene, acrolein, ammonia and particulates are dependent on the size of the particle and how readily the chemical dissolves in water. These properties determine where in the respiratory tract the chemical or particle is deposited and absorbed. Hydrogen chloride is very soluble therefore injury occurs in the upper airway as opposed to phosgene which effects mainly in the lower respiratory tract (the lungs).[3] At high dose exposure, particle size and solubility are less predictive of the site of injury and there may be a pan-airway inflammatory response involving upper and lower airways and even alveoli. The irritants cause injury to the epithelial lining of the respiratory tract and inflammation. As discussed above this causes a variety of symptoms such as cough, shortness of breath, chest pain and increased mucous production.

A number of studies of smoke inhalation in fire fighters have demonstrated increased symptoms, transient hypoxemia, hyperreactive (spasmodic or twitchy) airways and changes in pulmonary function test measurements. However, other studies have showed little effect and this is thought to be due to the increased use of respiratory protective equipment in more recent times.[4] A brief description of the studies of pulmonary function in fire fighters is found below.

Chronic Effects on Pulmonary Function, Respiratory Illnesses and Mortality

Studies of the long term effects of repeated exposure to smoke have not been conclusive. Many of the studies summarized below do not indicate that fire fighters have a significant decline in lung function over time. The findings of these studies may be influenced by factors such as fire fighters with respiratory disease transferring to non-firefighting duties or retiring or an underestimate of the effect because of the healthy worker effect. Improvement in respiratory protective equipment and its use is also likely preventing the development of chronic lung disease.[4]

SUMMARY OF STUDIES OF PULMONARY FUNCTION IN FIRE FIGHTERS

The Forced Vital Capacity (FVC) is the total amount a person can breathe in or out with a single breath. The Forced Expiratory Volume in the first second of exhalation (FEV_1) and Force Expiratory Flow measured in the mid-portion of exhalation (FEF_{25-75}) can be used as measures of airway resistance. More can be found about these and other pulmonary function tests in the separate chapter on pulmonary function testing in this book. What follows here is a brief description of the relevant literature on pulmonary functions in fire fighters.

Peters et al 1974: Measured pulmonary function at the start of the study and then one year later in 1,430 Boston fire fighters. The FVC and FEV_1 both decreased more than expected over a one year time period. The rate of loss for

both was significantly related to the number of fires fought, with increased rate of loss as the number of fires increased.[5]

Musk et al 1977a: Followed 1,146 Boston fire fighters from the same cohort as Peters et al for 3 years. The annual decline in FVC and FEV_1 over the study period was less than observed in the initial year of the study. Fire fighters who fought no fires had a higher rate of decline. This was thought to be related to fire fighters with lung disease being selected for duties not involving active fire fighting.[6]

Musk et al 1977b: The authors also followed a group of retirees from the Boston cohort for five years. They observed that if the fire fighter retired with a shorter length of service, the individual had a non-significant increased rate of lung function loss and was more likely to have chronic bronchitis. The values of the pulmonary function tests were slightly lower than the expected values predicted for the study population.[7]

***Musk et al 1979*:** In a group of 39 fire fighters the average decrease in FEV_1 following smoke exposure was 50 ml. The decline was related to severity of smoke exposure.[8]

Loke 1980: Fire fighters completed a self-administered respiratory and occupational history questionnaire and completed pulmonary function tests. Four of the 22 tested had evidence of airway obstruction on testing without symptoms. Seven of the fire fighters were tested again after exposure to heavy smoke. No difference in pulmonary function was detected comparing pre- and post-exposure tests.[9]

Musk et al 1982: 951 fire fighters from the Boston cohort were followed for six years. The declines in FEV_1 and FVC over the six years were similar to those expected for healthy, non-smoking adults and were not correlated to firefighting exposure. The authors concluded that increased use of protective equipment in the cohort was protecting against the long-term effects of exposure to fire smoke.[10]

Sheppard et al 1986: FEV_1 and FVC were measured before and after each shift and fire for 29 fire fighters over an 8-week period. Approximately one quarter of those measurements obtained within two hours of fighting a fire decreased by greater than two standard deviations. In some cases this decrement persisted up to 18.5 hours.[11]

Horsfield et al 1988: The pulmonary function tests of the controls which consisted of non-smoking men employed in occupations other than fire fighting declined at a faster rate over four years than in the fire fighters. This shows that fire fighters are healthier than the general population ("the healthy worker effect") and is discussed further at the end of this chapter. In this study, the healthy worker effect is greater than any potential negative affect from fire exposures.[12]

Brandt-Rauf et al 1989: For individuals not wearing respiratory protective equipment there was a significant post-fire decline in FEV_1 and FVC. The individuals in this study were participating in an environmental monitoring and medical surveillance program.[13]

Markowitz 1989: Followed a cohort of New Jersey fire fighters exposed to large quantities of hydrochloric acid in a PVC fire over approximately two

years. At the initial evaluation there was a significant increase in pulmonary symptoms including cough, wheeze, shortness of breath and chest pain. These symptoms with the exception of wheezing remained significantly increased at the second evaluation. Of the cohort nine percent were told that they had asthma and 14% bronchitis following the time of the exposure. This was nearly significant when compared to unexposed fire fighters.[14]

***Sherman et al 1989*:** Pulmonary function and methacholine challenge testing was completed pre- and post-shift on 18 fire fighters in Seattle. The mean FEV_1 and FEF_{25-75} significantly decreased.[15]

***Chia et al 1990*:** Twenty fire fighters were exposed to smoke in a smoke chamber. Airway reactivity to inhaled histamine was measured before and after exposure. Prior to exposure none had increased reactivity; however, following exposure 80% of the fire fighters had increased airway reactivity. Length of time as a fire fighter contributed to the relationship.[16]

***Large et al 1990*:** Significant declines in FEV_1 and FEF_{25-75} were measured in fire fighters following exposure. The other measures such as FVC also declined however not statistically significantly.[17]

***Rothman et al 1991*:** Cross-seasonal changes in pulmonary function and symptoms were studied in 52 wildland fire fighters. Respiratory symptoms significantly increased from the beginning to the end of the season. Declines in FVC and FEV_1 were noted; however, they were not significant.[18]

***Liu et al 1992*:** 63 wildland fire fighters both fulltime and seasonal were evaluated with questionnaires, spirometry and methacholine challenge testing before and after the fire season. The individual mean FVC, FEV_1 and FEF_{25-75} declined significantly across the season. Airway responsiveness as measured by the methacholine challenge test increased significantly by the end of the fire fighting season.[19]

***Betchley et al 1997*:** Investigated the cross-shift pulmonary effects in forest fire fighters. There was significant mean individual decline in FVC, FEV_1 andFEF_{25-75} from pre-shift to post-shift. Declines were also seen when comparing pre-season to post-season measurements.[20]

***Burgess et al 2001*:** The authors demonstrated acute changes in spirometry and lung permeability following fire overhaul despite the use of full-face cartridge respirators.[21]

***Mustaijbegovic et al 2001*:** Active fire fighters had significantly more respiratory symptoms as compared to unexposed controls. The higher prevalence of symptoms was related to duration of employment and smoking status of the individual. As length of employment increased the decline in FVC increased. Early signs of airway obstruction were observed on the pulmonary function tests.[22]

***Banauch et al 2003*:** New York City Fire Department rescue workers experienced massive exposure to airborne particulates at the World Trade Center site. Aims of this longitudinal study were to (1) determine if bronchial hyperreactivity was present, persistent, and independently associated with exposure intensity, (2) identify objective measures shortly after the collapse that would predict persistent hyperreactivity and a diagnosis of reactive airways dysfunction 6 months post-collapse. A representative sample of 179

NYC Fire Department rescue workers (fire fighters and EMS) stratified by exposure intensity to World Trade Center Dust (high, moderate, and control) without current smoking or prior respiratory disease were enrolled. Highly exposed workers arrived within two hours of collapse, moderately exposed workers arrived later on days one to two; control subjects were not exposed. Hyperreactivity (positive methacholine challenge tests) at one, three, and six months post-collapse was associated with exposure intensity, independent of ex-smoking and airflow obstruction. Six months post-collapse, highly exposed workers were 6.8 times more likely than moderately exposed workers and control subjects to be hyperreactive and hyperreactivity persisted in 55% of those hyperreactive at one and/or three months. In highly exposed subjects, hyperreactivity one or three months post-collapse was the sole predictor for reactive airways dysfunction or new onset asthma.[23]

***Banauch et al 2006*:** New York City fire fighters' pulmonary function (FVC and FEV-1) were studied for six years. In the five years pre-World Trade Center exposure, the mean annual decline in FVC and FEV-1 was not significantly different from the general population – averaging a 31 ml annual decrease in FEV-1. In the first year post-World Trade Center exposure, the mean decline in FEV-1 was 372 ml and there was an exposure intensity effect. This study demonstrates that annual declines in pulmonary function does not occur at an accelerated rate in fire fighters wearing modern respiratory protective equipment but when exposed to overwhelming irritants without respiratory protection, accelerated decline in pulmonary function can occur. Future studies are ongoing to determine if this effect is permanent.[24]

Gaughan et al 2008: Wildland fire fighters were studied with respiratory questionnaires, spirometry (FVC and FEV_1) and chemical measurements of inflammation (albumin, eosinophilic cationic protein, and myeloperoxidase) in sputum and nasal lavage fluid. Assessments were made pre-season, post-fire, and post-season. Fifty-eight fire fighters had at least two assessments. Mean upper and lower respiratory symptom scores were significantly higher post-fire compared to pre-season. Lung function declined with mean FEV_1 significantly lower post-fire as compared to pre-season and then recovered in the post-season. Individual increases in sputum and nasal measures of inflammation increased post-fire and were significantly associated with post-fire respiratory symptom scores.[25]

***Miedinger D et al 2007*:** The authors prospectively determined the diagnostic value of respiratory symptoms and various tests used for asthma assessments. A questionnaire, spirometry, direct and indirect airway challenge tests, exhaled nitric oxide, and skin-prick tests were administered prospectively to 101 of 107 fire fighters employed in Basel, Switzerland. Asthma was defined as the combination of respiratory symptoms with airway hyperresponsiveness. Asthma was diagnosed in 14% (14 of 101 fire fighters). Wheezing was the most sensitive symptom for the diagnosis of asthma (sensitivity, 78%; specificity, 93%). Other respiratory symptoms showed a higher specificity than wheezing but a markedly lower sensitivity. Bronchial airway challenge with mannitol was the most sensitive (92%) and specific (97%) diagnostic test for asthma. Using a cutoff point of 47 parts per billion, nitric oxide had a similar specificity (96%) but lower sensitivity (42%) compared to the direct (methacholine)

and indirect (mannitol) airway challenge tests. Asthma was considerably under-diagnosed in fire fighters. The combination of a structured symptom questionnaire with a bronchial challenge test identified fire fighters with asthma. The authors conclude that these tests should routinely be used in the assessment of active fire fighters and may be of help when evaluating candidates for this profession.[26]

FIRE FIGHTERS AND DISEASES OF THE RESPIRATORY SYSTEM

Attempts to establish associations between fire fighters and occupational diseases have yielded conflicting results, reflecting the challenges encountered in studying this population. Because fire fighters are selected for their abilities to perform strenuous tasks they should demonstrate a "healthy worker effect." The term "healthy worker effect" is used when a population has lower rates of disease and death than the general population thereby, accidentally masking exposure-response associations. To control for this, some studies rely on comparisons of fire fighters to police officers, a group presumed to be similar in physical abilities and socioeconomic status. Longitudinal dropout (due to job change or early retirement) may also reduce morbidity and mortality rates. Fire fighters who experience health problems related to their work may choose to leave their position, creating a survivor effect of individuals more resistant to the effects of firefighter exposures. Other issues that may influence morbidity and mortality rates in fire fighters are differences in exposures, both makeup and duration, between individuals and between different fire departments. In fact, the occupational exposures experienced by fire fighters varies greatly, influenced by the types of fires encountered, job responsibilities, and use of personal protective equipment. A further complication is that studies rarely account for non-occupational risk factors such as cigarette smoking due to lack of data. Finally, mortality studies frequently rely solely on death certificates even though it is well known that the occupation and cause of death may be inaccurate. Despite these difficulties, many important observations about the health of fire fighters have been made.

Overall, fire fighters have repeatedly been shown to have all-cause mortality rates less than or equal to reference populations. Increased death rates from non-cancer respiratory disease have not been found when the general population was used for comparison. To reduce the presumed impact of the "healthy worker effect", two studies used police officers for comparison. In both of these studies, fire fighters had increased mortality from non-cancer respiratory disease.[27, 28]

By definition, mortality studies do not identify the human cost of chronic debilitating lung disease. Very large exposures to pulmonary toxicants can lead to permanent lung damage and disability. At 22 months, 9.4% of fire fighters exposed to hydrochloric acid during a large PVC fire were diagnosed with asthma and 14.3% were told that they had bronchitis.[14] Asthma or reactive airways dysfunction has also been shown to occur in fire fighters exposed to WTC dust.[23, 29] Fire fighters have not been shown to be at an increased risk of death from lung cancer, but again these studies are also confounded by the "healthy worker effect" and longitudinal dropout.

More studies are needed but epidemiologic evidence increasingly suggests that fire fighters are at increased risk for the development of sarcoidosis. Sarcoidosis is discussed in detail in a later chapter in this book. A cluster of three cases in a group of 10 fire fighters who began training together in 1979 prompted an investigation involving active and retired fire fighters, police officers and controls. Fire fighting was significantly associated with one marker of immune system activation suggesting that fire fighters may be at increased risk for the development of sarcoidosis .[30] In addition, the annual incidence rate for sarcoidosis was increased in New York City fire fighters as compared to a concurrent New York City EMS pre-hospital healthcare worker control group and historic controls.[31] Nearly all of these fire fighters were asymptomatic with normal pulmonary and exercise function. After exposures at the WTC, a dramatic increase in the annual incidence of sarcoidosis in New York City fire fighters and EMS healthcare workers was demonstrated.[32] Furthermore, this group was symptomatic with evidence for obstructive airways disease, hyperreactivity and rarely arthritis.

Summary of Studies of Respiratory Morbidity and Mortality in Fire Fighters

***Musk et al 1978*:** Boston fire fighters were found to have a standardized mortality rate (SMR) for non-cancer respiratory disease of 0.93 as compared to the general male population of Massachusetts. A value of < 1 implies a decreased risk.[33]

Feuer et al 1986: When New Jersey fire fighters were compared to police officers a significant increase in the risk of death from non-cancer respiratory disease was observed (proportionate mortality ratio [PMR] 1.98) .[27]

***Vena et al 1987*:** Again using the general population as a comparison group fire fighters from Buffalo, New York were found to be at less risk for non-cancer respiratory disease (SMR 0.48). In addition risk of death from respiratory cancers was less than the general population (SMR 0.94) .[34]

Rosenstock et al 1990: Fire fighters in three northwestern cities had significantly increased mortality due to non-cancer respiratory disease (SMR 1.41) .[28]

***Sama et al 1990*:** A non-significant elevation in mortality due to lung cancer was found in fire fighters as compared to the general population (SMR 1.22) and to police officers (SMR 1.33).[35]

Beaumont et al 1991: Significantly less respiratory disease deaths were observed in San Francisco fire fighters as compared to the general population. The SMR was 0.63 for non-cancer and 0.84 for respiratory cancer deaths.[36]

***Grimes et al 1991*:** Observed less death related to respiratory disease as compared to the general population.[37]

***Guidotti 1993*:** A slight but non-significant increase in the risk of obstructive pulmonary disease was observed (SMR 1.57) .[38]

Aronson et al 1994: Observed less death related to respiratory disease as compared to the general population.[39]

***Burnett et al 1994*:** A large survey of fire fighters in 27 states showed decreased risk of death from non-cancer and cancer respiratory disease.[40]

***Tornling et al 1994*:** Observed less death related to respiratory disease as compared to the general population.[41]

***Prezant et al 2002*:** The first reported series of 332 fire fighters who developed severe and persistent cough, shortness of breath, gastroesophageal reflux, sinus congestion/drip and other upper/lower respiratory symptoms after exposure to WTC dust. Evaluation demonstrated that 63% had a bronchodilator response and 24% had bronchial hyperreactivity, both findings consistent with asthma and obstructive airways disease. The clinical and physiological severity was related to the intensity of exposure.[29]

***Ma et al 2005*:** In the most recent study to evaluate mortality in fire fighters there was a slight but non-significant increase in the risk of death from respiratory disease in female fire fighters as compared to the general population. Decreased risk was seen for the male fire fighters.[42]

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Chapter 2-1
Disorders of the Upper Aerodigestive Tract

By Dr. Michael Shohet, MD

INTRODUCTION

The upper aerodigestive tract, typically defined as the mucous membrane-lined structures from the nostrils and lips to the vocal cords and uppermost portion of the esophagus, is the portal for virtually everything that we inhale or ingest. Consequently, it is also the chief portal to workplace-related potential irritants. These irritants come in many forms, and the type of injury they produce is equally variable. Though certain exposures, especially those that cause allergies, are not considered serious or life threatening, increased research and experience has shown a much more prominent relationship between the upper airways and lung diseases. Additionally, the amount of disability related to chronic irritation of the upper airway such as the nose and sinuses, cannot be underestimated. If one just considers the economic impact of these disorders, it is clear that these diseases cannot be overlooked.

ANATOMY

Nose and Sinuses

The nasal passages are paired cavities separated by a midline partition called the nasal septum. The chief functions of the nose are for smell, breathing, defense, and humidification. Specialized types of mucous membrane achieve these functions. In order to optimize efficiency, there are bony projections within the nasal cavities called turbinates that are also lined by this specialized mucous membrane. These turbinates are also comprised of many blood vessels that allow them to swell and shrink as necessary in order to better humidify, warm, and filter the air we breathe. Though it is normal for the turbinates to swell and shrink as part of our normal nasal function, the phenomenon of these mucous membranes swelling to excessively large levels is what we perceive as nasal congestion. Congestion has many causes including response to allergens and irritants, and is a chief symptom of rhinosinusitis.

There are several air-filled hollows of the skull that are also lined by mucous membrane. These are found adjacent to the nasal cavities and are termed paranasal sinuses. The sinuses really serve no definitive function beside perhaps lightening the skull or protecting the brain from some forms of high-impact trauma. There are many ways that the sinuses can become a problem, however.

Oral Cavity, Pharynx, and Larynx

Fortunately, an explanation of the function of the mouth and tongue is likely not necessary. It should be noted that though we generally consider the tongue to be responsible for our sense of taste, the tongue really only gives us the sensations of sweetness, saltiness, bitterness, and sourness. The fine essences of food taste are accomplished by our sense of smell.

The oral cavity structures are also lined by specialized mucous membranes. They are separated from the nasal cavity by the hard and soft palate. The palate may vary in size and shape in each individual, and along with the back of the tongue and nose, have specialized lymphoid tissue attached to them termed tonsils and adenoids. These structures may become enlarged or swollen as a manifestation of upper airway irritation as well, and are components that may need to be addressed in the management of various types of upper airway obstruction including obstructive sleep apnea.

The rest of the throat is called the pharynx and larynx. Also lined by mucous membrane, the primary functions of the larynx are maintenance of a breathing passage, protection of the airway, and phonation. The cough reflex is important for protecting the airway during swallowing, but also in response to potentially noxious irritants that may be inhaled. The larynx is composed of cartilage, muscles, and nerves along with the vocal cords. The functions of speech, breathing, coughing, and swallowing are quite complex, with many ways for things to go wrong or become discoordinated. Given the larynx's role as a primary defense of the lower respiratory tract, its function and hygiene must not be taken for granted.

DISEASE

Rhinitis, Sinusitis, and Rhinosinusitis

Rhinitis means inflammation of the nasal cavities. Sinusitis means inflammation of the sinuses. Since the nasal cavities and sinuses are lined by the same type of specialized mucous membrane and the irritation and symptoms are often continuous and closely related to one another, the term rhinosinusitis has become popularized and preferred amongst specialists.

The extent of inflammation can be quite variable. Similarly, the symptoms can be quite diverse even within the same individual. This may range from simple congestion or runny nose to intense pain or pressure in the cheeks, around the eyes, or headache. Loss of smell, weakness, tiredness, cough (often more severe at night,) and drainage down the back of the throat (postnasal drip) are other common manifestations of rhinosinusitis (Table 2-1.1).

We typically classify rhinosinusitis as being one of two broad categories with different causes and courses: acute or chronic. Acute rhinosinusitis simply refers to an inflammatory episode lasting less than two weeks. Complete resolution of symptoms is typical in acute infections, as these are usually preceded or caused by viral infections of the nose and sinuses often called "colds." The typical scenario would be that someone catches a cold that results in inflammation of the nasal passages. If this inflammation is enough to impair the effective circulation and clearance of the sinuses, a bacterial infection of the sinuses (acute rhinosinusitis) may result. The symptoms of acute rhinosinusitis often

differ from those of chronic rhinosinusitis in that the pain is often more sharp and severe, often with tenderness when the sinus is touched. Fever, blood and foul nasal discharge are all more common in acute cases. Acute rhinosinusitis can frequently be avoided if the cold is treated effectively with decongestants and anti-inflammatory medications. If acute infections recur very regularly (greater than four episodes yearly,) the possibilities of anatomic predispositions or issues with the immune system should be considered. Similarly, if one develops a complication of acute rhinosinusitis such as a brain or eye infection, further investigations are warranted and may include specialized imaging such as a CT scan, blood work to evaluate the immune system and to check for diabetes, as well as examination by a specialist.

Signs and Symptoms of Chronic Rhinosinusitis
• **Facial pain and pressure including the cheeks, between the eyes, and forehead**
• **Nasal congestion or obstruction**
• **Drainage of discolored mucous from the nose or down the back of the throat (postnasal drainage)**
• **Alteration in the sense of smell or taste**
• **Aching of the upper teeth**
• **Headache**
• **Bad breath**
• **Fatigue**
• **Cough**

Table 2-1.1 Signs and Symptoms of Chronic Rhinosinusitis

In cases of rhinosinusitis where the symptoms persist for over 12 weeks (chronic rhinosinusitis) there is usually some form of more persistent irritation of the nasal passages such as allergens, irritants, temperature extremes, wood dust, metal dust and chemicals. It should be noted that a clear demarcation between allergies and other causes of chronic inflammation of the mucous membranes of the nose and sinuses could be difficult. Not only can both types of inflammation be present in the same individual, but also often one's allergic disease could become substantially worsened by occupational exposures. For this reason protection from environmental and occupational irritants can be helpful in both allergic and non-allergic individuals. The relationship between asthma and chronic rhinosinusitis has been well described, and can best be understood by the fact that the entire upper respiratory tract is lined by the same type of mucous membrane, and therefore may react to similar irritants or allergens.

The evaluation and management of chronic rhinosinusitis can be quite variable and complex. As the underlying cause is often exposure to some type of irritant whether it is a classical allergy or not, the detection of and protection from these irritants is quite helpful if possible. This evaluation may include formal allergy testing either by means of a blood test or evaluation by an allergist, and taking a careful history to determine if there is some preceding exposure or seasonal variation to the symptoms that may give some clue as to the irritant. In cases

where the offending agents can be determined, avoidance is recommended. If this cannot be practically achieved other options are considered and can be described as those that either decrease the body's exposure to the irritants, or those that attenuate the bodies response to the irritants. Practical ways of decreasing the body's exposure to airway irritants would include a mask or respirator designed to filter out the offending particles, or a nasal and sinus saline rinse applied immediately after a large exposure or on a regular basis in situations where the exposures are more persistent. (Table 2-1.2)

Steps for Minimizing Symptoms of Chronic Rhinosinusitis
• **Avoidance of airway irritants such as smoke, dust, and toxic fumes-sometimes by use of a mask or respirator**
• **Use of a saline nasal rinse to cleanse the nasal passages**
• **Room humidification (with a humidifier that is cleaned regularly)**
• **Allergy testing to learn of other possible triggers to avoid**
• **Ensure you are drinking plenty of fluids**
• **Avoid upper respiratory infections by washing your hands regularly and after any contact with people you suspect of being sick**
• **Consultation with a physician to discuss medications which may decrease your body's sensitivity to nasal irritants**

Table 2-1.2 Self-Care Steps for Minimizing Symptoms of Chronic Rhinosinusitis

There are a number of ways to alleviate the nasal response to airway irritants both allergic and non-allergic. This would include topical and systemic (usually taken by mouth) medications designed to minimize the inflammatory response. A good example would be the use of an antihistamine pill for seasonal allergies. Some medications and nose sprays are intended for symptomatic relief, and some are intended to minimize the development of symptoms. This distinction is very important, and should be clarified with your physician in order to ensure proper use.

In situations where symptoms persist even with carefully considered medical therapy, one must be evaluated for other factors. Certain defects of the immune system, either innate or acquired, may be considered. There are also anatomic factors that may warrant evaluation and possible treatment such as obstructing polyps, major deformities of the nasal septum, or narrowing or obstruction of the natural sinus openings. Benign and malignant tumors of the nasal cavities, though rare, have many of the same signs and symptoms as chronic rhinosinusitis, so evaluation is important if symptoms persist despite what would otherwise be considered adequate treatment. Sometimes a surgical procedure is helpful in addressing nasal obstructions or clearing the sinuses in order for them to clear more effectively. It should be noted that surgery is rarely if ever to be considered a cure for chronic sinusitis. It is simply one more tool that specialists have available in their armament in order to relieve most symptoms, and improve the body's ability to be more resilient when exposed to environmental allergens or irritants.

In cases where people tend to be much more symptomatic on one side, or if these symptoms persist despite aggressive treatment, the possibility of a

sinus tumor or cancer should be entertained and appropriate test ordered including sinus CT scans and endoscopy. As there are many occupational exposures that have been associated with higher incidences of certain types of sinus cancers, and the latency, or time between the actual exposure and the development of the resulting disease can be more than a decade, careful acquisition of all known exposures is important.

Pharyngitis, Laryngitis, and Laryngopharyngitis

Irritation of the throat has many names depending on where the irritation occurs. As the irritation is often not isolated to one specific area the term laryngopharyngitis, irritation of the throat and voice box, has become more favored. The main symptoms of laryngopharyngitis are throat soreness or change in voice. Throat dryness, cough, and trouble swallowing are other potential symptoms. Often one feels a tickling sensation, rawness, or lump in the throat. In some circumstances, the irritation can cause abnormal coordination of the vocal cords during normal breathing, resulting in a choking sensation, throat tightness, or even shortness of breath (Table 2-1.3). If the symptoms are severe, persistent, or progressive, prompt evaluation is necessary. Some forms of acute inflammation of the throat can progress to airway obstruction, and should be taken seriously. Persistent hoarseness can be a sign of something more serious, and should be evaluated if present for more than four to six weeks.

Signs and Symptoms of Chronic Laryngopharyngitis
• **Hoarseness or loss of voice**
• **Raw or sore throat**
• **Cough (typically dry)**
• **Difficulty breathing**
• **Sensation of a lump in the throat**
• **Trouble swallowing**

Table 2-1.3 Signs and Symptoms of Chronic Laryngopharyngitis

As the throat is a mucous membrane lined passage, the same potential irritants as those of the nose and sinuses exist. These include viral infections, airway irritants, and smoke. Additionally, overuse or abuse of the voice may increase the risk of laryngitis.

There are acute and chronic forms of laryngopharyngitis. A viral laryngitis, for instance, is typically acute (short-lived), while symptoms that are more long lasting usually point to a persistent irritating source such as severe allergies, smoking or chemical irritant exposure, habitual vocal strain, or acid reflux continually irritating the larynx.

While most cases of acute laryngitis are managed with self-care, chronic laryngitis, cases lasting for more than two weeks, should usually be managed only after discussing one's symptoms with a physician. Voice rest, adequate fluid intake, lubricants such as throat lozenges, and ensuring that the ambient air is humid without being contaminated with mold or fungus are excellent first steps to ensuring prompt recovery in cases of acute laryngopharyngitis.

The typical evaluation of chronic laryngopharyngitis or hoarseness is a thorough evaluation of one's exposures and risk factors. Cigarette smoking, allergies, repeated exposure to environmental irritants, and voice overuse are often substantial risk factors. In some situations, evaluation of the voice and the throat and vocal cords by a specialist is necessary. This exam is often aided by performing a laryngoscopy procedure in which a very small fiberoptic scope is placed in the throat in order to view the mucous membrane surfaces and architecture with excellent resolution. The coordination of the muscles of the larynx can be examined as well as the vibrations of the vocal cords when using specialized instruments. Biopsies can be taken if anything suspicious is seen.

As the treatment of chronic laryngopharyngitis largely depends on what is the underlying cause, a specialist evaluation is sometimes necessary in order to determine what that cause is. One common cause that warrants further discussion is chronic laryngopharyngitis due to reflux disease. This disorder refers to the backflow of stomach contents through the esophagus and potentially into the larynx and pharynx. When the reflux is limited to the esophagus, it may cause erosions that are experienced as heartburn (a burning sensation in the middle of the chest.) However, only half of patients diagnosed with reflux experience heartburn. This is due not only to the fact that the esophagus has more protective properties, but that the reflux is not spending enough time in the esophagus. As the esophagus is better suited to withstand the irritation of stomach contents such as acid, often a patient will have throat symptoms suggestive of laryngopharyngitis prior to experiencing traditional heartburn. Reflux can occur day and night, and often takes place even hours after a meal (Table 2-1.4).

Tips for Reducing Reflux

- **Quit smoking or using any tobacco**
- **Avoid caffeine (found in most coffee, tea, soda (especially cola), and mints)**
- **Avoid alcohol**
- **Avoid lying down two to three hours after eating**
- **Avoid eating excessively large meals**
- **Avoid eating foods that may trigger reflux including fatty or spicy foods, chocolate, onions, and tomato sauce**
- **Control your weight**
- **Loosen your belt and avoid tight-fitting clothes**
- **Raise the head of your bed by placing blocks under the head of the bed or placing a wedge under the mattress**

Table 2-1.4 Tips for Reducing Reflux

In addition to laryngoscopy, other testing may be necessary in order to definitively determine the underlying cause(s) of an individual's laryngopharyngitis. If allergies are suspected, they may be further evaluated with allergy testing. In cases where reflux is suspected, there are other tests that may confirm the presence of acid in the throat and the esophagus. PH monitoring incorporates a probe, with the ability to measure acidity of fluids,

placed into the throat for several hours. The data acquired is subsequently uploaded into a computer and provides an excellent picture of the amount and timing acid reflux. Another test uses an endoscope consisting of a light and camera that is inserted down the throat and into the esophagus. It can detect erosions or abnormal changes in the lining of the esophagus and stomach. If anything appears to be suspicious, a biopsy can be taken.

Less specific, yet often-helpful treatments for chronic laryngopharyngitis include voice rest, adequate hydration with non-alcoholic beverages, smoking avoidance, and avoidance of known upper airway irritants (Table 2-1.5).

Steps for Minimizing Symptoms of Chronic Laryngopharyngitis
• **Avoidance of airway irritants such as smoke, dust, and toxic fumes- sometimes by use of a mask or respirator**
•. **Avoid talking too loudly or for too long**
• **Avoid whispering which causes increased strain on the throat**
• **Avoid clearing your throat**
• **Keep your throat moistened and your body hydrated by drinking plenty of non-alcoholic fluids**
• **Avoid upper respiratory infections by washing your hands regularly and after any contact with people you suspect of being sick**
• **Treat potential underlying causes of laryngopharyngitis including reflux, smoking, or alcoholism**

Table 2-1.5 Steps for Minimizing Symptoms of Chronic Laryngopharyngitis

The use of antibiotics for management of chronic laryngitis is quite limited as most infectious cases are caused by a viral rather than bacterial infection. Potent anti-inflammatory medications including corticosteroids are sometimes helpful, and in circumstances when reflux is a major factor and conventional reflux lifestyle precautions fail to improve symptoms, antireflux medications or potent antacids may be prescribed.

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Chapter 2-2
Respiratory Infections – Bronchitis and Pneumonia

By Dr. Andrew Berman, MD and Dr. David Prezant, MD

INTRODUCTION

Respiratory tract infections are divided into two types: those of the upper respiratory tract and those of the lower respiratory tract. The upper respiratory tract consists of the nose, throat (pharynx), voice box (larynx) and the upper windpipe (trachea). Infections of the upper respiratory tract include the common cold, tonsillitis, sore throat (pharngitis), sinusitis, and laryngitis. These infections are commonly caused by viruses and are often self-limiting. In contrast, infections of the lower respiratory tract are more serious, often require antibiotics, and sometimes hospitalization. The lower respiratory tract includes the bronchi (the first main branches off the wind pipe into the lungs), bronchioles (smaller airtubes that branch off the bronchi), and alveoli (the air sacs at the end of the bronchioles). Infections in these areas include bronchitis, bronchiolitis and pneumonia. This chapter reviews upper and lower respiratory tract infections and their treatment. Details on sinusitis are discussed in a separate chapter on upper airways disease.

AIRWAY INFECTIONS

Acute Bronchitis

Acute Bronchitis is defined as inflammation of the trachea, bronchi, and/or the bronchioles of the lung in response to an infection. Inflammation of these large airways leads to airway narrowing and mucus production, and results in a cough which is self-limited. Among out-patients, acute bronchitis is one of the most common illnesses in the United States, especially during the winter and fall seasons.[1] Chronic bronchitis is a clinically-distinct disease and will be discussed separately.

Acute bronchitis is almost always caused by viruses, though these organisms are infrequently isolated.[2] The same viruses that cause a common cold can cause acute bronchitis, and are usually obtained in a similar manner including hand-to-hand contact and inhalation of aerosolized particles from coughing or sneezing. These viruses include adenovirus, influenza A and B virus, coronavirus, rhinovirus, herpes simplex, respiratory syncytial virus, and parainfluenza virus. For the influenza virus, the incubation period (the time between contact and infection) is two to four days and epidemics occur between

fall and early spring. Bacteria are much less likely to cause acute bronchitis and are not commonly isolated. Bacteria that may cause acute bronchitis include Hemophilus influenzae, Pneumococcus, Moraxella catarrhalis and certain atypical bacteria, such as Mycoplasma pneumoniae and Chlamydophila pneumonia. Acute bronchitis can also be caused by the bacteria that cause whooping cough (Bordetella pertussis).

Acute bronchitis is diagnosed based on clinical features. Most commonly, the patient complains of a cough, usually with discolored sputum. If the cough is severe, patients may cough up small amounts of blood (hemoptysis). Despite what many believe, thick discolored sputum does not mean there is a bacterial infection. The cough lasts at least five days and may persist for weeks.[3] Sore throat and mild shortness of breath may be reported. Patients often recall contact with an individual with similar symptoms. Fever is uncommon and if present, may suggest the diagnosis of pneumonia. Some patients develop wheezing due to bronchospasm and lung function studies may show reduced flow rates consistent with an obstructive pattern (ex. FEV_1 and FEV_1/FVC ratio). Bronchodilator response and airway hyperreactivity may also be demonstrated. Although wheezing is usually self-limiting and resolves in five to six weeks[4], viral bronchitis has been implicated as one cause of prolonged or even life-long asthma in children and adults.

Additional testing is often not necessary in diagnosing acute bronchitis, especially when vital signs and chest examination are normal. When temperature, respiratory rate or pulse rate is elevated, a chest x-ray may be performed to rule out pneumonia. The chest x-ray in patients with acute bronchitis does not show abnormalities, while "infiltrates" are commonly seen in patients with pneumonia (see below and the chapter on radiology). In the elderly, however, pneumonia may be present without altered vital signs, making these two conditions difficult to differentiate in this population without a chest x-ray. Sputum gram stain shows inflammatory cells and may show bacterial organisms, though since bacteria do not usually cause acute bronchitis, sputum studies are not recommended unless the chest x-ray is abnormal. If pertussis is suspected, nasopharyngeal cultures may be obtained.

Generally, acute bronchitis is self-limiting. Treatment centers on lessening symptoms (fever and body aches) and often includes agents such as nonsteroidal anti-inflammatory drugs (such as ibuprofen or Motrin), aspirin, or acetaminophen (Tylenol). Cough suppressants are usually not effective but can be used if the cough is severe or interfering with sleep. There is limited and inconsistent data for the role of beta-agonists as bronchodilators.[5] Inhaled anticholinergic agents are not recommended. Though inhaled corticosteroids are sometimes prescribed, there is no data supporting their use.

Antibiotics are commonly prescribed though are not indicated in the vast majority of bronchitis cases. In a published systematic review[5] where a series of studies were analyzed together, patients receiving antibiotics had a clinically insignificant shorter duration of cough (about one-half day less). However, there was also a trend towards an increase in adverse effects in the antibiotic group, leading the authors to conclude that any modest benefit was matched by the detriment from potential adverse effects. In another study, in patients with acute bronchitis without underlying lung disease, investigators found that antibiotic treatment did not differ from prescribing vitamin C.[6]

Despite this evidence, however, physicians continue to frequently prescribe antibiotics for acute bronchitis, with a trend towards the use of newer, more broad-spectrum agents. Inappropriate use of antibiotics leads to increased bacterial resistance and adverse effects including infectious diarrhea caused by alterations of the normal gut flora.

Published guidelines recommend antibiotic treatment only in certain cases.[7] Treatment of pertussis is recommended mainly to reduce transmission. Pertussis may be suspected as the causative agent when the patient reports coughing fits, with or without a whooping (or gasping) sound or post-cough vomiting. Treatment of pertussis is with an antibiotic from the macrolide class, such as azithromycin (Zithromax) or clarithromycin (Biaxin), though benefit is only observed if treatment is begun within the first week. If there is an influenza outbreak in the community, and infection with influenza A is suspected, therapy with the anti-influenza drugs, oseltamivir (Tamiflu) or zanamivir (Relenza), can be considered as the morbidity associated with this virus is great. Clinical benefit from treatment occurs when these drugs are initiated within two days of the onset of symptoms, and is defined as a patient having about one day less of symptoms. During an epidemic, these medications may also be used to prevent illness in high-risk individuals until vaccination can be administered. However, with increasing use of antiviral medications, resistance appears to be occurring. All high-risk patients (the elderly and those with chronic disease) should receive annual vaccination against the influenza strains most likely to be epidemic. Only if a bacterial etiology is suspected are antibiotics indicated.

Because influenza interferes with the immune system, patients with acute influenza bronchitis may rarely go on to develop secondary viral or bacterial pneumonia. Post-influenza pneumonia caused by a virus should be suspected when cough, shortness of breath and fever persist for weeks. Post-influenza pneumonia caused by bacterial should be suspected when there was improvement followed by reoccurrence of symptoms one to two weeks later. The most common bacterial causes include Pneumococcus pneumonia, Staphylococcus aureus, Haemophilus influenzae, and Gram-negative organisms from the gut.

Chronic Bronchitis

Chronic Bronchitis is a subcategory of Chronic Obstructive Pulmonary Disease (COPD). It is characterized by persistent inflammation of the airways and is defined as the presence of a daily cough with sputum production for 3 months, two years in a row, in a patient in who other causes of chronic cough have been excluded.[8] Common to this condition are periodic acute exacerbations, usually due to respiratory infections. As the disease progresses, the time between acute exacerbations shortens. This topic is covered in greater detail in a separate chapter.

Cigarette smoking is the main cause of chronic bronchitis. Other far less common causes include inhalational injury from occupational and environmental exposures. The airways of patients with chronic bronchitis are inflamed and produce extra mucus. In addition, mucus clearance is decreased. Both airway inflammation and extra mucus lead to narrowing of the airways which is why patients feel that it is hard for air to move out of the lungs and that they have mucus which is hard to get out. Overtime, inflammation and

mucus plugging can lead to progressive loss of lung function and patients may complain of breathlessness. Infections can cause acute exacerbations of chronic bronchitis and may worsen this condition, leading to further declines in pulmonary function.

Chronic bronchitis should be considered in any patient with a history of tobacco use with a chronic cough and sputum production. Patients may have shortness of breath, usually when walking up inclined surfaces or steps or when carrying bags. Lung exam may reveal decreased breath sounds or wheezing, especially during exertion. Also, the time spent in expiration is often more than the amount of time spent for inspiration. In such patients, spirometry should be performed to confirm the diagnosis and grade the severity. A reduced FEV/FVC ratio (usually less than 70%), bronchodilator response and/or airway hyperreactivity are all indicators of significant airway obstruction, although the latter two are more common in asthma than in COPD.

Patients with chronic bronchitis may have recurrent episodes of acute bronchitis, occurring one to two times per year, but the clinical picture and bacteriology differ from that seen in normal adults. Such episodes are termed acute exacerbations and are defined as an acute increase in symptoms beyond normal day-to-day variation. This generally includes one or more of the following: increased frequency and severity of cough, increases in volume and/or changes in the character of sputum production, and/or worsening shortness of breath.[8] Most exacerbations of COPD are due to viral or bacterial respiratory infections. As opposed to acute bronchitis, bacterial infection is implicated in approximately one-half of acute exacerbations of chronic bronchitis. It is often difficult to determine if the cause is viral or bacterial because patients with chronic bronchitis have bacterial colonization of their airways even in the absence of acute infection. Common viral causes are adenovirus, influenza, rhinovirus, coronavirus, herpes simplex, and respiratory syncytial virus. Common bacterial causes are Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Chlamydia and Mycoplasma pneumoniae.

Management and treatment of stable chronic bronchitis/COPD is discussed elsewhere in another chapter in this book. Antibiotics are generally reserved for use in acute exacerbations. As COPD progresses and lung function declines, the bacteria implicated in exacerbations change, and often require more broader spectrum antibiotics. Therefore, it is important to consider the patient's lung function when selecting an antibiotic regimen. Currently, effective antibiotics include amoxicillin combined with the B-lactamase inhibitor clavulanate (Augmentin), macrolides such as azithromycin (Zithromax) and clarithromycin (Biaxin), fluoroquinolones (such as Levaquin and Avelox), and doxycycline.

Antibiotics have been shown to have a significant benefit in patients with acute exacerbations. In an analysis of results of several studies looked at together, antibiotics increased the likelihood of clinical improvement, especially in patients with a severe exacerbation.[9,10] The Global Initiative for Chronic Obstructive Lung Disease (also known as GOLD) treatment guidelines, based on results from a randomized controlled trial showing significant benefit when antibiotics were given to patients who presented with shortness of breath and an increase in sputum volume and purulence, recommend antibiotic treatment in patients with these cardinal symptoms.[8] In addition, treatment

directed to airflow obstruction with bronchodilators and corticosteroids are frequently prescribed in an effort to break the cycle of chronic inflammation and recurrent airway injury.

Bronchiolitis

Bronchiolitis, an infection of the small peripheral airways, is primarily a viral infection occurring in infants. The most common causes include respiratory syncytial virus, parainfluenza virus type 3, influenza virus, adenovirus, and rhinovirus. Clinical presentation is cough, fever, and fatigue. The chest radiograph is typically normal but a high resolution chest CT scan shows small airway inflammation without infiltrates, often referred to as a "tree-in-bud pattern." Treatment is supportive with hydration, oxygen, and possibly bronchodilators. Recently, aerosolized ribavirin has been advocated to treat respiratory syncytial virus, a common cause of bronchiolitis in the midwinter and spring. Mycoplasma pneumoniae and Legionella pneumoniae are other infectious organisms that can cause bronchiolitis. When suspected, currently effective antibiotics include macrolides and fluoroquinolones.

Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)

Bronchiolitis obliterans with organizing pneumonia (BOOP) and now also called *crytogenic organizing pneumonia* is a specific form of bronchiolitis. It can result from a viral infection, though may also be the result of inhalational injury, drug effects, or inflammation from a noninfectious systemic illness such as rheumatoid arthritis. Patients present with chronic symptoms which commonly include a persistent dry cough and shortness of breath. Lung exam reveals crackles or a "velcro" sound. Unlike bronchitis where the chest radiograph should be normal, in BOOP the chest radiograph may show segmental infiltrates. A chest CT scan shows a classic picture of inflamed peripheral airways and segmental infiltrates. Pulmonary function tests show a restrictive pattern. BOOP is not responsive to antibiotics; instead treatment centers on oral corticosteroids. If initiated early, there is often a dramatic response in the first few days of steroid treatment. Treatment duration can vary though it is usually at least six months. Relapse can occur if steroids are discontinued too soon.

Bronchiectasis

Bronchiectasis is defined as destruction and permanent dilatation (widening) of the large airways. Dilated airways make it difficult to clear secretions, and can collapse causing airflow obstruction and recurrent infections. A person may be born with it or may develop it later in life as a result of airway infection or inhalation injury. Bronchiectasis may be isolated to a small area of the lung or may be extensive. While relatively uncommon in the United States, it's prevalence increases with age.[11] Once established, recurrent respiratory infections are common.

Bronchiectasis can result from recurrent infection of the airways. Many patients demonstrate abnormal defenses against infection due to problems with their immune system. Immunodeficiency states may be present at birth (congenital) such as hypogammaglobulinemia, or are acquired, such as AIDS. Bronchiectasis can also result from an infection that does not clear due to a blocked airway, which can occur as a result of a foreign body aspiration.

In adults, this is often aspirated food or a tooth. Certain lung infections (for example, tuberculosis or fungal infections) can lead to bronchiectasis. About half the cases of bronchiectasis in the United States today are caused by Cystic Fibrosis. This is an inherited multisystem disease that results in thick mucus which is difficult to clear. While most patients are children, up to seven percent are diagnosed at age 18 years or older.[12] Other systemic diseases that can cause bronchiectasis include rheumatoid arthritis, influenza, immotile cilia syndrome, or allergic bronchopulmonary aspergillosis.

Patients often report frequent bouts of "bronchitis" before they are diagnosed. When the patient reports cough and daily production of thick sputum for months or even years, the diagnosis of bronchiectasis should be explored. About one quarter of patients report coughing up blood, usually described as streaks.[13] Lung exam may reveal crackles and wheezing. The chest x-ray is abnormal in most patients with bronchiectasis, though findings can be nonspecific. A high resolution CT scan of the chest usually is needed to make the diagnosis and shows airway dilatation, bronchial thickening (Figure 2-2.1), and cysts (Figure 2-2.2). Once the diagnosis is made, an etiology is explored. A history of recurrent sinus infections may suggest an abnormality in host defense prompting specific studies of the immune system. A sweat test can be pursued to evaluate for cystic fibrosis.

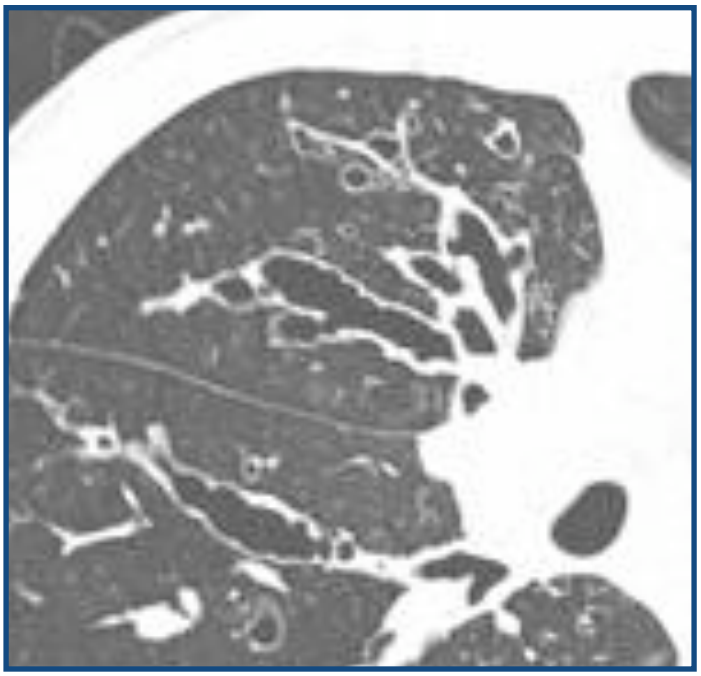

Figure 2-2.1: Bronchiectasis demonstrated by dilated, enlarged thickened airways (arrows)

During acute exacerbations of bronchiectasis, patients report an increase in sputum production over their usual amount, shortness of breath and/or wheezing. Since these clinical features are shared with COPD, patients who present during an acute exacerbation may be misdiagnosed. Further, some patients only report fatigue and lack of energy, with decreased appetite and

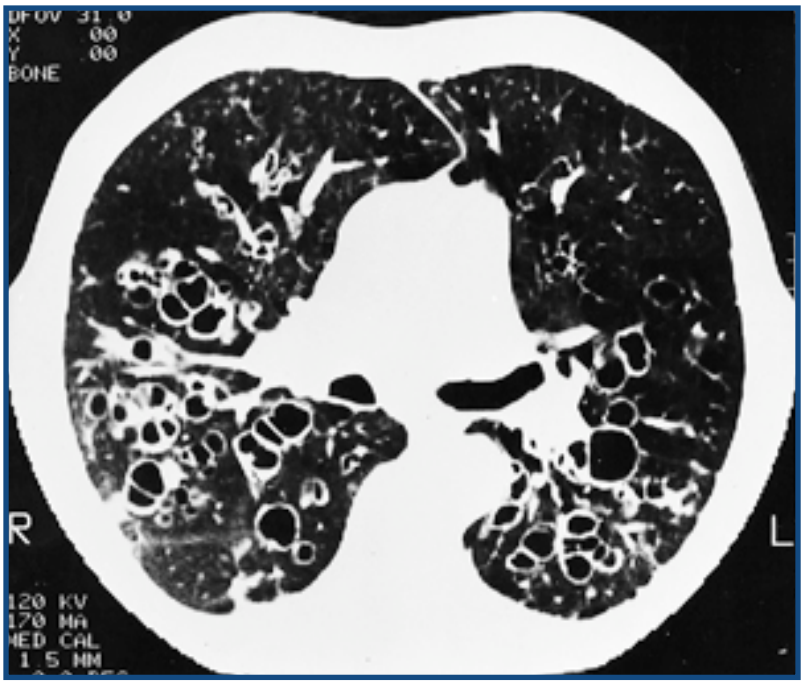

Figure 2-2.2: Cystic Bronchiectasis

weight loss, which may also lead to pursuit of an alternative diagnosis. Fever may or may not be present. During acute exacerbations, chest x-rays are often unchanged from prior evaluations. CT scans however may detect changes not appreciated on chest x-rays.

Treatment of bronchiectasis should focus on treating the underlying cause, controlling respiratory infections, managing secretions, and addressing complications. While the condition is irreversible, treatment can lessen symptoms and may be able to prevent additional damage. As noted above, patients can acquire bronchiectasis from several different pathways. When the cause is infection with airway obstruction due to an aspirated foreign body, a pulmonologist can try to retrieve the object by placing a flexible rubber tube into the airways called a bronchoscope. In those patients with recurrent infections due to low or missing immune system factors, replacement of the missing factor, when possible, leads to a significant reduction in the frequency of future infections. HIV disease (AIDS) can also lead to recurrent infections, and should be treated with appropriate anti-retroviral medications to improve the immune response. While the gene that causes cystic fibrosis has been isolated, there remains no available treatment for the primary defect.

Treating acute respiratory infections is paramount when treating bronchiectasis, since infections are not only the cause of the disease but also are the cause of disease progression. All patients should be asked to submit a sputum culture in an attempt to isolate bacteria and to determine which antibiotics would work best (reported as the sensitivity of the bacteria). Over time, resistance to some of the more common antibiotics is often demonstrated due to prior antibiotic treatments. After the most appropriate antibiotic is selected, treatment for acute exacerbations generally continues for 7 to 10 days.[14] Occasionally, an additional or longer course of antibiotics may be necessary in patients who do not adequately respond.

Antibiotic treatment is sometimes given before an acute infection arises. This approach of preventive antibiotic treatment is considered when a patient has frequent exacerbations. Treatment is usually with a regimen of oral antibiotics, though aerosolized antibiotics are also sometimes used. Side effects of aerosolized antibiotics include coughing, wheezing or shortness of breath. Despite treatment, sputum from the airways of patients with bronchiectasis can continue to grow organisms. When this occurs, the patient is said to be colonized. Patients colonized with the bacteria, Pseudomonas aeruginosa, have been shown to have impaired health-related quality of life.[15] Mycobacterium avium complex and the fungus, Aspergillus, are other colonizers that can be isolated in patients with bronchiectasis.

Managing secretions (known as bronchial hygiene) in patients with bronchiectasis is difficult, though central to management, since retained secretions can worsen this disease. Several techniques are available, such as maintaining adequate hydration and nebulizing saline. Chest physiotherapy by clapping ones hands on the patient's back and chest along with postural drainage are other techniques. Mechanical devices are also available including vests that shake your chest and handheld devices that you blow into and cause a vibration that travels back into the lungs. Each technique has the same goal: to loosen thick secretions. Bronchodilator therapy is often prescribed to manage secretions and to address airflow obstruction.

When treatment of the underlying cause plus antibiotics and bronchial hygiene does not lead to improvement, surgery can be considered if the bronchiectatic airways are mostly limited to one part of the lung. Surgery is also considered when persistent infections lead to destruction and bleeding that cannot be controlled by other measures. There are however no controlled studies to determine if surgery is more beneficial than non-surgical treatment.[16]

PNEUMONIAS

In the United States annually, community acquired pneumonia is responsible for over 50 million days of medical leave from work, over 1 million cases are hospitalized, and it is the sixth leading cause of death.[17, 18] Community-acquired infections may be viral, bacterial or rarely fungal and parasitic. Hospital-acquired or nosocomial pneumonia which have a far higher mortality rate, are usually bacterial in origin, although viral infections can also occur, particularly if hospital personnel with acute viral infections come to work and then spread their infection to patients. The risk for pneumonia is increased in patient populations due to immune suppression or underlying cardiopulmonary functional impairment. Among the elderly, the annual incidence of pneumonia is estimated to be between 180/10,000 and 440/10,000 as compared to 50/10,000 and 120/10,000 in the general population.[19, 20] In the elderly, pneumonia is the fourth leading cause of death.[21] In critically ill patients treated with mechanical ventilation, hospital acquired pneumonia develops in 10 to 70% of all patients, depending on the type of illness that led to intubation and mechanical ventilation.[22] Of even greater consequence is the fact that mortality rates are also dependent on the underlying disease. If the underlying disease responsible for respiratory failure was the adult respiratory distress syndrome (ARDS) and hospital acquired pneumonia occurs, then survival rates are less than 15% as compared to survival rates greater than 50% in ARDS

patients without hospital acquired pneumonia.[23] Other groups at increased risk for pneumonia include patients with cardiac disease, chronic obstructive lung disease, cystic fibrosis, bronchiectasis, splenic dysfunction or absence, cancer, cirrhosis (liver failure), renal failure, diabetes, sickle cell disease, any immunosuppressive therapy or disease state, alcoholism and malnutrition.[24, 25] Because these patient groups are at increased risk of infection, available vaccines to prevent respiratory infection are recommended (e.g. Influenza and Pneumococcal vaccines).

Pneumonia

Pneumonia is an infection of lung tissue involving the alveoli where gas exchange takes place. Infections that produce pneumonia often do so by causing the alveoli to fill with inflammatory cells and fluid. Everyday, bacteria are inhaled into the lower airways without causing bronchitis or pneumonia. When pulmonary infections occur, it is the result of a virulent organism, a large dose or an impaired immune system. Bacteria can reach the lung by any one of four routes: inhaling organisms in the air, aspiration from a previously colonized upper airway, spread from a bloodborne source, or spread from an adjacent, contiguous area of infection. Aspiration is the major cause for most forms of pneumonia. All of us aspirate small amounts of upper airway secretions every night, but as a percent of the population very few individuals actually develop pneumonia. This form of aspiration is distinguished from severe aspiration of large amounts of oral and gastric contents resulting from impaired consciousness (due to alcohol, drugs, seizures, shock, or neuromuscular disease) or altered respiratory tract anatomy. When aspiration involves primarily bacteria, pneumonia may occur.

When pneumonia involves an entire lobe of the lung, it is termed "lobar pneumonia," (Figure 2-2.3) and when severe, more than one lobe is involved.

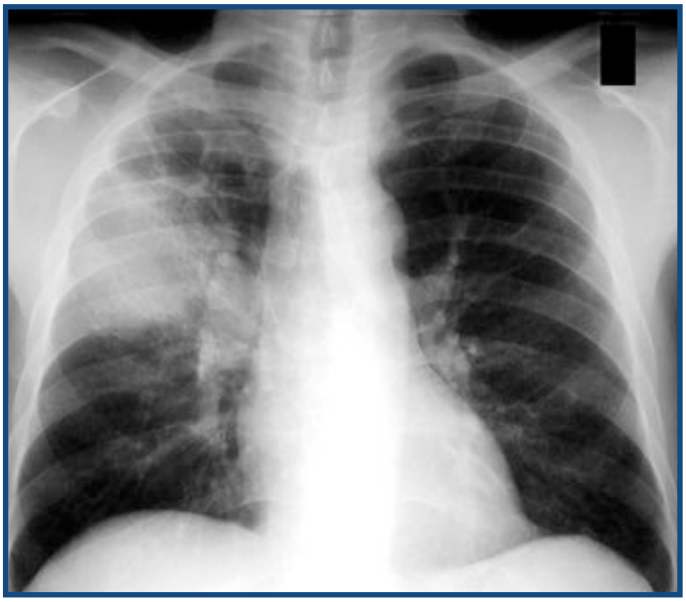

Figure 2-2.3: Chest radiograph showing community acquired pneumonia involving the right upper lobe.

Pneumonia can also occur as patchy infiltrates adjacent to bronchial airways and is then termed "bronchopneumonia." Pneumonias can be classified according to their clinical presentation as either "typical" or "atypical." Typical pneumonias are characterized by sudden onset of fever, chills, productive cough and pleuritic stabbing-like chest pain. Bacterial infections are the usual cause of typical pneumonias and common ones include: Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, aerobic Gram-negative bacteria, and anaerobes.[24, 25] Atypical pneumonia is characterized by fever without chills, nonproductive cough, headache, and body aches. Atypical pneumonias are most commonly due to viruses, Mycoplasma pneumoniae and Legionella pneumoniae .[24, 25] Despite this classification into typical and atypical pneumonia being useful clinically, it is often difficult to predict the specific infection that is actually causing the pneumonia and most guidelines do not rely solely on this classification for antibiotic recommendations.[26, 27] Organisms that cause pneumonia may produce clinical presentations that overlap both typical and atypical syndromes. Pneumonia also commonly occurs in patients who have coexisting illnesses which alter the clinical presentation. For example, if a patient has an impaired immune response (such as the elderly, alcoholics, diabetics, or patients with AIDS), typical pneumonia symptoms may be absent.

Mortality and Severity Assessment

Mortality rates from pneumonia, regardless of the organism responsible, are always highest in patients with coexisting serious illnesses such as cardiopulmonary diseases, cirrhosis (liver failure), renal failure, malignancy, diabetes, and in patients with immune deficiencies (regardless of cause). The mortality rate for severe pneumonia exceeds 25%.[28] Criteria for severe pneumonia include a respiratory rate above 30 breaths per minute; severe hypoxemia (low oxygenation), multilobar involvement, respiratory failure requiring mechanical ventilation, shock, acute renal failure, bacteremia (organisms in the blood) and/or extra-pulmonary spread of infection. Severity assessment scores have been developed to improve early identification and hopefully decrease mortality rates in these patients. The Pneumonia Severity Index (PSI) assesses points for each of several factors including:[28] age; coexisting illness (cancer, liver disease, cerebrovascular disease and kidney disease); physical exam findings (altered mental status, respiratory rate ≥30 breaths/min, heart rate ≥125 beats/min, systolic hypotension, high or low temperature); and laboratory findings (acidosis, renal failure, hyponatremia, hyperglycemia, anemia, hypoxia, pleural fluid). The more points, the greater risk of death within the first 30 days.

The organism responsible for causing a patient's pneumonia can be predicted by the status of the patient's underlying immune system and other coexisting diseases, as well as their place of residence - the community or a hospital/chronic care facility.[26, 27] In the community, viruses may account for up to one-third of all pneumonias. The most common bacterial organism responsible for community-acquired infection in all types of patients is Streptococcus or Pneumococcal pneumoniae. Other common organisms include Mycoplasma pneumoniae, Chlamydia pneumoniae, Hemophilus Influenzae, Legionella pneumonia and in certain patients with specific coexisting diseases Staphylococcus Aureus, Gram negative bacteria (Klebsiella pneumonia and Pseudomonas pneumonia),

and Pneumocystis carinii. Unusual organisms should be suspected if the patient has a recent travel or exposure history – tularemia (in hunters), plague (from exposure to small animals in the mid-western US), anthrax (in wool sorters and tanners), Cryptococcus (from pigeon droppings), Histoplasmosis (from river valleys or bat droppings), Coccidioidomycosis (in the southwestern United States), psittacosis (from infected birds), or parasitic infestation (from travel to the tropics).

Common Organisms Responsible for Community-Acquired Pneumonias

Streptococcus or *Pneumococcal pneumonia* is a Gram-positive, lancet-shaped diplococcus and is the most common cause of community acquired pneumonia in all populations, regardless of age or coexisting disease. Eight-five percent of all pneumococcal pneumonias are caused by any one of 23 serotypes. The pneumococcal vaccine (Pneumovax) provides protection against all 23 serotypes. Infection is the most common in the winter and early spring, and therefore it is not surprising that many patients report have a preceding viral illness. Spread is from person-to-person and pneumonia develops when colonizing organisms are aspirated at a high enough dose to cause infection. Patients with an intact immune response present with the "typical" pneumonia syndrome of abrupt onset of a febrile illness, appearing ill or "toxic" with a cough productive of rusty colored sputum and complaining of pleuritic stabbing chest pain. Chest radiographs can show a lobar or bronchopneumonia pattern. Physical examination of the chest may show evidence for consolidation with absent breath sounds. Bacteremia (organisms in the blood) can occur in 15 to 25% of all patients and mortality rates are substantially higher in such cases. While penicillin or erythromycin can be prescribed, current treatment for outpatients with community-acquired pneumonia usually includes macrolides such as azithromycin (Zithromax) and clarithromycin (Biaxin), based on an easier to comply with dosing interval and less gastrointestinal side effects. Also used are oral beta-lactams such as cefuroxime, amoxicillin, or amoxicillin-clavulanate. Fluoroquinolones with activity against Streptococcus pneumonia (such as Levaquin and Avelox) can be substituted when needed though some recommend against the use of this class of antibiotics as first-line therapy due to risk of developing resistance.

Unfortunately, the incidence of penicillin resistant pneumococci is rising. Ten percent of strains in the United States are intermediately resistant to penicillin but can still be treated with high dose penicillin, while one percent are highly resistant and require treatment with Vancomycin. With effective therapy, clinical improvement occurs in 24 to 48 hours. As is often the case in any type of pneumonia, radiographic improvement lags behind the clinical response and may take months to clear and become normal.

Legionella pneumonia is a Gram-negative bacillus first characterized after it led to a pneumonia epidemic in Philadelphia in 1976. Retrospective analysis of stored specimens has shown that Legionella pneumonia has caused human disease since at least 1965. At least 12 different serogroups have been described, with serogroup 1 causing most cases. The organism is water borne and can emanate from air conditioning equipment, drinking water, lakes and river banks, water faucets, hot tubs and shower heads. Infection is caused by

inhalation of an infected aerosol generated by a contaminated water source. When a water system becomes infected in an institution, endemic outbreaks may occur, as has been the case in some hospitals. Legionella infection can also cause sporadic cases. Person-to-person spread has not been documented, nor has infection via aspiration from a colonized oropharynx, although it may be possible that the infection can develop after subclinical aspiration of contaminated water. The incubation period is 2 to 10 days. Patients with *Legionella pneumonia* commonly present with high fever, chills, headache, body aches and elevated white blood cell counts. Features that can suggest the diagnosis specifically are the presence of pneumonia with preceding diarrhea, along with mental confusion, relatively slow heart rates, low blood sodium levels, and liver function abnormalities. The patient may have a dry or productive cough, pleuritic stabbing chest pain, and shortness of breath. The chest radiograph is not specific and may show bronchopneumonia, unilateral or bilateral disease, lobar consolidation, or rounded densities with cavitation. Symptoms are rapidly progressive, and the patient may appear to be quite ill or "toxic". Legionella pneumonia is a major cause of severe community acquired pneumonia. Some patients may develop renal failure and this combination of respiratory failure and renal failure has a high mortality rate. Currently, effective therapy is with macrolides and flouroquinolones.

Haemophilus influenza is a Gram-negative coccobacillary rod that occurs in either a typable, encapsulated form or a nontypable, unencapsulated form. Because pneumonia from Haemophilus influenzae occurs commonly in patients with impaired immune defenses, most patients will have an underlying illness, such as COPD, an immune deficiency, or alcoholism. Patients present with a sudden onset of fever, sore throat, cough and pleuritic stabbing chest pain. Children frequently have earaches. Complications include empyema (infected pleural space between the lungs and chest wall), lung abscess, meningitis, arthritis, and pericarditis. Adult mortality rates are high and mostly reflect the impact of the coexisting illness. Currently, effective therapy for H. influenzae infection, due to rising resistance, is either a combination of amoxicillin and clavulanic acid, third-generation cephalosporins, trimethoprim/sulfamethoxazole, macrolides or the fluoroquinolones. Many isolates are also resistant to ampicillin and erythromycin, therefore these antibiotics should not be used.

Mycoplasma pneumoniae commonly causes minor upper respiratory tract illnesses or bronchitis. Although pneumonia occurs in 10% or less of all Mycoplasma infections, this organism is still a common cause of pneumonia. In the general population, it may account for 20% of all pneumonia cases, and up to 50% in certain populations, such as college students. The disease occurs year-round, with slight increase in the fall and winter. All age groups are affected, but disease is more common in those under 20 years of age. The incubation period is anywhere from two to three weeks and when pneumonia occurs, the usual presentation is in the form of an atypical pneumonia. Patients commonly have a dry cough, fever, chills, headache, and fatigue. Up to half will have upper respiratory tract symptoms including sore throat and earache. Chest radiographs show interstitial infiltrates, which are usually unilateral and in the lower lobe, but can be bilateral and multilobar. The patient usually does not appear as ill as suggested by the radiographic picture. Most cases resolve in 7 to 10 days,

but rarely patients will have a severe illness with respiratory failure. When severe, infection is often characterized by its extrapulmonary manifestations including meningoencephalitis, meningitis, autoimmune hemolytic anemia, myocarditis, pericarditis, hepatitis, gastroenteritis, arthralgias, pancreatitis, and renal insufficiency. Currently, effective antibiotics include macrolides, doxycyline, and the fluoroquinolones.

Chlamydia pneumonia is a relatively common cause of pneumonia in teenagers and adults. Patients present with fever, chills, sore throats, hoarse voices, pleuritic chest pain, headache, and cough and only rarely progress to respiratory failure. Currently, effective treatment is doxycycline, macrolides and the fluoroquinolones. Duration of treatment is usually two to three weeks.

Staphylococcus aureus can cause community acquired pneumonia in normal patients recovering from influenza, in patients addicted to intravenous drug use, and in the elderly. Patients present with sudden onset of fever, shortness of breath, and cough productive of purulent sputum. The radiograph may show infiltrates, cavities, and/or lung abscess. An infected pleural effusion (fluid in the space between the lung and chest wall), called an empyema may also occur. Currently, effective treatment is with an anti-staphylococcal penicillin (methicillin) or if methicillin resistant (referred to as MRSA), then vancomycin. Strains resistant to methicillin have become increasingly common. Extrapulmonary complications include endocarditis (heart infection) and meningitis (brain infection).

Viruses may account for at least 20% of all community-acquired pneumonias. Viruses are spread by aerosol or by person-to-person contact through infected secretions. The common agents causing lower respiratory infection include adenovirus, influenza virus, herpes group viruses (which include cytomegalovirus), parainfluenza virus, and respiratory syncytial virus. Many patients with viral pneumonia have a mild “atypical” pneumonia with dry cough, fever, and a radiograph "looks worse than the patient." When bacterial superinfection is present, the illness is biphasic, with initial improvement from the primary viral infection followed by sudden increase in fever along with purulent sputum and lobar consolidation. Rash occurs with varicella-zoster, measles, cytomegalovirus, and enterovirus infections. Sore throat accompanies infection by adenovirus, influenza and enterovirus. Liver inflammation (hepatitis) is often present with infectious mononucleosis (Epstein-Barr virus) and cytomegalovirus. Viral pneumonia is an entirely different entity if the patient is immunocompromised. Patients with AIDS, malignancy, or major organ transplantation can develop severe viral pneumonia that progresses to respiratory failure requiring mechanical ventilation. Viruses that cause severe pneumonia in the immunosuppressed patient include cytomegalovirus, varicella-zoster, and herpes simplex virus. Patients with cytomegalovirus infection have been successfully treated with gancyclovir. Pneumonia from herpes simplex and varicella-zoster can be treated with acyclovir.

Klebsiella pneumoniae is a Gram-negative rod from the gut. Mortality rates may be as high as 50% because it generally affects patients with impaired immune systems, debilitated individuals with coexisting conditions such as patients with alcoholism, diabetes, cardiopulmonary diseases, renal failure, or cancer, or the elderly living in nursing homes. The onset is sudden with productive cough, pleuritic stabbing chest pain, shaking chills and fevers. Patients look

ill or “toxic". The chest radiograph shows dense consolidated infiltrates in the upper lobe with a fissure bulging downward. Lung abscess may result. Other complications include pericarditis, meningitis, and empyema. Diagnosis is suspected by finding Gram-negative rods in the sputum in a patient with a compatible illness and risk factors. Currently, effective antibiotics include third-generation cephalosporins, aminoglycosides, antipseudomonal penicillin, aztreonam, imipenem, or fluoroquinolones.

Pneumocystis carinii pneumonia (PCP) is common in immunosuppressed patients with AIDS HIV infection. The organism can easily be recognized by microscopic examination of induced sputum, bronchoalveolar lavage fluid from the lung, or lung biopsy. Most patients probably acquired Pneumocystis carinii from natural sources prior to the onset of AIDS and contained it within the lung. Once AIDS develops, the patient’s immune system no longer functions optimally and latent infection with Pneumocystis carinii may become reactivated. Alternatively, a new infection or even re-infection may occur. Like most patients with pneumonia, the clinical presentation includes fever, cough, shortness of breath and fatigue. However, with PCP the fevers are prolonged; the cough is dry; night sweats may occur; and weight loss can be severe. The chest radiograph usually shows bilateral diffuse infiltrates that are mostly in the lower lobes (Figure 2-2.4), although asymmetric focal infiltrates, nodules or even cysts (mini-cavities) may occasionally be seen.

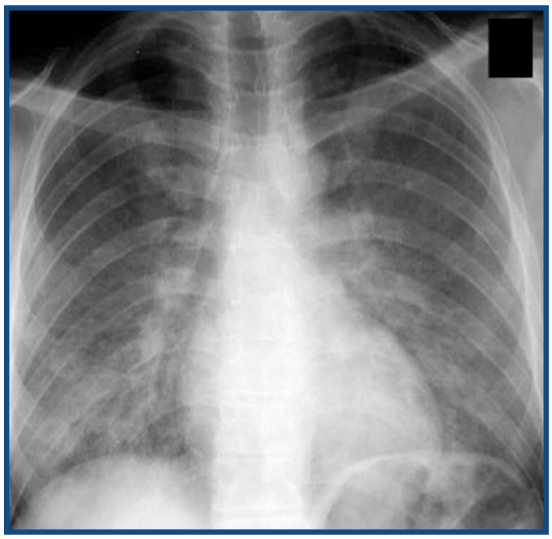

Figure 2-2.4: Chest radiograph showing Pneumocystis carinii pneumonia in an AIDS patient. Note that the bilateral lower lobe involvement

For many patients with *Pneumocystis carinii,* it is there first sign of AIDS. Therefore, all patients with this clinical presentation should be questioned for AIDS risk factors and Pneumocystis carinii should be considered. Findings that suggest the diagnosis are a compatible chest radiograph, low rather than elevated white blood cell counts, elevated lactate dehydrogenase (LDH) levels in the blood, fungal infection in the rear of the throat (oral candidiasis or thrush), and hypoxemia (low oxygenation) occurring with exertion that is out of proportion to that suggested by the chest radiograph. Pneumocystis carinii can also occur in immunocompromised patients without AIDS, such as lymphoma or after long-term oral corticosteroid treatment. With appropriate therapy over 90% survival rates are expected, especially if the clinical manifestations are not severe and it is the first episode of Pneumocystis carinii pneumonia. Treatment

is with trimethoprim-sulfamethoxazole (Bactrim) but for those who cannot tolerate this antibiotic, pentamidine or trimethoprim/dapsone may be used. The addition of oral corticosteroids to the therapeutic regimen has been shown to be highly effective in improving survival rates for those with hypoxemia. After recovery from pneumonia, patients should receive chemoprophylaxis against recurrent infection and antiviral therapy if HIV positive.

Hospital-Acquired Pneumonia

Hospital-Acquired Pneumonia or nosocomial pneumonia is different from community acquired pneumonias not only because the organisms responsible differ but more importantly because the patients differ, suffering from coexistent diseases and immunosuppression far worse than that encountered in the community.[24, 25, 26, 27, 28] Gram-negative organisms (particularly Pseudomonas aeruginosa) are the predominant cause of hospital acquired pneumonia. However, organisms responsible for community acquired pneumonia still occur in the hospitalized environment. Four major risk factors for hospital acquired pneumonia exist – (1) acute illness (such as ARDS, sepsis, shock, abdominal surgery/infection); (2) coexisting chronic illnesses such as cardiopulmonary diseases, diabetes, cancer, renal failure, liver failure, immunosuppression and other systemic illnesses; (3) therapeutic interventions; and (4) impaired nutritional status. All are associated with increased mortality rates.

OTHER LUNG INFECTIONS

Lung Abscess

Lung abscess is a necrotizing infection generally caused by aspiration of anaerobic bacteria occurring either in the community or the hospital. The radiograph will show single or multiple cavities each at least 2 cm in diameter.[24, 25] The cavity may contain an air-fluid level (Figure 2-2.5) and may be associated with or preceded by pneumonia. Patients present with low-grade fever, weight loss, and cough with foul-smelling sputum. The risk factors and microbiology of lung abscess are similar to those of community acquired pneumonia; lung abscess is usually a complication of aspiration.

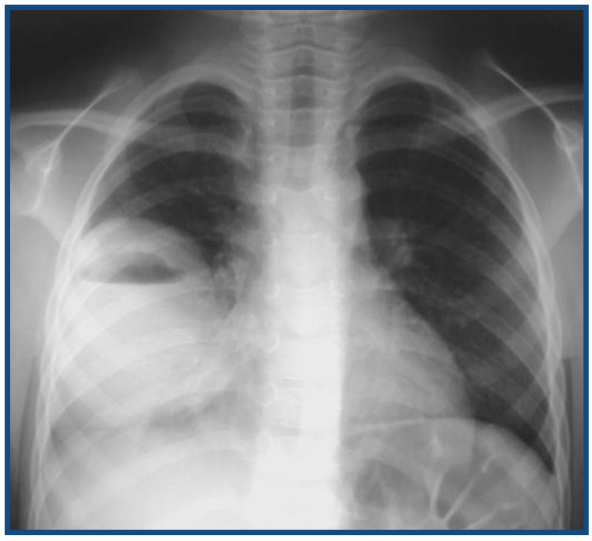

Figure 2-2.5: Chest radiograph showing right lower lobe lung abcess – a large cavity with air-fluid level.

Currently, effective treatment is with penicillin or clindamycin.[29] Patients may improve within a week of antibiotics but it may take several months for the cavity to close and the chest radiograph to clear. Antibiotic therapy should be continued until the chest radiograph clears. When lung abscess arise unrelated to aspiration, poor dentition or airway obstruction (lung cancer or a foreign body) should be suspected. Additionally, certain organisms should be considered such as tuberculosis, fungi, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Streptococci pneumonia. Complications of lung abscess include empyema (infection in the pleural space between the lung and chest wall), broncho-pleural fistula, and brain abscess.

Pleural Effusions and Empyema

Approximately 40% to 60% of bacterial pneumonias will have evidence on chest radiograph of pleural effusion (fluid between the lung and chest wall). Most commonly, this is an inflammatory reaction consisting of fluid but no bacteria or organisms within the pleural space/fluid. Characteristics of this fluid have been shown to be excellent predictors of clinical outcomes.[30, 31] If the fluid is high in protein content, acidotic or low in glucose content, then drainage is recommended. If not, then merely treating the associated pneumonia with antibiotics is usually sufficient. Empyema is a term reserved for fluid in the pleural space that is not just an inflammatory reaction to the pneumonia but is an actual infection with organisms in the space/fluid (Figure 2-2.6). Empyema is rare occurring in only one to two percent of hospitalized patients with community-acquired pneumonia.[30, 31, 32, 33] It is most often caused by Streptococci pneumonia, Staphylococcus aureus, and anaerobic infections.[32, 33] Empyema requires extensive drainage of the fluid and antibiotics. Antibiotics should be based on culture results from the pleural fluid.

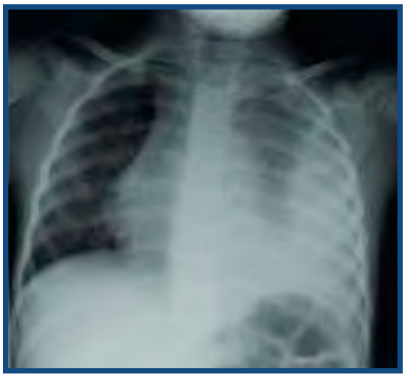

Figure 2-2.6: Chest radiograph showing left-sided pneumonia and pleural effusion which upon sampling was filled with bacteria indicating an empyema.

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Chapter 2-3
Tuberculosis: A Primer for First Responders

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INTRODUCTION

Tuberculosis (TB) is an airborne and potentially life-threatening infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex, a grouping of closely related species of mycobacteria (including *M. tuberculosis (M. tb)*, *M. bovis*, and *M. africanum*). These mycobacteria are sometimes referred to as tuberculous mycobacteria. Other mycobacteria are called nontuberculous mycobacteria because they do not cause TB, one common type being *Mycobacterium avium* complex. While nontuberculous mycobacteria can also cause disease, it is not transmitted by person to person contact.

TB disease is contracted when a person inhales air that contains the TB bacteria produced from a person who has the disease, either by coughing, talking, sneezing or singing. The disease mainly affects the lungs, but it can also affect other parts of the body such as the brain, kidneys, or the spine. A person with the pulmonary type of TB disease may manifest signs and symptoms such as prolonged cough, chest pains, weight loss or fatigue and is capable of transmitting the bacteria to other people. TB disease that affects other parts of the body can have various signs and symptoms depending on the site and is rarely infectious unless it also affects the lungs. An untreated person with TB can die from the disease; however, it is nearly 100% curable with an appropriate medical regimen.

In contrast, latent TB infection (LTBI) is the presence of *M. tb* organisms in the body, but the body's immune system is keeping the bacteria from reproducing. Most people with LTBI have a positive test for TB infection (TTBI), either a tuberculin skin test or blood test. However, those who have LTBI cannot transmit the disease to others. These people are asymptomatic and usually have a normal chest x-ray. See Table 2-3.1 for a comparison of the two conditions.

This chapter discusses TB disease and LTBI including epidemiology, pathogenesis, diagnosis and treatment of these two conditions.

A Person with Active TB Disease	A Person with LTBI
Has active TB bacteria in his/her body	Has TB bacteria in his/her body that are alive, but inactive
Usually has a skin test or blood test result indicating TB infection	Usually has a skin test or blood test result indicating TB infection
Usually has an abnormal chest x-ray, and positive sputum smear or culture	Usually has a normal chest x-ray and has negative sputum tests
Usually feels sick and may have symptoms such as coughing, fever, and weight loss	Does not feel sick
May spread TB bacteria to others	Cannot spread TB bacteria to others
Needs treatment with appropriate antibiotics against active TB disease	Needs treatment with appropriate antibiotics for latent TB infection to prevent TB disease

Table 2-3.1. The Difference Between Latent TB Infection and Active TB Disease (Adapted from CDC (2007) TB Elimination: The difference between latent TB infection and active TB disease. Retrieved from http://www.cdc.gov/tb/pubs/tbfactsheets/LTBIandActiveTB.htm

EPIDEMIOLOGY OF TB

TB disease is one of the leading infectious causes of death worldwide, yet it is preventable and, in most cases, curable. Each year, about nine million people develop TB disease and two million people die worldwide. In fact, among those older than five years of age, TB disease is one of the leading causes of death due to infectious disease in the world.

Within the United States (US), physicians and other health care providers are required by law to report TB cases to their state or local health department. Each year the 50 states, the District of Columbia, New York City, Puerto Rico, and seven other jurisdictions in the Pacific and Caribbean report TB cases to the Centers for Disease Control and Prevention, who in turn compiles the data and provides an annual summary of TB cases in the United States.

In 1953, when nationwide TB reporting first began, there were more than 84,000 TB cases in the US (the 50 states and District of Columbia). From 1953 through 1984, the number of TB cases decreased by an average of 6% each year. In 1985, the number of cases reached a low of 22,201. Between 1985 and 1992 there was a resurgence of TB, with the number of new cases increasing from 22,201 in 1985 to 26,673 in 1992, an increase of about 20% (Figure 2-3.1). The resurgence in TB cases between 1985 and 1992 was attributed to at least these five factors:

- Inadequate funding for TB control and other public health efforts.
- The HIV epidemic.
- Increased immigration from countries where TB is common.
- The spread of TB in congregate settings.
- Development and transmission of multidrug-resistant TB (MDRTB) strains which are more difficult to treat.

In 1993, the upward trend of new TB cases reversed. From 1993 through 2006, the number of TB cases reported annually in the US steadily declined. (Figure 2-3.1) In 2006, there were a total of 13,779 new TB cases resulting in the lowest number of reported cases since national reporting began in 1953.

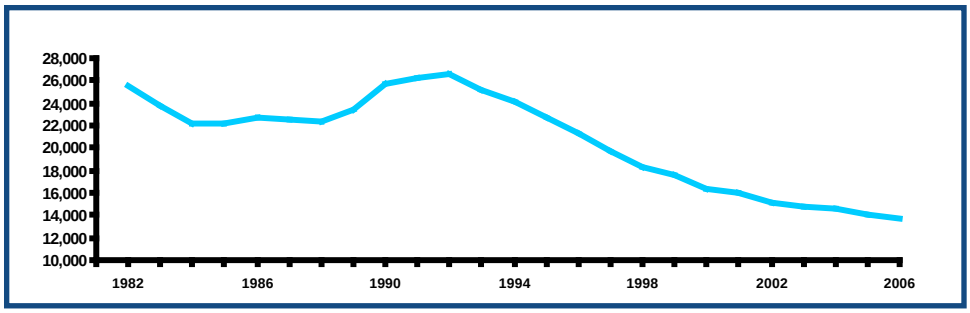

Figure 2-3.1 TB Cases Reported in US (Reported TB in the United States, 2006. Atlanta, GA: U.S. Department of Health and Human Services, CDC, September 2007)

The continued decline in reported TB cases since 1993 may be attributed to the increase in resources used to strengthen TB control efforts. The increase in federal, state, and other funds and resources allowed TB programs to improve efforts in TB control by promptly identifying persons with TB, initiating appropriate treatment for TB cases and ensuring completion of treatment.

Despite this national trend reflecting a steady decline in the number of TB cases reported annually, there are still several areas of ongoing concern:

- TB cases continue to be reported in every state and have actually increased in some areas.
- More than half of all TB cases in the US are among non-US born residents.
- Due to socioeconomic reasons, TB continues to affect minorities disproportionately (Hispanics, non-Hispanic blacks or African Americans, and Asians have higher TB rates than non-Hispanic whites).
- Multidrug resistant TB (MDRTB) and extensively drug resistant TB (XDR TB) remain a serious public health concern. Patients who do not complete therapy or take their therapy inappropriately can develop and spread strains of TB that are resistant to available drugs.

PATHOGENESIS, TRANSMISSION, INFECTION AND PROLIFERATION

TB primarily affects the lungs, although it can also affect other parts of the body such as the brain, the kidneys, or the spine. Transmission of TB occurs when an infectious patient expels small droplets containing TB bacteria into the air when he/she coughs, sings or speaks and a susceptible person inhales the bacteria and becomes infected. (Figure 2-3.2) These tiny droplets float in air, the fluid evaporates and the living bacteria may remain airborne for several hours until inhaled.

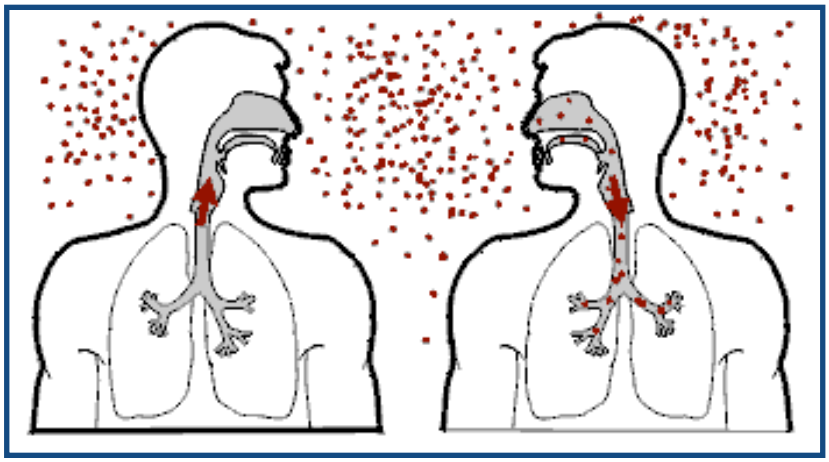

Figure 2-3.2: TB is spread from person to person through the air. The dots in the air represent droplets containing TB bacteria. (Source: CDC. Core Curriculum on Tuberculosis. By CDC. 2000. 18 August 2008. http://www.cdc.gov/nchstp/tb/pubs/corecurr/default.htm

The factors that determine the likelihood of transmission of M. tb are:

- The number of bacteria being expelled into the air.
- The concentration of bacteria in the air determined by the volume of the space and its ventilation.
- The length of time an exposed person breathes the contaminated air.

Approximately 10% of individuals latently infected with TB who are not given therapy will develop active TB. The risk in developing TB disease is highest in the first two years after infection. Patients with certain medical conditions have an increased risk of developing TB disease. When the immune system is weakened, the body may not be able to control the multiplication and spread of TB bacteria. Patients who are HIV infected are thought to be more likely to become infected with *M. tb* after exposure than persons without HIV. Also people infected with *M. tb* and HIV are more likely to develop TB disease than people who are infected with *M. tb* alone. However, they are no more likely to transmit *M. tb* to other persons. The risk of developing TB disease is 7% to 10% each year for people who are infected with both *M. tb* and HIV, particularly for those who are not taking antiretroviral therapy, whereas it is 10% over a lifetime for people infected only with *M. tb*. For people with LTBI and diabetes, the risk is three times as high, or about 30% over a lifetime. Figure 2-3.3 illustrates the risks to disease progression.

Host Immune Response

Within 2-12 weeks after exposure and subsequent infection with *M. tb*, the body mounts an immune response to limit further replication of the TB bacteria. This cellular immune response is the basis for the tests for TB infection currently used for testing: the tuberculin skin test (TST) and the blood test (QuantiFERON®-Gold). Some bacteria remain quiescent in the body and are viable for many years.

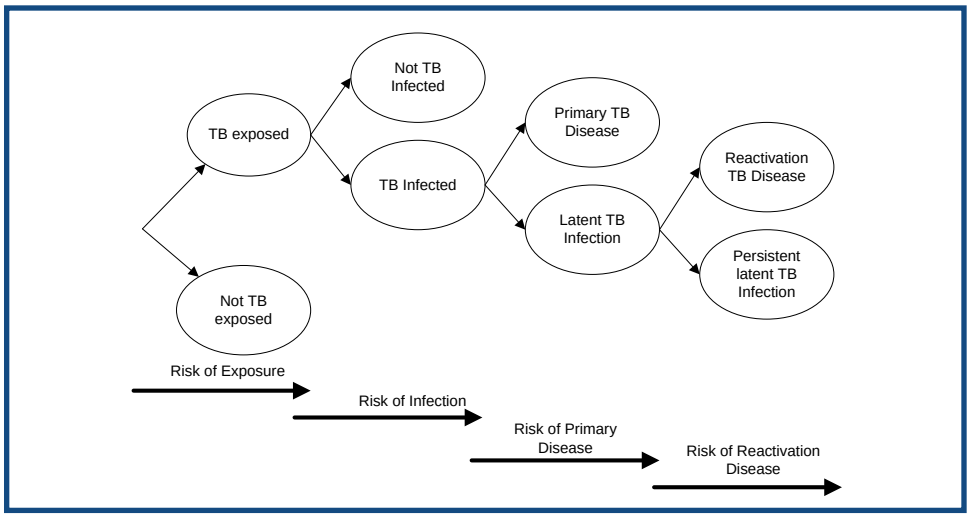

Figure 2-3.3: Time course of events from exposure to disease and definition of transition risks (Adapted from Horsburgh CR, Moore M, Castro K. (2005). Epidemiology of TB in the United States; TB (second edition). Edited by William N. Rom and Stuart M. Gray. Philadelphia: Lippincott, Williams & Wilkins.)

In the body, a characteristic pathologic lesion typical of TB infection called a granuloma is formed, which is a spherical collection of inflammatory cells with a small area of central cheeselike (caseous) necrosis. In up to 90% of the individuals who become infected with the TB bacteria, these small granulomas remain localized and quiescent, and may become calcified. The primary immunologic response that follows infection is generally inapparent both clinically and radiographically.

Progression From Infection To Active Disease

Not everyone who is infected with TB develops TB disease. The risk of progression to active TB is determined by certain risk factors which will be discussed later in the chapter. There are two terms to describe a patient who progresses from TB infection to active TB disease: primary TB and reactivation TB. Primary TB is rapidly progressive without a period of latency in the weeks to months following initial infection. It occurs most commonly in infants with immature immune systems, elderly people with waning immunity and HIV-infected persons. The site of disease reflects the path of infection, appearing as enlarged hilar or mediastinal lymph nodes and lower or middle lung field infiltrates on chest x-ray. Reactivation TB occurs after a period of latency (usually within two years), but sometimes decades after primary infection. When this occurs, the site of disease is most commonly the apices of the lungs, but may also include other sites seeded during the primary infection.

If the infection is not kept contained, the bacteria will multiply, provoking the release of inflammatory agents which lead to more inflammation, tissue destruction and disease progression. Ultimately, this inflammation may cause the formation of a tuberculous cavity in the lung. From this cavity, the disease may progress to other parts of the lung.

Clinical Aspects of TB Disease

Progressive primary or reactivation pulmonary TB often presents with a gradual onset of non-specific symptoms that may be tolerated by the patient. The duration of symptoms before presentation may vary widely, from days to months. Presenting features may initially be related to the respiratory system and/or present as constitutional symptoms of cough, chest pain and dyspnea. Cough typically lasts at least two to three weeks, but can persist longer (months) and is usually productive of mucoid, muco-purulent or blood tinged sputum. Massive hemoptysis (coughing of blood) can also be a presenting feature. Fever with sweats (mostly at night) and chills are common. Other nonspecific symptoms include weakness, anorexia (loss of appetite), and unintended weight loss. TB disease involving other organs of the body is termed extrapulmonary TB, and the related symptoms depend on the affected organ.

Evaluation of Persons with Suspected Active TB Disease

When a person is suspected of having TB, he/she should have a medical evaluation including a history, physical examination, a TTBI (either a TST or a blood test), chest x-ray or other diagnostic imaging, and specimens for acid fast bacilli (AFB) smear microscopy and cultures depending on site of disease.

When evaluating a patient's medical history, clinicians should ask about the patient's history of TB exposure, infection, or prior TB disease. It is also important to consider demographic factors that may increase the patient's risk for exposure to TB (e.g., immigration from countries with high rates of TB, homelessness, incarceration or health care work). Also, clinicians should determine whether the patient has other medical conditions, especially HIV infection, that can increase the risk of LTBI progressing to TB disease.

Chest radiographic features of pulmonary TB are not characteristic and can simulate other diseases. These include upper lobe infiltrates or consolidation, cavitations (which may occur in approximately 40% cases), bilateral infiltrates or infiltrates with pleural effusions, and scarring, fibronodular or calcific changes. A normal chest x-ray does not exclude pulmonary TB and has been reported in approximately 10% of immunocompetent and 20% of immunocompromised patients.

Computed tomography (CT) of the chest can be used as an adjunct to identify lesions suggestive of TB such as cavitation, mediastinal and paratracheal lymphadenopathy, endobronchial TB, and dissemination to the lung parenchyma (miliary TB).

Diagnostic Microbiology

The gold standard for diagnosing TB is by culturing a specimen from an appropriate disease site. For pulmonary TB, a respiratory specimen such as sputum is generally collected. There are two advantages in collecting samples for culture: 1) It is more sensitive because it allows differentiation of mycobacteria that are part of the *M. tb* complex from those that are nontuberculosis mycobacteria and 2) it allows for drug susceptibility testing to determine if the bacteria is resistant to any of the anti-TB drugs. However, since TB is a slow growing bacterium, results with this method can take up to eight weeks to obtain.

In general, the AFB smear test is the first test to diagnose TB in the specimen. This test evaluates the number of bacteria in the specimen by looking under the microscope. The number of bacteria seen under the microscope generally correlates with the infectiousness of the patient. However, absence of the bacteria from any specimen does not rule out disease. Although the AFB smear suggests presence of the TB bacteria, a culture is still needed to confirm that the AFB are *M. tb*. Culture examinations should be completed on all specimens regardless of AFB smear results.

Another detection method is the use of nucleic acid amplification (NAA) techniques. NAA tests identify genetic material unique to *M. tb* complex directly in pre-processed clinical samples. The test is used to detect *M. tb* in respiratory specimens from previously untreated patients with a high clinical suspicion for TB, and since the test does not require growth of the TB bacteria, results can be available in a few days. A positive NAA in an AFB smear positive respiratory specimen is highly suggestive of TB disease, but the diagnosis should still be confirmed by culture so drug-susceptibility testing can be performed. A negative NAA result is suggestive of nontuberculous mycobacteria, but it does not rule out the diagnosis of TB in a smear negative or positive respiratory specimen. The diagnosis would also depend on the overall clinical picture, clinical judgment and the culture results. Since NAA tests can detect nucleic acid from dead as well as live organisms, a positive result from dead bacteria can remain for long periods of time even after the patient has been on appropriate treatment or after completing treatment. Therefore, this method is used only for initial diagnosis of untreated TB patients.

Treatment of Patients with Active TB Disease

All individuals with highly suspected TB should begin treatment as soon as appropriate specimens are collected. Treatment should not be delayed while waiting for confirmation by culture or susceptibility results. Most patients with drug susceptible TB (TB that can be treated with the first-line TB treatment drugs) can be treated with a standard six-month drug regimen. Treatment is divided into two phases: the intensive phase and the continuation phase. Since susceptibility results are not available at the beginning of therapy, patients are started on a standard four-drug regimen of isoniazid (INH), rifampin, pyrazinamide and ethambutol. Regimens should be adjusted as soon as susceptibility results become available. The length of the continuation phase depends on the therapy prescribed and the susceptibility results. Treatment of TB resistant to one or more drugs is more complex, and should be managed by a physician that is experienced in the treatment of TB. Current recommendations for treatment of TB in adults who are HIV infected are, with few exceptions, the same as for the rest of the population.

Directly observed therapy (DOT), the standard of care in TB treatment, is the best way to ensure that patients complete an adequate course of treatment for TB. DOT means that a health care worker, or another responsible individual, directly observes and supervises every dose of anti-TB medication taken by the patient. DOT regimens may be daily, or prescribed in higher doses to be taken two or three times a week. When TB treatment is complicated by interactions between drugs used for TB and those used for HIV infection, there is a paramount need for close medical evaluation and supervision to assure the continuity of TB therapy.

Drug-Resistant TB

Drug-resistant TB is caused by *M. tb* organisms that are resistant to at least one of the first-line TB treatment drugs (INH, rifampin, pyrazinamide, and ethambutol). Drug-resistant TB can be transmitted in the same way as drug-susceptible TB. However, drug-resistant TB can be more difficult to treat because it can survive in a patient's body even after treatment with the first-line drugs is started. Furthermore, if patients are not properly diagnosed with drug-resistant TB and are given an inadequate treatment regimen, they may be infectious for a longer period of time and develop additional drug resistance.

A patient is diagnosed with multidrug-resistant TB (MDRTB) if the TB bacteria are resistant to at least INH and rifampin. A patient is diagnosed with extensively drug-resistant TB (XDRTB) if the TB bacteria are resistant to INH and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (such as amikacin, kanamycin, or capreomycin).

Drug-resistant TB can manifest in two different ways: primary and secondary (acquired). Primary resistance is caused by person-to-person transmission of drug-resistant organisms. Secondary resistance develops during TB treatment, either because the patient was not treated with the appropriate treatment regimen or because the patient did not follow the treatment regimen as prescribed. Treatment of drug resistant TB can be more complicated and may take longer to treat, and can involve second line medications which may be more difficult for the patient to tolerate. Patients should be managed by a physician, expert in treating drug resistant TB. Drug-resistant TB patients should also be closely monitored to see if they are responding to treatment and should be on daily or twice daily DOT, to monitor medications given twice a day.

Latent TB Infection

A person with latent TB infection (LTBI) may develop reactivation of TB disease, usually when his or her immunity has diminished or he or she develops a clinical condition that increases the likelihood of progression from LTBI to active TB disease. The most efficient way to decrease the incidence of TB disease is to prevent this reactivation from occurring. Identifying and treating those individuals with LTBI, especially those who are at the highest risk for developing disease, benefits both the infected persons and other susceptible persons in their communities.

In April 2000, the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) revised their guidelines for the treatment of LTBI, which were subsequently endorsed by the Infectious Disease Society of America and the American College of Physicians. These recommendations described the intended intervention more accurately as the "treatment of LTBI" rather than "preventive therapy" or chemoprophylaxis", to promote a greater understanding that one is treating an infection, rather than just trying to prevent a disease.

DIAGNOSTIC TESTS FOR TB INFECTION

Tuberculin Skin Test (TST)

Currently, there are two tests for TB infection (TTBI): TST and a blood-based test. The TST is the most commonly used test. It requires the injection of a purified protein derivative (PPD) of the TB bacteria under the skin. The test is read between 48-72 hours by a trained health care worker who will look for swelling and hardness (induration) at the site of the injection and must record the result in millimeters and not simply as "positive" or "negative". The three cut-off points for defining a positive TST result are ≥5mm, ≥10mm, and ≥15mm of induration which is determined according to patients' medical and epidemiologic risk factors (Table 2-3.2). A TST is not necessary for individuals with a reliable history of, or a previously documented positive TST result.

Determination of a Positive Skin Test	
≥ 5 mm for	Persons with HIV-infection Recent contacts of persons with active TB Persons with evidence of old, healed TB lesions on chest x-rays Persons with organ transplants and other immunosuppressed persons, such as patients receiving prolonged corticosteroid therapy [the equivalent of >15 mg/d of prednisone for one month or more],TNF-alpha blockers and chemotherapy
≥ 10 mm for	Persons who have immigrated within the past 5 years from areas with high TB rates Injection drug users Persons who live or work in institutional settings where exposure to TB may be likely (e.g., hospitals, prisons, homeless shelters, single room occupancy units (SROs), nursing homes) Mycobacteriology laboratory personnel Persons with clinical conditions associated with increased risk of progression to active TB, including: Silicosis Chronic renal failure Diabetes mellitus Gastrectomy/jejunoileal bypass Some hematologic disorders, such as leukemias or lymphomas Specific malignancies such as carcinoma of the head, neck or lung Body weight ≥ 10% below ideal or BMI <18.5 Children <5 years of age or children/adolescents exposed to adults in high-risk categories Persons with prolonged stay (> 1 month) in areas with high TB rates
≥ 15 mm for	Persons at low risk for TB disease for whom testing is not generally indicated

Table 2-3.2: Determination of a Positive Tuberculin Skin Test: The reaction to a TST is classified as positive based on the individual's risk factor(s) and the following measurements of induration.

Patients who have a positive TST reaction should undergo clinical evaluation, including a chest x-ray (CXR) to rule out TB disease (See evaluation of TB disease). If the initial CXR is normal, repeated chest x-rays for screening purposes are not indicated unless the individual develops signs or symptoms of TB. The decision to begin treatment for LTBI in someone who is found to be TST-positive is based on CDC/ATS guidelines.

Blood tests (eg. QuantiFERON®-TB Gold)

The blood test, QuantiFERON®-TB Gold (QFT-G), is a blood test approved by the US Food and Drug Administration (FDA) in 2005 for detection of TB infection. As an alternative to the TST, QFT-G may offer clinicians a simpler, more accurate, reliable and convenient TB diagnostic tool. QFT-G is highly specific, and a positive test result is strongly predictive of true infection with *M. tb*. The test is approved for use in diagnosing *M. tb* infection in persons with active TB disease or with LTBI; however, it cannot differentiate between the two.

QFT-G specifically detects immune responses to two proteins made by *M. tb*. These proteins are absent from all BCG vaccine preparations and from all nontuberculous mycobacteria (NTM), with the exception of *M.kansasii, M.marinum* and *M.szulgai*. As a result, the QFT-G test is not affected by the individual's BCG vaccination status nor by the individual's sensitization to most NTMs, thus providing a more accurate test of TB infection compared to the TST. At present, the major drawback to this test is that blood samples must be processed within 12 hours of the blood draw. In addition, the test has not been fully studied in many groups, including children, those with impaired immune function and in contacts to active TB cases. The ability of QFT-G to predict risk of LTBI progressing to active TB disease has not yet been determined.

The QFT-G can be used to assess any patient for LTBI who would otherwise be a candidate for a TST. It can also be used to aid in the initial diagnosis of active TB. However, it should not be used for patients currently receiving anti-TB drugs for active TB, or for patients receiving treatment for LTBI (while there is no specific FDA recommendation against using QFT-G in patients receiving treatment, there is evidence that such treatment will effect results). The test is reported as positive, negative or indeterminate:

- A negative QFT-G result should be interpreted as a negative TST result, suggesting TB infection is unlikely, and in general no further evaluation is needed. A patient who has symptoms of TB despite a negative QFT-G result should be evaluated appropriately.
- A positive QFT-G result should be interpreted as a positive TST result, and suggests TB infection is likely. TB disease will still need to be excluded by a medical evaluation, chest x-ray and if indicated sputum or other specimen studies. (See Clinical Evaluation for LTBI section below).
- An indeterminate QFT-G result cannot be interpreted due to a lack of response by the test control groups. In this situation a repeat QFT-G or administering the TST could be done. QFT-G results may be indeterminate due to laboratory errors, a result being very near the cut-off point between positive and negative readings or patient anergy (See Anergy below). If two different specimens from a patient

yield indeterminate results, the QFT-G for that person should not be repeated, since a third test is not likely to give a non-indeterminate result.

QFT-G can be cost effective by eliminating the need for a second patient visit for test interpretation and by the elimination of common false-positive results, which typically involve both unnecessary clinical evaluation to rule out active TB and treatment for LTBI. In addition, QFT-G can eliminate the need for the repeat TST when two-step testing is required for health care worker screening (see Two-Step Tuberculin Skin Testing). That, in turn, may lower administrative costs of maintaining testing compliance in health-care facilities, which may offset the slightly higher cost of QFT-G, compared to TST.

Newer versions of blood tests, which may address some of the limitations of the QFT-G, have recently been approved by the FDA, including QFT-G "In-Tube" and T-SPOT.*TB*. TB diagnostics is a rapidly evolving field, and these guidelines may change as more data becomes available. Blood testing (QFT-G) is increasingly becoming an alternative to the TST for identifying TB infection. Table 2-3.3 outlines the differences between QFT-G and TST.

QuantiFERON®-TB Gold Test	Tuberculin Skin Test
• In vitro, controlled laboratory test with minimal inter-reader variability • M.tb specific antigens used • No boosting; two-step testing not needed • One patient visit possible • Unaffected by BCG or most environmental mycobacteria • Simple positive / indeterminate / negative result independent of risk of disease • Ability to predict the risk of latent TB infection progression to TB disease has not yet been determined	• In vivo, subject to errors during implantation and interpretation • Less specific purified protein derivative used • Boosting, with repeated testing • Two patient visits minimum • False-positive tests can occur after BCG and environmental mycobacteria exposure • Interpretation based on patient's risk of TB or development of disease • Risk of progression to active disease is known for many high risk patients

Table 2-3.3: Differences between QFT-G and TST (Adapted from the New York City Department of Health and Mental Hygiene (2008). Treatment of Pulmonary TB; In Clinical Policies and Protocols (4th ed., pg 184). New York)

POPULATIONS WHO SHOULD BE TESTED FOR LTBI

Targeted testing, or screening for LTBI should be focused on populations who would benefit by treatment. Persons at high risk for developing TB disease have either been recently infected with *M. tb* or, if already infected, are at increased risk for developing TB disease due to clinical conditions that are associated with an increased risk of progression of LTBI to active TB. In general, populations at low risk for LTBI (no medical risk factors and low risk of exposure to TB) should not be tested since false positive reactions are common. Table 2-3.4 lists the characteristics of individuals who should be tested for LTBI.

Close contacts of persons with active TB disease should receive a baseline TTBI immediately after exposure. Since it can take up to eight weeks (window period) after *M. tb* infection for the immune system to respond to a TTBI, a negative TTBI result during this period may not be accurate. It is therefore

recommended that close contacts with negative TTBI results during the window period should be retested eight weeks from the contact's most recent exposure to the active TB case. If the second test is negative, the contact would then be considered "not infected" (unless in severely immunosuppressed patients) due to the exposure. If the test is positive anytime after exposure, regardless of the eight week period, the person should be evaluated to rule out TB disease.

Individuals Who May Have Been Recently Infected	Individuals With Clinical Conditions Associated with Progression from LTBI to Active TB
Persons who have had close contact with individuals with active TB. Retesting may be necessary eight weeks after original test Persons who have immigrated to the US within the past five years from areas with high TB rates* should be tested the first time they enter the health care system in the US Persons with prolonged stay (>one month) in areas with high TB rates Persons who live or work in clinical or institutional settings where TB exposure may be likely *(CDC and local guidelines recommend testing annually)*: • hospitals • prisons • homeless shelters • nursing homes • mycobacteriology labs Persons who provide emergency medical response, including EMS personnel and fire fighters Children/adolescents exposed to adults in high-risk categories	Persons with HIV infection should be tested as soon as possible after diagnosis of HIV infection, and at least once a year afterward Injection drug users Persons with evidence of old, healed TB lesions on chest x-ray Underweight persons (≥ 10% under ideal body weight) Persons with any of the following medical conditions or risk factors for TB disease: • Diabetes mellitus • Silicosis • Cancer of the head, neck or lung • Hematologic and reticuloendothelial disease (e.g., leukemia and Hodgkin's disease) • End-stage renal disease • Gastrectomy or jejunoileal bypass • Chronic malabsorption syndromes • Organ transplants or on transplant lists • Receiving prolonged corticosteroid therapy or other immunosuppressive therapy (e.g., receiving the equivalent of ≥ 15mg of prednisone for ≥ one month, TNF-alpha blockers or chemotherapy)

Table 2-3.4: Individuals who should be tested for LTBI

All individuals who are HIV-positive should receive a TTBI as soon as HIV infection is diagnosed. The test should be considered for such patients, especially those at high-risk for TB exposure, on an annual basis or as soon after an exposure to active TB occurs.

Recent immigrants (i.e., those who have been in the United States for less than five years), who have come from countries with high rates of TB, such as those listed in Table 2-3.5, should be tested for TB infection when they enter the medical care system in the U.S. They should also be tested any time after they return to their native country or after a prolonged (more than one month) stay abroad. Additionally, individuals who have had a prolonged stay (more

than one month) abroad in areas where TB rates are high should be evaluated immediately after return or at their next medical examination.

Countries with High TB Rates

Africa
All countries except
Seychelles

Eastern Mediterranean
Afghanistan
Bahrain
Djibouti
Egypt
Iraq
Morocco
Pakistan
Qatar
Somalia
Sudan
Yemen

Europe
Armenia
Azerbaijan
Belarus
Bosnia and Herzegovina
Estonia
Georgia
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Moldova (Rep. of)
Romania
Russian Federation
Tajikistan
Turkmenistan
Ukraine
Uzbekistan

North, Central and South America
Belize
Bolivia
Brazil
Columbia
Dominican Republic
Ecuador
El Salvador
Guatemala
Guyana
Haiti
Honduras
Mexico2
Nicaragua
Panama
Paraguay
Peru
Suriname

Southeast Asia
Bangladesh
Bhutan
India
Indonesia
North Korea (DPRK)
Maldives
Myanmar
Nepal
Sri Lanka
Thailand
Timor-Leste

Western Pacific
Brunei Darussalam
Cambodia
China
China (Hong Kong SAR)
Guam
Kiribati
Lao PDR
Macao (China)
Malaysia
Marshall Islands
Micronesia
Mongolia
New Caledonia
Northern Mariana Islands
Palau
Papua New Guinea
Philippines
Solomon Islands
South Korea (ROK)
Vanuatu
Viet Nam

Notes:

1. *Source: World Health Organization. Global TB Control-- Surveillance, Planning, Financing: WHO Report 2007. Geneva, World Health Organization (WHO/HTM/TB/2007.376). http://www.who.int/tb/publications/global_report/2007/pdf/full.pdf "High-incidence areas" are defined by the New York City TB Control Program as areas with reported or estimated ≥20 new smear-positive cases per 100,000 persons.*
2. *Has an estimated incidence of < 20 smear-positive cases per 100,000 persons; however, the Mexican community in NYC has a high burden of disease.*

Table 2-3.5: Countries/Areas with an Estimated or Reported High Incidence of TB, 2005

Individuals who live or work in institutional settings (e.g., prisons, hospitals, nursing homes, shelters) and emergency medical responders come under testing recommendations that vary according to the risk of transmission based on local and CDC guidelines. Most guidelines recommend annual testing of these employees.

Individuals with immunosuppressive conditions or who are being treated with immunosuppressive agents should be evaluated and treated for LTBI, either at the time that the condition is diagnosed or before starting treatment with immunosuppressive therapies such as prolonged corticosteroids (equivalent of prednisone ≥15mg/kg/d for at least one month) and TNF-alpha blockers (infliximab, etanercept and adalimumab). Patients awaiting transplant should be evaluated for LTBI. TST results in immunosuppressed individuals may be falsely negative, either due to the drug therapy or to an underlying medical condition causing anergy (discussed below).

Interpretations: Causes of False Positive and False Negative TST Reactions

TST results must be interpreted with caution if an individual experiences one of the following factors listed in Table 2-3.6. In medicine, a false positive test is when the patient has a positive test result for a medical condition, but in reality does not have the condition. A false negative test is when the patient has a medical condition but the test for the condition is negative. TST may show false positive or false negative results due to co-morbidity with various infections, inappropriate timing in the administration of both the TST and other live virus vaccines, concomitant medical conditions, reactions with drugs that suppress the immune response and fluctuation of induration size from repeated TSTs.

BCG Vaccinated Individuals

TTBIs are not contraindicated for persons who have been vaccinated with Bacille Calmette Guérin (BCG). A history of BCG vaccination should not be considered, either when deciding to test and/or when determining if the test result is positive in high-risk individuals. Although BCG vaccination can cause a false positive cross-reaction to the TST, BCG-related sensitivity to tuberculin is highly variable and tends to decrease over time. There is no way to distinguish between a positive reaction due to BCG-induced sensitivity and a positive reaction due to true TB infection. Therefore, a positive reaction to the TST in BCG-vaccinated persons should be interpreted as indicating infection with *M. tb* when the person tested is at increased risk of recent infection or when the person has a medical condition that increases the risk of progression to active TB disease. Prior BCG vaccination is not a concern when using the QFT-G test, as the test will distinguish between TB infection and the BCG vaccination.

Factors	False-Negative Reactions	False-Positive Reactions
Infections	Viral illnesses (HIV, measles, varicella) Bacterial illnesses (typhoid fever, pertussis, brucellosis typhus, leprosy Early TB infection (< 12 wks.) Severe TB disease (meningitis, miliary) Fungal disease (Blastomycosis)	Exposure to nontuberculous mycobacteria
Live virus vaccines	Measles Polio Varicella Smallpox	Bacille Calmetter-Guerin vaccine (BCG)
Concomitant medical conditions	Metabolic abnormalities Chronic renal failure Primary immunodeficiencies Malignancies (e.g. Hodgkin's disease, lymphoma, leukemia) Sarcoidosis Poor nutrition Newborns and children < two years of age Low protein states	Transfusion with whole blood from donors with known positive TST
Drugs and technical factors	Corticosteroids or other immunosuppressive medications Chemotherapy Material: poor quality; inadequate dose (one TU); improper storage (exposure to heat/light)); expired Administration: not injected intradermally; too long in syringe Reading: inexperienced or biased reader; recording error, read too early/late	Inexperienced or biased reader
Interpretative	Decreasing mm induration	Increasing mm induration

Table 2-3.6: Factors Associated with False Negative or False Positive TST Reactions

Vaccination with Live Attenuated Vaccines

Vaccination with live attenuated viral vaccines such as measles, mumps and/or rubella (MMR), oral polio, varicella and others can cause a false-negative reaction to the TST. The Advisory Committee on Immunization Practices recommends that the TST can be administered on the same day as the live vaccine because immunosuppression does not appear until after the first 48 hours post-vaccination. If a skin test is needed, and was not given at the same time of the vaccination, it is recommended to wait four to six weeks before administering it. The effects of live attenuated vaccines have not been studied in relation to using the QFT-G test. The current recommendation is to perform the QFT-G test on the same day as the vaccination, as with the TST.

Anergy

Anergy is the inability to respond to a skin test antigen such as the TST, to which a person should normally react. An impaired immune response is directly related to medical conditions that affect the cellular immunity. Individuals who mount a response to any antigen are considered to have relatively intact cellular immunity, whereas those who cannot mount any response are considered "anergic". Anergy may be caused by many factors, such as HIV infection with low CD4 cell count, severe or febrile illness, measles or other viral infections, Hodgkin's disease, sarcoidosis, live-virus vaccination, or the administration of corticosteroids or immunosuppressive drugs. Overwhelming TB disease can also lead to false-negative reactions.

In the United States, anergy testing is no longer recommended as part of routine screening for TB infection among individuals infected with HIV due to the lack of standardization and outcome data that limit evaluation of its effectiveness. It also has no role in the evaluation of contacts. In general, HIV-infected close contacts of a person with pulmonary or laryngeal TB should receive an evaluation and treatment for LTBI, regardless of the TST result. HIV infected individuals who are not known to be contacts should be evaluated for treatment for LTBI according to their risk for TB exposure and infection. On average, 10 to 25% of patients with TB disease have negative reactions when tested with a TST at diagnosis before treatment.

TWO-STEP TUBERCULIN SKIN TESTING

In most individuals, TST testing sensitivity persists throughout life. However, in some TB-infected individuals, the ability to react to a TST diminishes over time, so the size of the skin test may decrease or disappear altogether. Thus, infected individuals who are skin tested many years after infection may have a negative TST reaction. However, if they are retested within the next year, they may have a positive reaction. This phenomenon, called the "booster phenomenon," occurs because the first TST "boosted" the immune response that had diminished over the years. Boosting is most common in persons age 55 and older and can also occur in BCG vaccinated persons. The booster phenomenon can complicate the interpretation of TST results in settings where testing is done repeatedly since a boosted reaction to a second TST may be mistaken for a recent conversion. Consequently, an infection acquired years ago may be interpreted as a recent infection.

Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection. Individuals who will be tuberculin skin tested repeatedly as part of routine periodic evaluations should undergo two-step testing the first time they are tested. This would include health care workers and employees or residents of congregate settings. With this type of testing, an initial TST is done. If the result is negative, a second TST is given one to three weeks later. The result of the second test is then used as the baseline. A positive reaction to the second test probably represents a boosted reaction (past infection or prior BCG vaccination), and the patient is considered previously infected. Some experts recommend two-step testing in immunosuppressed individuals. This would not be considered a positive test from a recent infection. If the second test is negative, the patient is considered uninfected. In these persons, a positive reaction to any subsequent test is likely to represent new infection with *M. tb* (skin test conversion). The QFT-G test eliminates the need for two-step testing, for those who are recommended to have it.

CLINICAL EVALUATION FOR LATENT TB INFECTION

When a patient has been has been diagnosed to have LTBI based on his/her risk and the TST or QFT-G results, further evaluation is deemed necessary in order for the physician to make a treatment decision. Not everyone with latent infection is a candidate for treatment. However, all high-risk individuals who test positive for TB infection should receive treatment for LTBI as soon as active TB has been ruled out.

Medical History and Physical Examination

Every patient who tests positive for TB infection should be examined by a physician, both to rule out TB disease and to be evaluated for treatment of LTBI. The clinical evaluation should include a medical history, physical examination, chest x-ray, and sputum smear and culture if indicated.

All patients should be asked about risk factors which may put them in a high risk category for the development of TB disease, including recent close contact with a person who has TB. However, some patients are not aware that they are contacts.

All patients should be asked about previous treatment for LTBI. Additionally, those who have completed a course of treatment for LTBI in the past should be asked about recent close contact with a person who has TB. If the patient is a contact and meets the criteria for any of the following, the patient should be considered for a repeat course of treatment for LTBI:

- Less than five years of age.
- Between the ages of 5-15 years at the physician discretion.
- HIV infected or otherwise immunosuppressed.
- A behavioral risk for HIV infection who has declined HIV testing.

All patients 13 years of age or older, especially those who have a positive TTBI or have risk factors for HIV, should be offered counseling and testing for HIV unless they have documentation of (1) a positive HIV antibody test or (2) a negative HIV antibody test obtained within the last six months. Those younger

than 18 years should be counseled and offered testing if they have behavioral risk factors for HIV and have no documented history of a positive HIV test.

All patients should be evaluated for and asked about their history of alcohol ingestion, liver disease and hepatitis, and if indicated perform a blood count and baseline liver function tests (LFT), as well as a viral hepatitis screening profile. All patients should be assessed for contraindications to treatment for LTBI.

Chest X-Ray

Everyone considered for LTBI treatment should have a posteroanterior-lateral (PA-Lat) chest x-ray to rule out pulmonary TB disease. If the chest x-ray is normal and there are no symptoms consistent with active TB present, TTBI-positive persons may be candidates for treatment of LTBI. If radiographic or clinical findings are consistent with pulmonary or extrapulmonary TB, further examination (e.g., medical evaluation, bacteriologic test, and a comparison of the current and old chest radiographs) should be done to determine if treatment for active TB is indicated.

Due to the risk for progressive and/or congenital TB, pregnant women who have a positive TST or who have negative skin-test results, but who are recent contacts of persons with infectious TB disease should have a chest x-ray (with appropriate lead shielding) as soon as feasible, even during the first trimester of pregnancy.

Sputum Examinations

Most persons with LTBI will have a normal chest x-ray, or have calcified pulmonary nodules and therefore do not require bacteriologic examination of the sputum. However, persons with chest radiographic findings suggestive of prior healed TB should have three consecutive sputum samples, obtained on different days, submitted for AFB smear and culture. If the results of sputum smears and cultures are negative and any respiratory symptoms (if present) can be explained by another etiology, the person would then be a candidate for treatment of LTBI. If sputum bacteriologic results are negative, but the activity or etiology of a radiographic abnormality remains questionable, further diagnostic evaluation (i.e. bronchoscopy, needle aspiration biopsy) should be undertaken to further evaluate for TB disease.

Consideration of Pregnant Women as Candidates for Latent TB Infection Treatment

Pregnant women should receive a TTBI only if there is either a risk factor for LTBI or for increased risk for progression of LTBI to TB disease. Although the need to treat active TB during pregnancy is unquestioned, treatment of LTBI in pregnant women is more controversial, since the possible risk of hepatotoxicity must be weighed against the risk of developing active TB. However, for women who are HIV-positive or who have been recently infected with TB (such as contacts of active TB cases or known recent conversions), the start of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. Pregnant patients treated for LTBI should have careful clinical and laboratory monitoring for hepatitis.

Treatment should be started during the first trimester of pregnancy if the TST is ≥5mm for:

- Pregnant women who are HIV-positive or who have behavioral risk factors for HIV infection, but decline HIV testing.
- Pregnant women who have been in close contact with a smear positive pulmonary TB patient. At the physician's discretion, start of treatment can be delayed until after the second trimester but the patient should be under close observation for development of TB symptoms.

If the pregnant patient has a documented TST conversion in the past two years, treatment should be started promptly after the first trimester. For all other pregnant women with other risk factors, including those with radiographic evidence of old healed TB, treatment for LTBI should be started two to three months after delivery. In pregnant women known or suspected to be infected with a TB strain resistant to at least INH and rifampin (MDRTB), treatment for LTBI should be delayed until after delivery. This will avoid possible adverse effects of the medications on the developing fetus. A CXR should be obtained initially and again if the woman develops symptoms suggestive of TB disease. A lead shield should be used when performing CXRs on pregnant women.

LTBI TREATMENT REGIMENS

Isoniazid

Single drug treatment of LTBI should not be started until active TB has been excluded. The optimal regimen for treatment for LTBI in individuals with no known exposure to a drug resistant case of TB is isoniazid (INH), given daily or twice weekly for nine months (Table 2-3.7). For adults who are HIV negative, six months of INH is an acceptable alternative if the nine-month regimen cannot be given. However, six months of INH is not recommended for HIV-positive persons, children younger than 18 years of age and individuals with fibrotic lesions consistent with TB on CXR. The nine-month regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection.

Contraindications to treatment of LTBI with INH are:

- A history of an INH-induced reaction, including hepatic, skin or allergic reactions, or neuropathy.
- Close contact with a person who has INH resistant TB.
- Severe chronic liver disease.
- Pregnancy, unless the woman is HIV infected, a recent TST converter or a close contact.

The risk of INH toxicity has been shown to increase with age, particularly in older adults. Those who are contacts, or who have clinical conditions associated with increased risk of progression to active TB, should be treated regardless of age. However, the risk-benefit ratio from INH may not favor treatment of older adults whose only risk factor is recent immigration. This group should be closely monitored for INH toxicity and should even possibly be excluded from treatment.

Treatment for Latent TB Infection

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring[1]	
Isoniazid (INH) Children: 9 months Adults: 9 months	Children: 5-10 mg/kg (max 300 mg) Adults: 5 mg/kg (max 300 mg) Completion Criteria 270 doses within 12 months	Children: 20-30mg/kg (max 900 mg) Adults: 15 mg/kg (max 900 mg) Completion Criteria 76 doses within 12 months	**Symptoms include:** Unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, and arthalgia. **Signs include:** Elevated LFTs, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels, possible interaction with disulfiram (Antabuse®) **Clinical evaluation:** LFTs (if baseline is abnormal or patient has risk factors for toxicity) [2]	Preferred regimen for all individuals. - Vitamin B6 (25 mg/day) or pyridoxine may decrease peripheral and CNS effects and should be used in patients who are: • Abusing alcohol • Pregnant • Breastfeeding infants on INH • Malnourished Or have: • HIV • Cancer • Chronic renal or liver disease • Diabetes • Pre-existing peripheral neuropathy *Note: Aluminum-containing antacids reduce absorption.*
Rifampin (RIF) Children: 6 months Adults: 4 months	Children: 10-20 mg/kg (max 600 mg) Completion Criteria 182 doses within nine months Adults: 600 mg [range 8-12 mg/kg] (max 600 mg) Completion Criteria 120 doses within six months	Children: Not recommended Adults: 600 mg[3] [range 8-12 mg/kg] (max 600 mg) Completion Criteria 34 doses within six months	**Symptoms include:** Nausea, vomiting, loss of appetite, rash, fever or flu-like symptoms, easy bruising **Signs include:** Elevated LFTs, hepatitis, rash, thrombocytopenia. Reduces levels of many drugs, including methadone, warfarin, hormonal contraception, oral hypoglycemic agents, theophylline, dapsone, ketoconazole, PIs, and NNRTIs. **Clinical evaluation:** LFTs (if baseline is abnormal or patient has risk factors for toxicity) 2 CBC, including platelets as needed	May be used to treat persons who have been exposed to INH-resistant, rifampin-susceptible TB or who have severe toxicity to INH, or are unlikely to be available for more than 4-6 months **Be aware that:** -There will be orange discoloration of secretions, urine, tears, and contact lenses - Patients receiving methadone will need their methadone dosage increased by an average of 50% to avoid opioid withdrawal. - Interactions with many drugs can lead to decreased levels of either or both. - Rifampin may make glucose control more difficult in diabetics. - Rifampin is contraindicated for patients taking most PIs and NNRTIs[4] - Patients should be advised to use barrier contraceptives while on rifampin.

Table 2-3.7: Treatment for Latent TB Infection

Rifabutin (RBT) Children: 6 months Adults: 4 months	Children: 5 mg/kg (max 300 mg) (Little data) Completion Criteria 182 doses within nine months Adults: 5 mg/kg (max 300 mg) Completion Criteria 120 doses within six months	Children: Not recommended Adults: 5 mg/kg (max 300 mg) Completion Criteria 34 doses within six months	**Symptoms include:** Stomach upset, chest pain, nausea, vomiting, headache, rash, muscle aches, redness and pain of the eye. **Signs include:** Elevated LFTs, hepatitis, neutropenia, thrombocytopenia. Reduced levels of many drugs including PIs, NNRTIs, dapsone, ketoconazole, and hormonal contraception. However some drugs, including PIs and some NNRTIs do increase levels of rifabutin. **Clinical evaluation:** LFTs (if baseline is abnormal or patient has risk factors for toxicity) 2 CBC, including platelets as needed	May be used to treat LTBI in HIV-infected persons who fit the criteria for rifampin treatment but for whom rifampin is contraindicated, or for others who need a rifamycin but are intolerant to rifampin. Be aware that: -There will be orange discoloration of secretions, urine, tears, and contact lenses - Interaction occurs with many drugs. - For HIV-infected persons, it is necessary to adjust the daily or intermittent dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity, if taken concurrently with PIs and NNRTIs.4 - Methadone dosage generally does not need to be increased. - Patients should be advised to use barrier contraceptives.

Abbreviations: CBC=complete blood count, CNS=central nervous system, LFTs=liver function tests, NNRTI=non-nucleoside reverse transcriptase inhibitors, PI=protease inhibitor

1. Baseline LFTs should be done for everyone over the age of 35, all HIV-infected persons, pregnant and postpartum women (up totwo to three months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users, and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifamycin-containing regimen.

2. Monthly LFTs should be conducted for all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users, and those on treatment with other potential hepatotoxic agents. Those whose baseline LFTs were abnormal should be monitored monthly regardless of other conditions.

3. There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.

4. Please see the NYC Bureau of TB Control's HIV/TB treatment guidelines (www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf).

Table 2-3.7 (continued): Treatment for Latent TB Infection

Patients should be identified for possible risk factors for hepatotoxicity prior to starting therapy for LTBI. Baseline blood tests including a blood cell count, LFTs, as well as a viral hepatitis screening profile should be obtained in patients who:

- Are HIV-positive.
- Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis.
- Are pregnant or postpartum (up to two to three months after delivery).
- Have a history of drug injection.
- Are older than 35 years.
- Are starting treatment for LTBI with two or more anti-TB drugs.
- Are already taking hepatotoxic drugs for other medical conditions.

If the LFTs are three to five times above the normal limit at baseline, consideration for delaying LTBI therapy should be made while further evaluation is done for cause of the hepatic condition. Otherwise, the regimen for LTBI should be selected based on the indication for therapy and the risk of drug induced liver injury (i.e., rifampin may be considered in INH-resistance contacts or a need to complete treatment in a shorter time).

Directly Observed Therapy (DOT) for LTBI is an effective method for promoting adherence to treatment. Due to limited resources, however, most public health programs cannot provide DOT to all patients receiving LTBI therapy. However, if DOT is being provided to an active case, the household contacts receiving LTBI therapy can also receive home-based DOT. Patients receiving DOT treatment for LTBI may be considered candidates for twice-weekly therapy.

Rifampin

An alternative regimen to INH is to give adult patients (with or without HIV infection) four months of rifampin for treatment of LTBI. This course is especially recommended if there are adverse reactions or resistance to INH, but not to rifampin; or if the individual will not be available for more than four to six months and is thus unlikely to complete a nine-month INH regimen. If a rifampin- containing regimen is chosen for HIV-infected patients with LTBI, the drug to drug interactions and dose adjustments for antiretroviral drugs and rifamycin need to be taken into consideration, and rifabutin given where appropriate.

Children (with or without HIV infection) who have been exposed to INH-resistant, rifampin-susceptible TB should be treated with at least six months of rifampin. Although INH is the only drug that has been studied on a large scale for treatment for LTBI, rifampin is probably equally effective. If needed, rifabutin can be substituted for rifampin.

Rifabutin may be used with regimens containing the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine, or many protease inhibitors (PIs) used in the management of HIV. There is insufficient data on the use of rifabutin in antiretroviral regimens containing combinations of NNRTIs and PIs, or other multiple PI combinations. The websites: www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf or www.cdc.gov/tb/TB_HIV_Drugs/default.htm or www.AIDSinfo.nih.gov are continuing sources of information on this subject, as recommendations are consistently changing. Contraindications to the use of rifampin in treating LTBI are:

- A history of rifampin-induced reactions, including skin and other allergic reactions, hepatitis or thrombocytopenia.
- Severe chronic liver disease.
- Pregnancy, unless the woman is HIV-infected, a recent TST converter, a close contact of an INH-resistant case or is intolerant to INH and needs to be treated (see above).
- Current treatment with certain PIs or NNRTIs (an alternative is to use selected antiretroviral drugs with rifabutin, see above).

Rifampin & PZA Combination

The two-month regimen containing rifampin and pyrazinamide as an option for LTBI treatment is no longer recommended due to high rates of hospitalization and death from liver injury associated with the use of a daily or twice-weekly two-month regimen of rifampin plus pyrazinamide. As a result, this regimen should generally not be offered to HIV-negative or HIV-positive persons with LTBI.

CONTACTS TO MULTIDRUG RESISTANT TB (MDRTB) CASES

There have been no controlled trials of treatment for LTBI with drugs other than INH and rifampin. Therefore, treatment protocols for contacts of patients with INH- and rifampin-resistant TB are largely empirical, and all regimens must be individualized. Therapy should be initiated by a physician expert in treatment of this condition. TB disease must be excluded before any therapy regimens for LTBI are initiated. Regimens given for LTBI are comprised of two medications to which the organism of the index case is susceptible for 6-12 months. If the contact chooses not to take LTBI therapy, he/she should be followed for the next two years with a symptom review and chest x-ray.

Treatment of Close Contacts with a Prior Positive Test for TB Infection

Close contacts to a TB case with a documented previous positive TTBI should be treated again for LTBI after active TB is ruled out if they are HIV positive, or at risk for HIV disease but have declined testing. Treatment should also be considered for the following individuals who have a previous positive TTBI, but who have subsequently been in close contact with a person who has infectious pulmonary TB:

- Persons with immunosuppressive conditions and other medical risk factors for TB, other than HIV infection.
- Children younger than 18 years of age.
- Asymptomatic, HIV-negative persons who have had heavy exposure to a person with highly infectious pulmonary or laryngeal TB (i.e., the presence of secondary cases or documented conversions in the close contacts).
- The regimen for LTBI again should depend on the susceptibility of the index case isolate.

Monitoring Patients During Treatment

All patients receiving treatment for LTBI should be monitored on a monthly basis, with directed clinical examinations and blood tests as needed. Patients also need to be educated about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment and clinical evaluation should symptoms occur.

Adverse effects with INH or rifampin may include unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and/or feet, persistent fatigue, weakness or fever lasting three days or more, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding and arthralgia. Appropriate educational materials in the patient's language should be provided.

Monthly liver function tests (LFTs) should be done in patients who:

- Are HIV-positive.
- Have a history of alcohol abuse, liver disease, chronic hepatitis.
- Are pregnant or postpartum women (two to three months after delivery).
- Are currently injecting drugs.
- Are on potentially hepatotoxic agents.
- Have baseline abnormal LFTs not due to the conditions above.

In addition, laboratory testing should be used to evaluate specific adverse events that may occur during treatment. If the patient develops hepatotoxicity, medication should be stopped, and the patient's LFTs should be monitored closely. If indicated, other possible risk factors for hepatotoxicity should be identified.

SUMMARY

Despite the fact that TB is preventable and curable, it remains a public health threat in the US and around the world. There have been great strides in reducing the number of cases of active TB over the years due to increased resources allotted to TB control programs and aggressive initiation of DOT in the treatment of TB. However we still face many challenges in TB control programs today including the prompt identification of cases and contacts and placing them on appropriate treatment and also the increasing emergence of MDRTB and XDRTB. There is a large group of individuals who have LTBI globally and finding new modalities to reduce the percentage of this group who remain at substantial risk for subsequent active TB has and will continue to be difficult. DOT remains one of the most effective methods to ensure patients complete treatment for TB disease, yet many TB programs do not have enough resources to apply the use of DOT when treating LTBI patients, and therefore completion of treatment among these patients remains low. The future of reducing TB disease and latent infection will depend on the continued vigilance of case finding, contact identification and treatment of contacts. Despite the advances made over the years, there is a continued need to develop new diagnostic tools and therapies to combat this complex disease.

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Chapter 2-4
Asthma

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Asthma is a chronic inflammatory disease of the airways.[1] This inflammation can lead to airway hyperreactivity when exposed to triggers (such as irritants, allergens, temperature/humidity change, stress and exertion) and acute airflow limitation producing symptoms, such as cough, wheeze, chest tightness and shortness of breath. These symptoms are at least partially reversible with bronchodilator medications. Airway inflammation is present even in mild disease.

EPIDEMIOLOGY

An estimated 23.4 million Americans have asthma and the prevalence has been steadily increasing.[2,3] The incidence of asthma is greater in childhood compared to adulthood. Each year, there are nearly 500,000 hospitalizations and close to two million visits to the Emergency Department. Nearly one quarter of adults with asthma missed work during the prior year due to asthma and over one third of parents of asthmatics missed work in the prior year. The annual direct and indirect health cost is estimated at over 16 billion dollars. Fortunately the overall mortality of asthma in the United States appears to be decreasing. Of concern, the mortality rate appears to be higher among African Americans and Puerto Rican Americans, perhaps due to factors such as health care access, environmental factors, and/or genetic influences.

RISK FACTORS

Both genetic and environmental risk factors have been sited for the development of asthma. Some studies have shown a more than 25% chance of having a child with asthma if one of the parents has asthma. Numerous studies have also linked asthma to allergic diseases which occur in families with a genetic predisposition towards the development of a hypersensitivity reaction to environmental allergens. There have been many reports describing the identification of potential asthma-susceptibility genes, and such research and genetic findings will lead to better disease classification and treatment.

Environmental risk factors include exposure to maternal smoking during pregnancy, chemical sensitizers, air pollutants, allergens and infections of the respiratory tract. Studies have shown a two-fold risk of a child developing asthma if the mother smokes while pregnant. Environmental tobacco smoke may also be linked to adverse asthma-related outcomes.[4,5] Vigorous outdoor exercise in regions with high levels of ozone also has been shown to predispose to the development of asthma, and particulate air pollution from motor vehicles has been suspected of contributing to the increased prevalence.[5] The indoor environment is just as important, perhaps more-so, where exposure

to such allergens as house dust mites, cats, dogs, cockroaches, and molds may be associated with allergic asthma. Interestingly, it has also been shown that exposure to cat or dog allergen early in life may actually be protective against later development of asthma. Certain bacterial infections including Chlamydia pneumoniae and Mycoplasma pneumoniae, as well as a number of viral infections, can stimulate local inflammatory reactions, and may be associated with asthma. Low or high birth weight, prematurity, and obesity have been shown to increase the risk of asthma. Just as with coronary artery disease, consumption of oily fish (salmon, tuna, shark) rich in omega-3 fats may be protective.

Work related asthma includes occupational asthma and work-aggravated asthma. Occupational asthma is airflow limitation and/or airway hyperresponsiveness caused by exposure to a specific agent or conditions in a particular work environment.[6] Recent data from the Sentinel Health Notification System for Occupational Risk (SENSOR) program indicates that exposure to irritants are frequently reported as causes of new-onset asthma.[7] The intensity of the exposure is likely to be a risk factor for irritant-induced asthma. Several cohort studies have suggested that work-related exposure to machining fluid, chemicals, laboratory animals, flour and latex may be associated with new-onset asthma. In contrast to work-related asthma, work-aggravated asthma is defined by preexisting asthma that is made worse or exacerbated by the work environment.

Reactive Airways Dysfunction Syndrome (RADS) is defined as persistent respiratory symptoms and airway hyperreactivity in patients with a history of acute exposure to an inhaled agent (gas or aerosol) and without a prior history of allergies, smoking or asthma.[8] However, for practical purposes, RADS can be assumed to be present when there are new episodic respiratory symptoms with spirometric evidence of lower airways obstruction, especially when the obstruction can be reversed by administration of bronchodilating drugs. Although RADS was initially reserved for only acute exposures to chemical gases and fumes,[8] it's use has been extended by some to include chronic exposures to gases and fumes and recently even to acute/chronic exposures to particulates. Others argue that extending the definition of RADS clouds any distinction between RADS and irritant-induced asthma. Regardless of this controversy in terminology, RADS or irritant induced asthma has been reported after smoke inhalation in both civilians and fire fighters.[9,10,11]

Currently, not enough is known about bronchospastic inflammatory airways diseases to know if there are important distinctions, such as mechanism of occurrence, degree of severity, response to treatment, or prognosis, between RADS, irritant-induced asthma, occupational asthma, allergic asthma or non-specific asthma. What we do know is that clinically these distinctions are currently meaningless. All of these illnesses have in common provocability (reaction to airborne irritants, allergens, temperature/humidity and exercise), at least partially reversible airways obstruction in response to asthma medications (see below) and may rarely progress to irreversible lower airways obstructive disease (airway remodeling).

The risk of lung diseases including asthma following the collapse of the World Trade Center (WTC) towers is discussed in greater detail in a separate chapter. WTC studies have allowed us to describe the incidence of bronchial

hyperreactivity, RADS or irritant-induced asthma after a major disaster and to evaluate its persistence longitudinally in large cohorts. In a sample of rescue workers from the Fire Department of the City of New York (FDNY) whose bronchial hyperreactivity was measured six months after 9/11/01, those who arrived at the WTC site on 9/11 were 7.8 times more likely to experience bronchial hyper-reactivity than were those fire fighters who arrived to the site at a later date and/or had lower exposure levels.[12,13] A dose response was evident in this FDNY study: RADS emerged in 20% of highly exposed (present during the morning of collapse) and 8% of moderately exposed rescue workers (present after the morning of 9/11 but within the first 48 hours).[13] In the NY/NJ Consortium Program for non-FDNY WTC workers/volunteers, 45% reported symptoms consistent with lower airway disorders, including asthma and asthma variants.[14] The WTC Registry has published its findings on self-reported "newly diagnosed asthma (post-9/11/01) by a doctor or other health professional" in 25,748 WTC workers from a diverse range of occupations/organizations but all without a prior history of asthma.[15] Newly-diagnosed asthma was reported by 926 workers, for a three-year incidence rate of 3.6%, or 12-fold higher than the expected risk in the general population. Earlier arrival, total duration of work, exposure to the dust cloud, and working on the pile at the WTC site increased the risk asthma.

PATHOPHYSIOLOGY

Asthma is characterized by chronic inflammation of the airway wall which is present even in the asymptomatic patient. Microscopically, there is a patchy loss of the epithelium or cellular layer covering the airway, leaving airway nerves exposed. There is accumulation of inflammatory cells, including eosinophils, which can release their contents and cause further inflammation. Enlargement of airway smooth muscle, increased number and size of bronchial blood vessels, and an accumulation of abnormal mucus in the airways all contribute to worsening airflow obstruction. Persistent inflammation may lead to a change in the structure of the airway due to the development of fibrosis (scar-like tissue) beneath the cellular layer covering of the bronchus. This process is referred to as airway remodeling (Figure 2-4.1).

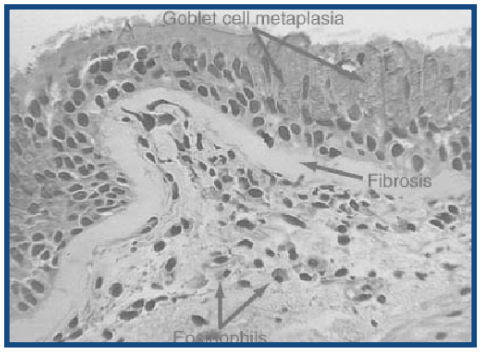

Figure 2-4.1: Airway pathology in asthma is detected in this photomicrograph of a section from an endobronchial biopsy taken during bronchoscopy from a subject with mild chronic asthma. Goblet (mucus) cell metaplasia, subepithelial fibrosis, and eosinophilic infiltration of the submucosa are shown. (Hematoxylin and eosin stain; ×1200.) *Courtesy of Murray and Nadel's Textbook of Respiratory Medicine, 4th edition.*

CLINICAL MANIFESTATION

Patients usually present with difficulty breathing (dyspnea), audible wheezing, and tightness in the chest. Cough can occur in association with these symptoms or be the only symptom, a condition called cough-variant asthma. Patients may report coughing mainly at night, which can awaken them from sleep. Breathing problems (cough, wheeze and/or shortness of breath) can be triggered by physical activity, during particular seasons, or after exposure to allergens, irritants, or changes in temperature/humidity. A history of persistent respiratory tract infections is sometimes found.

Physical findings on examination include tachypnea (increased respiratory rate), wheezing, and a prolonged time-phase for expiration. When the presentation is more severe, decreased breath sounds, excessive use of respiratory muscles and rarely even cyanosis (low oxygen levels causing bluish discoloration of skin and mucous membranes) can be found.

DIAGNOSIS

A definitive diagnostic test for asthma does not yet exist. Family history, symptoms, and physical examination may suggest the diagnosis of asthma.[16] Provocable or triggerable symptoms with reversibility following either removal of the trigger or administration of a bronchodilator medication are the hallmark of asthma. Lung function testing may confirm the diagnosis and exclude other causes of these symptoms. Spirometry is a test most commonly used to evaluate the two main characteristic features of asthma: airflow obstruction, which is at least partially reversible, and airway hyperresponsiveness. During spirometry, patients are asked to forcibly exhale after taking a full breath in. After consistent measurements are obtained, a bronchodilator is administered and the testing is repeated to assess change. Airway obstruction is present when the ratio of the amount exhaled in one second (referred to as the FEV_1 or forced expiratory volume at one second) to the total amount exhaled (referred to as the FVC or forced vital capacity) is less than 0.7 or when ratio is within the lower limit of normal (LLN) distribution. NIOSH provides an excellent spirometry reference value calculator (based on NHANES III reference equations) which allows determination of the LLN for a specific age, gender, race and height (see: http://www.cdc.gov/niosh/topics/spirometry/RefCalculator.html). Reversibility is documented when the FEV_1 or FVC increases by 12% and 200cc of volume after the bronchodilator is given. Peak expiratory flow rate (PEFR) measured with a hand-held peak flow meter can be used to assess changes in lung function at the work place to help diagnose work-related asthma and to document the relationship of lung function to suspected triggers. This method however is more effort dependent and less reproducible than spirometry. Tests of pulmonary function are described in another chapter in greater detail.

Bronchoprovocative tests measuring airway hyperresponsiveness can be done if baseline spirometry is normal or near-normal but the patient has symptoms suggestive of asthma. In this test, a substance that induces or provokes asthma is inhaled in increasing doses and spirometry is repeated until the FEV_1 falls 20% or the highest dose is delivered without a significant FEV_1 change. Methacholine challenge testing is the most commonly used bronchoprovocative test in the United States and Canada, though some centers

use cold-air or exercise, histamine or mannitol challenge testing. A negative methacholine challenge test virtually excludes asthma due to its high sensitivity.

Several other tests are often done to evaluate a patient with suspected asthma, but are not diagnostic. Skin testing is often performed on patients with allergies and asthma. The presence of positive skin tests may help the patient avoid specific allergens that can trigger or worsen asthma. Sputum analysis and chest x-rays are generally non-specific in asthma, but are more useful in excluding other disease processes. Chest CT scans may show bronchial wall thickening and/or air-trapping in asthma and other obstructive airways diseases (ex. emphysema, chronic bronchitis, bronchiolitis obliterans, etc.) but are most useful in excluding other disease processes. Oxygenation is usually not a problem during most asthma attacks but measurement of oxygen saturation is helpful in severe exacerbations. A new measure of asthma severity is the amount of exhaled nitric oxide, a marker of inflammation.

DIFFERENTIAL DIAGNOSIS

Several diseases can mimic asthma by producing similar symptoms, and has lead to the saying, "all that wheezes is not asthma."[17] Other diseases that can be misdiagnosed as asthma include:

- Upper airway obstruction, due to multiple causes including inhaled or aspirated foreign body, tumor, abscess, or epiglottitis (medical emergency in children secondary to infection/inflammation of the epiglottis, the lid-like structure overhanging the entrance to the larynx at the back of the throat).
- Vocal cord paralysis/dysfunction, characterized by an inappropriate closing of the vocal cords during respiration causing upper airway obstruction.
- Upper-airway and/or lower-airway respiratory infections.
- Chronic bronchitis, which is often due to smoking and is defined as the presence of a chronic productive cough for three months during each of two successive years, and is part of the condition known as chronic obstructive airways disease (COPD), described in another chapter.
- Endobronchial lesions (mass-lesions inside the lower airways due to inhalation or aspiration of foreign bodies, scarring or tumors), which can cause localized wheezing.
- Congestive heart failure causing wheezing due to pulmonary edema or fluid filling air sacs.
- Gastro-esophageal reflux disease (GERD), the disease with reflux of the stomach and duodenal contents into the esophagus.
- Pulmonary embolism (a blood clot that travels to the lungs).

CLASSIFICATION OF ASTHMA SEVERITY

In 2005, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH/NHLBI) published a guideline for evaluation of asthma severity based on the symptoms and pulmonary function (FEV_1 and PEFR). The primary goal of this classification is to determine who has intermittent and

who has persistent asthma. Patients with intermittent asthma are treated with short-acting bronchodilators, used when needed. All other patients should be treated with daily inhaled corticosteroids. Additional asthma medications are prescribed as asthma severity worsens.

In 2007, the NIH/NHLBI guidelines were modified to effectively classify patients as either under control or poorly controlled, based on impairment and risk.[18] Impairment is based on the frequency of symptoms, night-time awakenings, frequency of need for rescue (short-acting) bronchodilator therapy, and functional limitations. Risk is the likelihood that the patient will experience an asthma exacerbation. Based on impairment and risk criteria (as seen in Table 2-4.1), treatment can be stepped up or stepped down. The stepwise approach to asthma treatment is discussed later in this chapter.

Risk	Impairment					Level of Severity	Recommended Initial Treatment
Exscerbations Requiring OCS	Symptons	Night-time Awakenings	Use of SABA for Symptom Relief	Interference with Normal Acitivity	Lung Function		
0-1/year	≤2 days/wk	≤2x/month	≤2 days/wk	None	FEV_1 normal between exacerbations (>80%); FEV_1/FVC normal	Intermittent	Step 1
≤2/year	>2 days/wk, not daily	3-4 x/month	> 2 days/wk, not daily or >1 x/day	Minor limitation	FEV_1 >80%; FEV_1/FVC normal	Mild persistent	Step 2
	Daily	>1 x/wk, not nightly	Daily	Some limitation	FEV_1 >60% but<80%; FEV_1/FVC reduced 5%	Moderate persistent	Step 3 and consider short course of OCS
	Throughout the day	Often 7x/wk	Several x/day	Extremely limited	FEV_1 <60%; FEV_1/FVC reduced 5%	Severe persistent	Step 4 or 5 and consider short course of OCS

Table 2-4.1: Assessing asthma control in patients 12 years old to adult. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity. OCS, oral corticosteroids; SABA, short-acting beta agonists. The National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Summary Report, 2007.

MANAGEMENT OF ASTHMA

Generally the goals for management of asthma are:

- Minimal or no symptoms, including nighttime symptoms.
- Minimal asthma episodes or attacks.
- No emergency visits to physicians or hospitals.
- Minimal need for reliever medications.
- No limitations on physical activities and exercise.
- Nearly normal lung function.
- Minimal or no side effects from medication.

To achieve these goals, asthma management must include patient education, monitoring, and avoidance of known triggers. Unless there are specific medical contraindications (e.g., allergy to vaccine content), all asthmatic patients, regardless of their asthma severity, should receive a flu vaccine every year. The U.S. Centers for Disease Control (CDC) recently recommended that adults with asthma also receive the pneumonia vaccine (pneumovax). Individualized

management plans, developed by the physician and patient for co-management of asthma attacks, should be understood by the patient.

MEDICATIONS

Asthma medications are classified as quick-relief (rescue) and long-term control (maintenance) medications. Quick-relief medications are taken to promptly reverse airflow obstruction and relieve symptoms. Long-term control medications are taken daily to maintain control of persistent asthma with the goal of reducing the number of attacks and their severity. Generally, the treatment is based on the severity of asthma (refer back to Table 2-4.1).

Quick-Relief Medications

Short-Acting Beta-Agonists (SABA)

Short-acting beta-agonists act primarily on beta-adrenergic receptors to relax bronchial smooth muscle contraction. They do not reduce airway inflammation and therefore are not control medications. The beta-agonists are usually delivered by an inhaler or nebulizer. The most commonly used beta-agonist in the United States is albuterol. The action begins within five minutes of use and lasts as long as four hours, and may require re-dosing. They are used as needed only. Common side effects are tremor, nervousness and tachycardia. Recent regulations from the Environmental Protection Agency (EPA) have led to a ban of the substance that was previously used to propel albuterol from the inhaler.[19] This is not because the propellant was dangerous to the patient but rather because it was harmful to the earth's ozone layer. Currently, albuterol is available as albuterol HFA which does not have these propellants. Other agents in this class are marketed in the United States under the trade names Ventolin®, Proventil®, Proair® and Maxair®. Studies have shown that the old and new preparations of albuterol are equally as effective, although you may notice that HFA inhalers do not seem to be hitting your throat with the same force. Long-acting preparations of beta-agonists are also available but should never be used as quick-relief medications and should never be used without an inhaled corticosteroid. This class will be discussed in the control medication section.

Anticholinergics

Anticholinergics, such as ipratropium bromide (marketed as Atrovent®), also promote smooth muscle relaxation, though beta-agonists are more effective bronchodilators in the asthmatic population. These agents have a slower onset of action but may last longer. Common side effects of anticholinergics are nausea and dry mouth. In general, these agents are used when there is intolerance to beta-agonists, but in certain cases they may be used in combination (albuterol plus ipratropium bromide, marketed as Combivent®). A long-acting anticholinergic medication, tiotropium (marketed as Spiriva®), is currently available but not indicated for asthma at this time.

Long-Term Control Medications

Inhaled Corticosteroids (ICS)

Inhaled corticosteroids are currently the mainstay of asthma treatment for all patients except those with mild intermittent asthma (refer to Table 2-4.1). Inhaled steroids are potent anti-inflammatory agents that require daily use. Numerous studies have shown that inhaled steroids reduce daily asthma symptoms, reduce the severity and frequency of asthma exacerbations, reduce the need for bronchodilator therapy, and improve lung function. Most importantly, regular use of inhaled steroids is associated with reduced asthma mortality. They can be delivered by a metered dose inhaler, dry powder inhaler or nebulizer. Common side-effects are oral thrush (fungal infection), change of voice, and cough. It is extremely unusual for inhaled corticosteroids to cause the side-effects associated with oral corticosteroids (see below). Currently there are multiple inhaled corticosteroids available in the United States and marketed under the names Pulmicort®, Flovent®, Asmanex®, Asmacort®, QVar®, etc. They are also available in combination with long acting beta-agonists and marketed under the trade names Advair® and Symbicort®.

Long Acting Beta-Agonists (LABA)

Long acting beta-agonists are available in the form of salmeterol (marketed as Serevent®) and formoterol (marketed as Foradil®). Both have significantly longer half lives than albuterol, thereby requiring dosing only every 12 hours. Onset varies, with formoterol working quicker. One large study raised concern regarding asthma mortality and use of long-acting beta-agonists as monotherapy. It remains unclear if this was a reflection of a drug side-effect or underlying asthma disease severity. Until this is known, these agents should always be used in combination with inhaled steroids This combination is indicated in those patients who have moderate or severe persistent asthma. Single inhalers containing both a long acting beta-agonist and an inhaled corticosteroid (marketed as Advair® and Symbicort®) are available to promote compliance and to help prevent the use of these agents as monotherapy.

Leukotriene receptor antagonists (LTRA)

Leukotriene antagonists are generally an add-on therapy in the patients who are on inhaled corticosteroids, who cannot tolerate inhaled corticosteroids or who have a very strong allergy history with co-existent allergic rhinitis (nose drip/congestion). Leukotriene antagonists block leukotrienes which are substances released from inflammatory cells and that cause bronchoconstriction. This class of medication, of which the most commonly used is montelukast (marketed as Singulair®) is available in pill form, and is usually taken at nighttime. They may play a role in treating patients with environmental allergies as well as aspirin-sensitive asthma. Side-effects may include headache and flu-like symptoms.

Mast Cell Stabilizers

Mast cell stabilizers include cromolyn (marketed as Intal®) and nedocromil. They are another possible add-on therapy in patients who are on inhaled corticosteroids and who cannot tolerate inhaled corticosteroids, or who have a very strong allergy history with co-existent allergic rhinitis (nose drip/

congestion). They are delivered by metered dose inhalers. Dosing intervals tend to make compliance difficult. They are not commonly prescribed in the adult population. Side-effects are rare, but can include cough and dry throat. Overall, the role of this class of medication in the treatment of adult asthmatics is considered limited.

Methyxanthines

Methylxanthines, such as theophyline (marketed as Theodur® or Unidur®), are one of the oldest classes of asthma medication. They are taken in pill form. It is not currently recommended as a first line medication, but can be considered as an add-on therapy to inhaled steroids. Many common medications interfere with the metabolism of this class of medications that can result in high blood levels and side-effects that can range from nausea and vomiting to seizures and cardiac arrhythmias.

Anti IgE Antibody

Omalizumab (marketed as Xolair®), an anti-IgE antibody, is a fairly new treatment for patients with allergic asthma who are poorly controlled on inhaled steroids and have high circulating IgE blood levels.[20] Treatment is usually, but not always, reserved for patients with high circulating IgE blood levels. Anti IgE antibody prevents the release of inflammatory mediators from inflammatory cells. This medication is given through subcutaneous injection every two to four weeks. It has been shown to reduce asthma exacerbations, lessen asthma severity and reduce the need for high dose steroids. Common side-effects are injection-site reaction and viral infection. Cases of anaphylaxis (a severe life-threatening allergic reaction) have been reported.

Immunotherapy

Immunotherapy, or "allergy shots," can be considered as a treatment option, in addition to optimal asthma treatment, in patients with fair control and a significant allergic component. Their usefulness in the control of asthma is controversial but studies do show some level of improvement in asthma patients with allergic rhinitis. They should not be used in asymptomatic patients who have positive skin or blood tests for an allergen. The purpose is to give low doses of allergen to reduce the immediate hypersensitivity reaction, a process known as desensitization. The common side-effects are injection-site reaction and viral infection. The potential serious complication is anaphylaxis.

STEPWISE APPROACH TO THERAPY

The NIH/NHLBI recommended treatment for asthma is based on the patient's severity and control and is presented in Table 2-4.2. Step 1 is the treatment for intermittent asthma. Steps 2-5 are treatment regimens for patients with persistent asthma. Mild asthma is treated according to Step 2, moderate; Step 3, and severe, Step 4 or 5. If the patient's asthma is not controlled, therapy can be stepped up one or two steps. A short-course of oral corticosteroids is sometimes necessary (Step 6). For patients with asthma that is well controlled for several months, therapy can be stepped down. Monitoring to ensure maintained control is necessary. It is not uncommon for patients to step up or down depending on season, stress, infection etc.

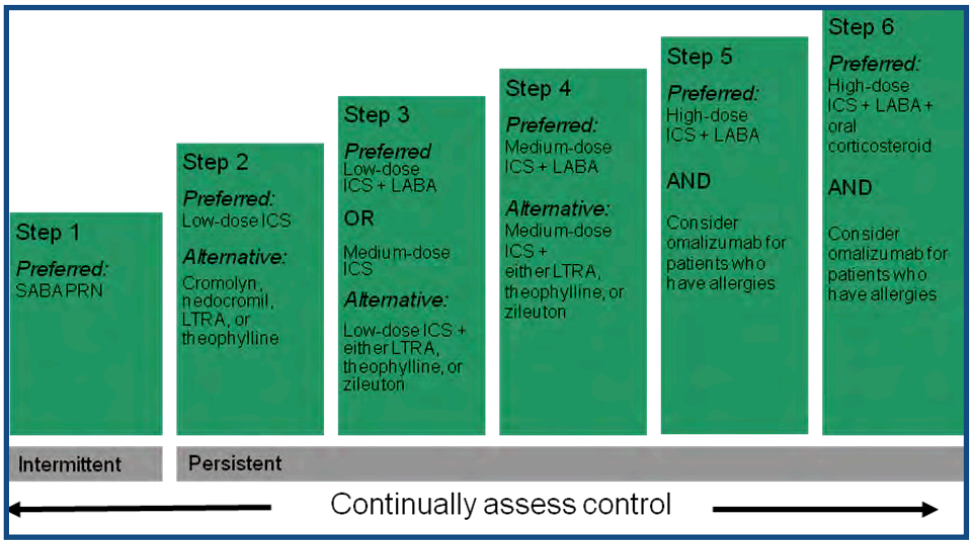

Table 2-4.2: Stepwise approach to therapy. From the Expert Panel report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007). NIH Item No. 08-4051. Available at http//www.nhlbi.nih.gov/guidelines/asthgdln.htm

THE ASTHMA CONTROL TEST

One useful and easy-to-use tool to measure control is the Asthma Control Test (see Table 2-4.3).[21] This test is a validated questionnaire that is aligned with the above NIH goals of asthma step-therapy. It is a simple five-question quiz that patients can fill out with their physician. A score of ≤19 suggests asthma may not be controlled as well as it could be.

									SCORE
1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	
2. During the past **4 weeks**, how often have you had shortness of breath?	More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	
5. How would you rate your **asthma** control during the **past 4 weeks**?	Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	
											TOTAL

Table 2-4.3: The Asthma Control Test

Non-Pharmacologic Therapy

Reduction in trigger exposure can improve asthma symptoms. In a large home-based study looking into environmental interventions among urban children with asthma, encasing pillows, mattresses and box springs with impermeable covers and using HEPA filters in heating/cooling systems reduced the number of days with asthma symptoms. A list of preventive actions to reduce exposure to environmental allergens is presented in Table 2-4.4.

RISK FACTOR	ACTIONS
Domestic dust mite allergens (so small they are not visible to the naked eye)	Wash bed linens and blankets weekly in hot water and dryer or the sun. Encase pillows and mattresses in air-tight covers. Replace carpets with linoleum or wood flooring, especially in sleeping rooms. Use vinyl, leather, or plain wooden furniture instead of fabric-upholstered furniture. If possible, use vacuum cleaner with filers.
Tobacco smoke (whether the patient smokes or breathes in the smoke from others)	Stay away from tobacco smoke. Patients and parents should not smoke.
Allergens from animals with fur	Remove animals from the home, or at least from the sleeping area.
Cockroach allergen	Clean the home thoroughly and often. Use pesticide spray -- but make sure the patient is not at home when spraying occurs.
Outdoor pollens and mold	Close windows and doors and remain indoors when pollen and mold counts are highest.
Indoor mold	Reduce dampness in the home; clean any damp areas frequently.
Physical activity	Do not avoid physical activity. Symptoms can be prevented by taking a rapid-acting inhaled beta$_2$ agonist, a cromone, or a leukotriene modifier before strenuous exercise.
Drugs	Do not take beta blockers or aspirin or NSAIDs if these medicines cause asthma symptoms.

Table 2-4.4: Common asthma risk factors and actions to reduce exposure From Global Initiative for Asthma (GINA), NHLBI. Global strategy for asthma management and prevention; Bethesda (MD); 2005

ASTHMA EXACERBATION

An acute asthma attack is the most common respiratory emergency. The most common precipitating factor is an acute viral infection, though other common triggers include noxious odors, weather extremes, irritant exposure, allergen exposure, and emotional crises. Lack of adherence to the asthma medication plan is often a contributing factor.

Treatment should be started as soon as possible. Clues for a severe attack include shortness of breath precluding sleep, need to sleep upright to reduce shortness of breath, unable to speak in full-sentences, use of accessory respiratory muscles in the neck to help move air in and out, cyanosis, fatigue, and mental status changes. Beta-agonists are the main treatment in an acute asthma attack, and can be given via a nebulizer or by metered dose inhaler with a spacer, every 20 minutes for the first hour. When the attack is severe, beta-agonists can be given by direct injection into the skin or muscle. Anticholinergics can be used concomitantly. Increasing the dose of inhaled corticosteroids during an asthma exacerbation is not effective and is not recommended.[22] Systemic corticosteroids should be prescribed for all patients with asthma attacks who do not favorably respond to beta-agonist therapy. A typical regimen is prednisone 40-60 mg/day for 7 to 10 days, with or without a taper over days to weeks. The need to treat a life-threatening severe, persistent asthma attack overrides any potential concern about oral corticosteroid side-effects, such as acne, weight gain, hypertension, elevated blood glucose levels, or osteoporosis.

Hospitalization may be required for patients that did not respond to the initial treatment. In addition, hospitalization should be considered for those patients who have previously had respiratory failure associated with an exacerbation, and for those with psychosocial issues such as inadequacy of home support and lack of access to medical care and medications, as these all have been associated with fatal asthma attacks.

Asthma cannot be cured but it can be controlled. The earlier the treatment is started, the better the outcome is. This applies to both maintenance and rescue therapy. Following the above NIH/NHLBI stepwise guidelines, asthma management plans should be co-developed by the physician and patient. This joint effort allows the plan to be tailored to meet the patient's individual needs and will inevitably improve patient adherence. Following this plan, patients should self adjust their asthma treatment at home based on symptoms and peak flow measurement, and communicate changes with their health care provider.

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Chapter 2-5
Chronic Obstructive Pulmonary Disease

By Dr. Kenneth Pinsker, MD and Dr. Leah Spinner, MD

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease marked by cough and shortness of breath, and characterized by limitation of airflow, making it difficult to empty the lungs. It is a major cause of sickness and mortality (death) in the United States and throughout the world. Many people remain undiagnosed and suffer for years, or die prematurely due to its complications. COPD is currently the fourth leading cause of death in the world, and further increases in its prevalence are predicted in the coming years, as the general population is living longer with continued exposure to risk factors. There are about 14 million people known to have COPD in the United States. Some of the current goals in the management of COPD are to improve awareness, recognition, and prevention of this disease among both healthcare providers and patients, as well as to impress upon healthcare policymakers the burden of this disease.

Definition

COPD is defined by chronic airflow limitation in the lungs which is treatable and preventable, with some effects outside the lung that contribute to its severity in individual patients. The airflow limitation is not completely reversible, and is usually progressive over the course of the disease. One of the major differences between COPD and asthma is that the airflow limitation of bronchospasm in COPD is not nearly as reversible as it is in asthma. COPD is associated with an abnormal inflammatory response in the lungs. Overall, cigarette smoking is the greatest risk factor for the development of COPD. However, inhalation exposures, occupational or environmental are important additional sources of risk. For fire fighters, these exposures occur not only during fire suppression but also during overhaul when SCBA is far less likely to be used. Air pollution and in other countries air pollution from burning of biomass fuels also contributes to the risk of COPD.

Some of the non-pulmonary effects of COPD include muscle wasting, weight loss, nutritional abnormalities and congestive heart failure. Because of the relationship between COPD and smoking, patients also have other diseases that are related to or worsened by smoking such as lung cancer, coronary artery disease, stroke, peripheral vascular disease and diabetes. Therefore, a comprehensive approach is required when treating COPD patients in order to identify and treat all the conditions associated with it and to improve the patients' overall quality of life.

Pathology

COPD affects the three major components of the lungs: the airways which consist of multiple generations of branching bronchial tubes, the tissue that supports these tubes and contributes to the exchange of gases such as oxygen and carbon dioxide, and the blood vessels that surround them. The chronic inflammation which underlies the pathologic changes in COPD causes structural distortions in the airways and destruction of lung tissue. This leads to a decreased number of these gas exchange elements (called alveoli) from the rest of the airways and a decrease in the elastic property of the lungs. There is also enlargement of the mucus-producing glands, which produce excessive mucus and sputum. Another contributing factor to the pathologic changes in COPD is an imbalance between the proteins that break down the supporting tissue in the lungs and those that protect against it, favoring the destructive ones. The end result of all these changes is a decreased ability of the airway to remain open during expiration, resulting in airflow limitation, or obstruction.

In the past, COPD was defined by the terms "emphysema" and "chronic bronchitis". Emphysema is defined by permanent enlargement of the air sacs at the end of the branching airways accompanied by destruction of their walls, and is really a pathological definition of COPD. This represents one of many other changes that occur in patients with COPD. Normally the lungs are elastic and have inherent stretchiness and springiness. In emphysema, they loose their elasticity and it takes a lot of effort to empty the air out of them. Because the lungs do not empty efficiently, they contain more air than normal and this produces the air trapping or hyperinflation. Obstruction of airflow occurs because the walls of the bronchial tubes are unable to stay open during exhalation but rather collapse, preventing the lungs from expelling the air. Chronic bronchitis is defined as the presence of cough and sputum production for at least three months in each of two consecutive years and which is not due to another cause. It is a clinical diagnosis which does not reflect the severity of airflow limitation. It develops secondary to constant swelling and irritability of the airway tubes with excessive mucus production. Airway obstruction occurs in chronic bronchitis because the swelling and excessive mucus cause narrowing of the breathing tubes and prevent air from reaching the air alveoli and the lungs from emptying fully. Cough and sputum production may precede the development of airflow limitation in chronic bronchitis; on the other hand, patients with emphysema may have significant airflow limitation without chronic cough and sputum. Chronic bronchitis and emphysema are useful to define a spectrum of clinical and pathological changes in COPD without necessarily placing patients strictly into one or the other category as most patients have components of each disease process.

Natural History

The natural history of COPD is variable. It usually begins insidiously, without the patient being aware of its presence until symptoms become noticeable. COPD is generally a progressive disease, especially with continued exposure to risk factors such as cigarette smoke or environmental pollutants. Stopping exposure can result in some improvement in lung function and can even stop

the progressive decline in lung function, but once it develops, COPD cannot generally be cured and must be treated continuously. Treatment can reduce symptoms, improve quality of life, reduce exacerbations and may improve mortality, but cannot cure the disease. For fire fighters this highlights the importance of preventing inhalation exposures whenever possible through proper use of SCBA and through longitudinal monitoring of pulmonary function at the annual medical or whenever symptoms occur in order to identify reductions in lung function in excess of normal aging.

Clinical Manifestations

The most common clinical features of COPD are cough, sputum production and shortness of breath. Cough is the most frequent symptom reported by patients but it is often the breathlessness and decreased exercise tolerance that causes them to seek medical attention. Sputum production initially goes unnoticed or is described as scant. Later in the course it may become thicker and more of a daily problem, being difficult to expectorate, especially in the morning hours. Sputum production is also related to smoking status, with smokers having much more sputum than nonsmokers. Shortness of breath occurs initially with exertion, and as the disease progresses it occurs with less and less effort, to such an extent that many patients avoid exertion in order to prevent breathlessness and become quite inactive. Eventually activities of daily living such as working or even eating may cause symptoms. In addition to coughing up infected and discolored sputum, some patients with COPD may cough up blood. This typically occurs in patients who have chronic bronchitis and in association with an episode of infection. It can also be a manifestation of lung cancer, to which this population is susceptible.

As previously mentioned, patients with COPD also have extrapulmonary manifestations of the disease, such as muscle wasting and congestive heart failure. Therefore they may appear extremely thin and emaciated, or they may have swelling of their extremities (edema) from congestive heart failure. Many patients will also have hypoxia, which refers to low oxygen levels, and may have a cyanotic or bluish discoloration to their skin, especially their lips and nails. Physical examination of the lungs can be normal in some patients. In others it may reveal decreased breath sounds or high pitched noises such as wheezing or rhonchi (lower raspy noises). The most consistent finding is a prolonged expiratory time during which inspired air is being exhaled, and is indicative of significant airway obstruction. As patients become breathless on minimal exertion or even at rest they will be observed to have purse-lipped breathing and sitting forward and leaning on their elbows or supporting their upper body with extended arms.

The natural course of COPD is characterized by periods of stability interrupted by an acute worsening of symptoms termed exacerbations, which are characterized by cough, shortness of breath and sputum production. These episodes are often associated with viral or bacterial respiratory tract infections. Overall the progressive nature of the disease and the frequent exacerbations result in patients having poor quality of life, and depression is often present.

CLASSIFICATION AND DIAGNOSIS OF COPD

COPD is classified according to severity by using spirometry to measure lung function. The two most useful measures are the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV_1). These are measurements of volume and are obtained by having the patient blow into a flow meter that records the volume of air exhaled as well as the rate of flow. For the FVC the patient takes a maximal deep breath and then exhales as forcefully and rapidly as possible until the lungs cannot empty any further. The FEV_1 is the volume of air exhaled in the first second of the FVC test, and it is the most reproducible of all the lung volumes obtained by spirometry. The reduction in these volumes is reflective of the pathological changes in COPD. In emphysema, lung tissue is destroyed and lost, and lung elasticity is decreased. The airways are narrowed and there is increased resistance to flow. These lead to a decrease in maximal flow as reflected by a decrease in FEV_1 and to a lesser degree FVC. In chronic bronchitis the thick secretions in the airways and the structural distortion lead to narrowing of the airway, increased resistance to flow, and decreased maximal flow.

In order to be considered an obstructive pattern as in COPD, the FEV_1 to FVC ratio should be below 70%, and the FEV_1 should be less than 80% of the predicted normal value. Even more accurate than expressing lung function as percent predicted is identifying whether that lung function is below the lower limits of normal (LLN). Use of the LLN to avoid false-diagnosis is especially important in older or taller individuals. Spirometry if abnormal should then be performed before and after the patient is administered an inhaled bronchodilator, with the post-bronchodilator FEV_1 and FVC used to classify the disease into four stages.

- Stage I: Mild COPD – characterized by mild airflow limitation (FEV_1/FVC < .70 or preferably LLN <5%; $FEV_1 \geq 80\%$). Symptoms of chronic cough and sputum production may be present, but not always. At this stage patients are usually unaware that their lung function is abnormal. To avoid false-diagnosis of disease, Stage I should not be used in the occupational settings unless symptoms are present.
- Stage II: Moderate COPD – characterized by worsening airflow limitation (FEV_1/FVC <.70 or preferably LLN <5%; $50\% \leq FEV_1 < 80\%$ predicted or preferably LLN <5%), with shortness of breath typically developing on exertion and cough with sputum production also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.
- Stage III: Severe COPD – characterized by further worsening of airflow limitation (FEV_1/FVC <.70; $30\% \leq FEV_1 \leq 50\%$ predicted), greater shortness of breath, reduced exercise capacity, fatigue, and frequent exacerbations that have an impact on patients' quality of life.
- Stage IV: Very Severe COPD – characterized by severe airflow limitation (FEV_1/FVC < .70; FEV_1< 30% predicted or FEV_1< 50% predicted plus the presence of chronic respiratory failure). Respiratory failure is defined by continuous symptoms and low oxygen in the blood and may include signs of congestive heart failure (Table 2-5.1).

Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV_1	
Stage I:	$FEV_1/FVC < 0.70$ or preferably LLN <5% $FEV_1 \geq 80\%$predicted
Stage II:	$FEV_1/FVC < 0.70$ or preferably LLN <5% $50\% \leq FEV_1 < 80\%$predicted
Stage III:	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$predicted
Stage IV:	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$predicted or $FEV_1 < 50\%$predicted, plus chronic respiratory failure

Table 2-5.1: Spirometric Classification of COPD Severity

The diagnosis of COPD should be considered in any patient who has symptoms of cough, shortness of breath, sputum production, or a history of exposure to risk factors such as smoking. It should also be considered in anyone with a family history of chronic respiratory illness. To actually diagnose COPD, spirometry with an FEV_1/FVC ratio < 70% or preferably LLN <5% is required, or the patient must meet the criteria for chronic bronchitis. CT scan evidence of emphysema is also diagnostic of COPD and is especially important when it is associated with pulmonary function abnormalities. The aforementioned FEV_1 cut-off points are used for purposes of simplicity and do not perfectly correlate with clinical symptoms. Furthermore, symptoms of COPD may precede the onset of airflow limitation by many years, while airflow limitation may develop without any symptoms. Therefore this staging system is most useful to identify patients with abnormal lung function and initiate prevention and treatment early. It is also useful in predicting health status, utilization of healthcare resources, development of exacerbations and mortality in COPD.

A tool to evaluate the clinical severity of COPD is the Medical Research Council Dyspnea (breathlessness) Scale. Zero (0) is not troubled with breathlessness except with strenuous exercise. One (1) is troubled by shortness of breath when walking up a slight hill or hurrying. Two (2) is walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on level. Three (3) is stops for breath after walking approximately 100 meters or after a few minutes on level ground. Four (4) is too breathless to leave the house or breathless when dressing or undressing.

Burden of COPD

There is significant variation in the prevalence (percentage of the population that is affected with a disease at a given time) of COPD across countries. This is due to a number of reasons including differences in diagnostic criteria for COPD. For example, using airflow limitation by spirometry measurements versus using clinical symptoms. Furthermore, depending on whether or not FEV_1 and FVC are obtained pre or post administration of a bronchodilator, patients will be classified differently. Other sources of variation in prevalence are due to

different survey methods and variable reporting rates across countries. This is generally due to a major under-recognition and under-diagnosis worldwide. As such, the prevalence data that exist actually underestimate the total burden of COPD because many patients are diagnosed late in the course of the disease. This explains why improving awareness of COPD has become such a major theme in the field of pulmonary medicine in the last few years.

In general, the prevalence of COPD is higher in smokers and ex-smokers than non-smokers, in men than in women, and in those over forty. The World Health Organization estimated that the worldwide prevalence of COPD in 1990 was 9.34 for every 1,000 men and 7.33 for every 1,000 women. In terms of mortality, COPD is currently the fourth leading cause of death in the world, and even mortality data underestimate COPD as a cause of death because it is more likely to be cited as a contributing factor rather than a cause, or not listed at all on the death certificate. Large studies have projected that by the year 2020 COPD will be the third leading cause of death worldwide. This is due to increased trends in smoking and to more of the population living longer. This trend in COPD mortality is in contrast to that seen in three other leading causes of death, namely cancer, stroke and heart disease where the death rates are on the decline. Mortality rates for women are also rising as women smoke more than in the past. Therefore the importance of smoking cessation in the management of COPD cannot be overemphasized.

COPD is a very costly disease with both direct costs (value of healthcare resources allocated to diagnosis and medical treatment) and indirect costs (financial consequences of disability, missed work, premature death, and caregiver costs). In the United States in 2002 direct costs were estimated at $18 billion and the indirect costs totaled $14.1 billion. In developing countries where financial gain is directly related to human productivity, indirect costs have a greater impact on the economic burden of COPD than do direct costs. There is a direct relationship between the severity of COPD and costs – the sicker the patient, the greater the costs.

Risk Factors

Risk factors are identifiable causes that place people at risk for developing a disease. Identification of risk factors is important in the design of prevention and treatment plans for COPD. COPD risk factors can be classified as genetic or environmental, and there is a complex relationship between these factors. For example, for two individuals with similar smoking histories, one may develop COPD because of different genetic predisposition or longer life span.

COPD is a disease that is related to multiple genetic abnormalities, but not all are required to produce the disease. The best documented genetic defect is called alpha-1 antitrypsin deficiency, which is a hereditary defect of a protein in the lungs. This protein is involved in repairing the lungs from injury due to other destructive proteins. When there is an imbalance between injury and repair, as in alpha-1 antitrypsin deficiency, premature and accelerated development of emphysema may occur. There is considerable variability among individuals with this risk factor in the severity of COPD and decline in lung function, and smokers are at even greater risk. This is a good example of how genetic and environmental factors interact to produce the final outcome of disease in individuals.

Another risk factor in the development of COPD is inhalational exposure of noxious particles. Cigarette smoke is by far the most common risk factor. It is estimated that 15-20% of smokers develop clinically significant COPD, but this is likely an underestimation as many more will develop abnormal lung function if they continue to smoke. Cigar and pipe smokers are also at risk, but not as great as cigarette smokers. The risk for cigarette smokers is related to total number of packs smoked, age at starting to smoke and current smoking status, however some smokers may never develop COPD, suggesting that genetic factors play a role in modifying the risk. Exposure to secondhand smoke should also be considered in the evaluation of patients with COPD. In the surgeon general's latest report in 2006 on the effects of secondhand smoke in relation to COPD, it stated that "the evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease." It went on to state that "the evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease." In other words, secondhand smoke may be a risk factor for COPD, but in those who already have COPD it is unclear whether secondhand smoke can cause any further lung damage. Despite the progress that has been made in reducing exposure to secondhand smoke, 60% of American nonsmokers still have evidence of secondhand smoke exposure.

Other inhalational exposures include occupational dusts and chemical fumes, which are linked to the development of disease in fewer than 10 - 20% of patients with COPD. This is especially true for fire fighters. In other countries, there is increasing evidence that indoor air pollution from burning biomass fuels in poorly ventilated areas may also be a risk factor for COPD. The role of outdoor air pollution in causing COPD is also important, but appears to be small when compared to cigarette smoking (Figure 2-5.1).

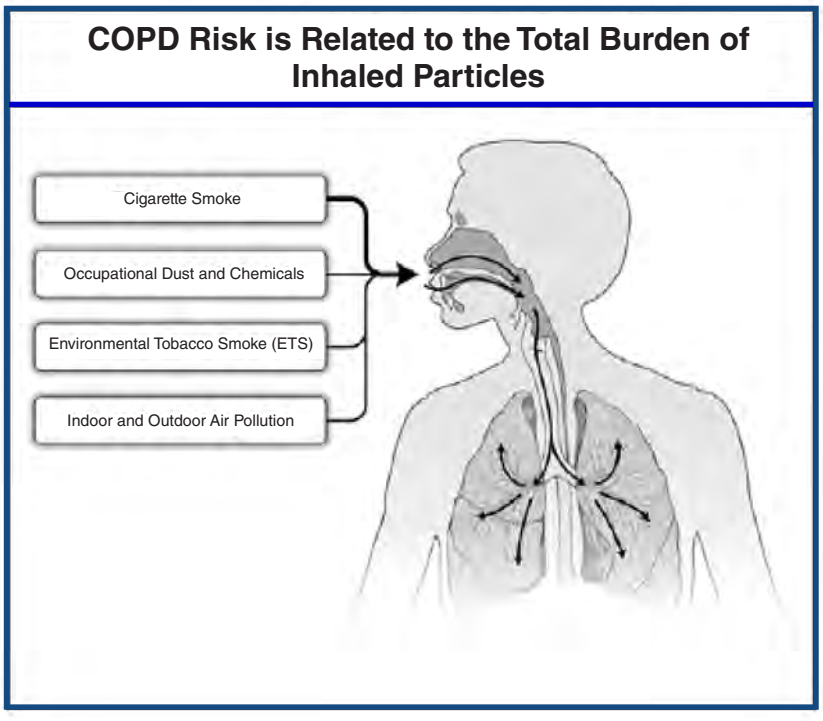

Figure 2-5.1: Inhaled Particles and COPD Risk[3]

A few other risk factors deserve mention, such as lung growth during gestation and in childhood. Any process that affects lung maturation during this time can increase one's risk for COPD. A history of repeated childhood respiratory infections plays a role in the development of reduced lung function, and may possibly be a risk factor for COPD. The role of gender in COPD risk is unclear. Previous studies have shown that COPD prevalence and mortality were greater in men. However, now that women are smoking more the prevalence is almost equal. Women are also more susceptible to the effects of cigarette smoking, which will likely have a further effect on prevalence and mortality rates. Poor socioeconomic status is related to the development of COPD, but it is unknown whether this is due to the effects of pollution and malnutrition (which is an independent risk factor for COPD). Finally, asthma may be a risk factor although the evidence is inconclusive. Many patients with asthma may develop inflammation similar to that in COPD, especially in asthmatics who smoke. One report on the course of patients with obstructive airways disease found that asthmatics had a 12-fold higher risk of acquiring COPD than those without asthma, after adjusting for smoking status. Therefore, it can sometimes be difficult to distinguish between the two diseases, referring to patients simply as having asthma/COPD.

MANAGEMENT

Effective COPD treatment includes four components: assess and monitor disease; reduce risk factors; manage stable COPD; manage exacerbations. The goals of COPD management are to: prevent disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations, and reduce mortality.

A diagnosis of COPD should be assessed in anyone who has cough, sputum production, shortness of breath or exposure to risk factors for the disease. A key component in disease assessment is educating patients, physicians and the public that these symptoms should be evaluated seriously. Patients should be identified as early as possible in the course of the disease and spirometry should be available to healthcare providers to confirm the diagnosis. In addition to spirometry, patients should have a complete physical examination, chest x-ray, and measurements of oxygen levels. Follow-up visits should include a discussion of new or worsening symptoms, inquiries about exposure to risk factors, monitoring for complications, and assessment of lung function (Figure 2-5.2).

Key Indicators for Considering a Diagnosis of COPD	
Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.	
Dyspnea that is:	Progressive (worsens over time) Usually worse with exercise Persistent (present every day) Described by the patient as an "increased effort to breath", "heaviness", "air hunger" or "gasping"
Chronic Cough:	May be intermittent and may be unproductive
Chronic Sputum Production:	Any pattern of chronic sputum production may indicate COPD
History of Exposure to Risk Factors, *especially*:	Tobacco smoke Occupational dusts and chemicals Smoke from home cooking and heating fuels.

Figure 2-5.2: COPD and Key Indicators[3]

COPD is a progressive disease and the patterns of symptom development are well established. In mild COPD, cough and sputum production can be present for many years before the development of airflow limitation, and symptoms are often ignored by patients. In moderate COPD, patients experience breathlessness which may interfere with their daily activities. This is the stage at which they seek medical attention and may be diagnosed with COPD. Some patients do not have any of these symptoms and only come to attention when airflow limitation becomes so severe that they cannot breathe, often at times of an acute pulmonary infection or a cardiac event. This is the stage where patients are at risk for developing chronic respiratory failure, congestive heart failure, muscle wasting, and where oxygen levels become limiting (Figure 2-5.3).

Suggested Questions for Follow-Up Visits

Monitor exposure to risk factors:
Has your exposure to risk factors changed since your last visit?

- Since your last visit, have you quit smoking, or are you still smoking?
- If you are still smoking, how many cigarettes/how much tobacco per day?
- Would you like to quit smoking?
- Has there been any change in your working environment?

Monitor disease progression and development of complications:

- How much can you do before you get short of breath?
- (Use an everyday example, such as walking up flights of stairs, up a hill, or on flat ground.)
- Has your breathlessness worsened, improved, or stayed the same since your last visit?
- Have you had to reduce your activities because of your breathing or any other symptom?
- Have any of your symptoms worsened since your last visit?
- Have you experienced any new symptoms since your last visit?
- Has your sleep been disrupted by breathlessness or other chest symptoms?
- Since your last visit, have you missed any work/had to see a doctor because of your symptoms?

Monitor pharmacotherapy and other medical treatment:
What medicine are you taking?
How often do you take each medicine?

- How much do you take each time?
- Have you missed or stopped taking any regular doses of your medicine for any reason?
- Have you had trouble filling your prescriptions (e.g., for financial reasons, not on formulary)?
- Please show me how you use your inhaler.
- Have you tried any other medicines or remedies?
- Has your treatment been effective in controlling your symptoms?
- Has your treatment caused you any problems?

Monitor exacerbation history:

- Since your last visit, have you had any episodes/times when your symptoms were a lot worse than usual?
- If so, how long did the episode(s) last? What do you think caused the symptoms to get worse? What did you do to control the symptoms?

Figure 2-5.3: COPD and Follow-Up Visits[3]

The second component in the management of COPD is the identification, reduction and control of risk factors (Figure 2-5.4 and Figure 2-5.5). For fire fighters, prevention is the focus through a mandatory SCBA program and longitudinal monitoring of pulmonary function at the annual medical examination or whenever symptoms occur in order to identify reductions in lung function in excess of normal aging. In those that are tobacco users, smoking prevention and cessation programs are of equal importance. Smoking cessation is the single most effective and cost-effective way to reduce the risk of developing COPD and to stop its progression. Tobacco is addictive and leads to dependence, in most cases requiring pharmacologic therapy to overcome it. This comes in the form of nicotine replacement (gum, patch, inhaler, nasal spray, sublingual tablet, or lozenge) or the antidepressant bupropion. Another medication which was recently introduced is varenicline, functioning as a

nicotine replacement. Tobacco cessation programs and medications are discussed in a separate chapter in this book.

Brief Strategies to Help the Patient Willing to Quit	
ASK:	Systematically identify all tobacco users at every visit. *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.*
ADVISE:	Strongly urge all tobacco users to quit. *In a clear, strong, and personalized manner, urge every tobacco user to quit.*
ASSESS:	Determine willingness to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).*
ASSIST:	Aid the patient in quitting. *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.*
ARRANGE:	Schedule follow-up contact. Schedule follow-up contact, either in person or via telephone.

Figure 2-5.4 Tobacco Quit Strategies[3])

US Public Health Service Report: Treating Tobacco Use and Dependence; A Clinical Practice Guideline -- Major Findings and Recommendations
1. Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved.
2. Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments.
3. Clinicians and health care delivery systems must institutionalize the consistent identification, documentation, and treatment of every tobacco user at every visit.
4. Brief smoking cessation counseling is effective and every tobacco user should be offered such advice at every contact with health care providers.
5. There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness.
6. Three types of counseling were found to be especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment.
7. Five first-line pharmacotherapies for tobacco dependence – bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch – are effective and at least one of these medications should be prescribed in the absence of contraindications.
8. Tobacco dependence treatments are cost effective relative to other medical and disease prevention interventions.

Figure 2-5.5: Treating Tobacco Use and Dependence[3]

Counseling is especially effective in smoking cessation and includes the following strategies: strongly advise all smokers to quit; determine willingness to attempt quitting; assist the patient in quitting by providing practical

counseling, social support and medications. There is a strong positive relationship between the intensity of counseling and cessation success. Even short periods of counseling can achieve cessation rates of 5-10%. Occupational exposures can be reduced by efforts to control and monitor exposure in the workplace. Reducing the risk of indoor and outdoor pollution requires protective steps taken by individual patients and initiatives by public policy-makers. Regulation of air quality is an important aspect of this initiative.

The third component in the management of COPD is the treatment of stable disease which requires a multidisciplinary approach including patient education, medication, oxygen therapy, rehabilitation and exercise, vaccination, and surgery. Patient education is important in improving coping skills, medication compliance, smoking cessation, and patient responses to exacerbations. Because most medical regimens include inhaled pumps which can be difficult to use, proper education on inhaler technique is essential to achieve medication effectiveness. Education about the progressive nature of COPD is necessary in order to have discussions on end-of-life issues with patients who have severe disease and do not wish for aggressive care at the end of their life.

Medical treatment of stable COPD is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. Most of the medications do not modify the long-term decline in lung function, however this should not deter patients from using them. The two main classes of medications are bronchodilators and inhaled steroids. Bronchodilators are inhaled medications that widen the airways by targeting protein receptors in the airways. They relax the muscles surrounding the airways that tend to maintain them in a narrower position. Consequently these drugs dilate the airway, improve emptying of the lungs, reduce air trapping at rest and during exercise and allow people with COPD to breathe better. The actual changes in FEV_1 are smaller than the clinical effects.

The two principal bronchodilators are the beta-agonists and the anticholinergics. They differ in their protein receptor targets but both achieve the same airway widening. Some of the inhalers work for a short period of time while others last for many hours. For patients with mild and intermittent symptoms, inhalers are prescribed for as-needed usage, but as symptoms progress patients are instructed to take them on a regular basis. Regular use of the long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Long-acting bronchodilators should be taken with inhaled steroids. A combination inhaler containing both a beta-agonist and an anticholinergic may produce additional improvements in lung function than taking either alone. A combination also leads to fewer exacerbations than either drug alone. In the last few years a new long acting, once daily anticholinergic appeared on the market called Tiotropium. This drug was a welcome addition to the bronchodilators because of its convenient dosing and relatively easy use. Compared to other anticholinergics, studies have shown that Tiotropium is more effective in improving breathlessness, reducing frequency of exacerbations, slowing the decline in lung function over one year as measured by FEV_1, and improving quality of life. Studies have further demonstrated that compared to long acting beta-agonists, Tiotropium was better at improving lung function as measured by FEV_1. Patients should be aware that these medications do

have occasional side effects. The main side effects with beta-agonists include increased heart rate, possible heart rhythm disturbances and a hand tremor. The main side effects reported for anticholinergics are mouth dryness and a bitter, metallic taste in the mouth.

Inhaled steroids are another mainstay in the treatment of stable COPD. They do not modify the decline in lung function over time, however regular treatment is appropriate for patients with severe and very severe COPD (stage III and IV) to reduce inflammation in the bronchial tubes, exacerbations and therefore improve quality of life. Combination inhalers containing steroids and long-acting beta-agonists are more effective than using both components individually. It is not recommended to use steroid pills to treat COPD on a continuous basis, as effectiveness has not been definitively proven in clinical trials and there are too many side effects, especially in the elderly patients. The use of oral or intravenous steroids for exacerbations however is usually necessary.

Patients with COPD have frequent exacerbations which can be associated with viral and bacterial respiratory tract infections. Therefore an extremely critical part of maintenance therapy is vaccination for influenza and pneumonia.

Pulmonary rehabilitation is another aspect of COPD management. This consists of exercise training, nutrition counseling, and education. Some of the benefits of pulmonary rehabilitation include: improving exercise tolerance and quality of life, reducing breathlessness and the frequency of exacerbations, and diminishing the occurrence of anxiety and depression associated with COPD. There may be some benefit on survival, but the studies are somewhat lacking.

The only treatment which has been proven unequivocally to improve survival is oxygen therapy when given on a long-term and continuous basis. Oxygen is generally indicated when the blood oxygen level drops below a certain level at rest or during exercise, or if congestive heart failure is present.

Surgery is a controversial issue in the treatment of COPD. Some studies have reported success in removing damaged parts of the lungs but it was limited to select patients. Much more information is required before surgery is incorporated as a mainstay of COPD management. In patients with very severe emphysema, lung transplantation can improve quality of life and general ability to function, but survival benefit may disappear after two years.

Exacerbations are important events in the course of COPD. The most common cause of an exacerbation is infection, bacterial or viral, and therefore antibiotics are part of the treatment plan. Intravenous steroids are also beneficial because they shorten recovery time and help to restore lung function more quickly. Sicker patients often require oxygen during this time and for a few weeks to months following the episode. Of course patients continue to take bronchodilators, although they are usually administered in a humidified form. Finally, when patients are in respiratory failure they may require placement on a mechanical ventilator (discussed further in another chapter).

SUMMARY

In summary, COPD is a progressive disease of airflow obstruction characterized by the symptoms of cough, shortness of breath especially on exertion, and excessive sputum production. It is the fourth leading cause of death in the world today with projections for increased mortality over coming years. COPD is preventable and therefore strategies aimed at prevention must focus on minimizing occupational and environmental exposures, smoking cessation, and a pulmonary function monitoring program performed at annual medical examinations in order to identify early but significant changes in lung function. Treatment plans are multifaceted, focusing on amelioration of symptoms and slowing the unavoidable decline in lung function, with the ultimate goal being to maintain quality of life.

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Chapter 2-6
Sarcoidosis

By Dr. David Prezant, MD

Sarcoidosis is a multiorgan system inflammatory disorder that typically occurs in early adulthood.[1,2] It can affect almost any organ, with over 90% of cases having involvement of the lungs and intra-thoracic lymph nodes. These lymph nodes are located in 3 areas of the chest – hilar, mediastinal and paratracheal, which when involved are engorged with inflammatory cells leading to their enlargement. This is referred to as adenopathy or lymphadenopathy. Extra-thoracic involvement may be evident in as many as 52% of cases.[1,3] Other organs frequently involved are the skin and eyes. Less than 10% of the cases involve other organs (heart, liver, brain, nerves, endocrine glands, bones, joints, etc.). Figure 2-6.1 is a photomicrograph of biopsy material from an involved organ and shows a non-caseating or non-necrotizing granuloma (an epitheloid cell surrounded by a rim of lymphocytic inflammatory cells and fibroblasts). Non-caseating granulomas are formed by an unfettered immune response involving inflammatory cells – specifically T-lymphocyte helper cells (TH1) producing cytokines (ex. interferon-y, interleukin-2, and tumor necrosis factor) that attract greater numbers of inflammatory cells.[1]

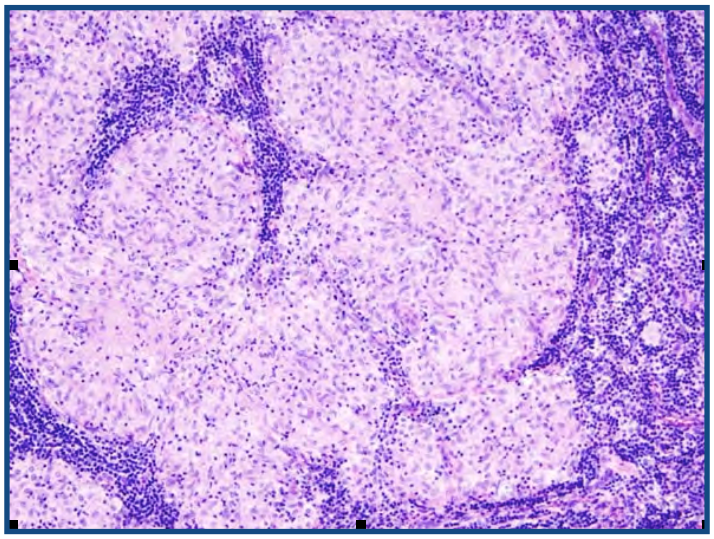

Figure 2-6.1: Microscopic image of a Granuloma – The Classic Pathologic Biopsy Finding in Sarcoidosis

Criteria needed for the diagnosis of sarcoidosis include (1) a clinical and radiographic picture compatible with the diagnosis; (2) biopsy proven evidence of non-caseating granulomas; and (3) exclusion of other conditions that can produce similar pathology, including lymphoma, infections (tuberculosis

or fungal), autoimmune diseases or rheumatologic diseases (Wegeners, Lupus, Sjogren's syndrome, etc.) and inhalational diseases (hypersensitivity pneumonitis or foreign body reactions).[1-3]

In this chapter, we will review the basic epidemiology of sarcoidosis (prevalence rates in different populations), symptoms, organs involved, prognosis and treatment. We then conclude by discussing existing evidence for an increased rate of disease in certain occupations such as firefighting.

Sarcoidosis occurs worldwide. The exact cause is unknown but it is unlikely that sarcoidosis is caused by a single agent or antigen. The current hypothesis is that sarcoidosis is an autoimmune disease that results from a variety of genetic-environmental interactions that have yet to be characterized. Genetic influences appear to play a role because sarcoidosis is more common in African-Americans and Hispanics of Puerto Rican descent than among Caucasians or Asians.[4-10] Tobacco smoke is not associated with an increased prevalence rate of sarcoidosis.[1,4] Infections (Atypical Mycobacterium, Chlamydia, viruses and others) were thought to be potential causative agents. However, tissue analysis, culture, and molecular identification methods have not supported infection as a likely mechanism. Environmental agents that do appear to be associated with increased prevalence rates include microbial bioaerosols, pesticides, wood burning stoves (wood dust or smoke),[11] chemical dust,[12] man-made fibers,[13] silica,[14] and metals.[15] One particular metal deserves special mention. Chronic beryllium exposure produces a disease that is clinically, radiographically and pathologically indistinguishable from sarcoidosis.[16] Most cases of sarcoidosis have no evidence for beryllium exposure by either history or laboratory testing (beryllium lymphocyte proliferation blood test). When evidence for beryllium sensitivity is present then the disease is no longer called sarcoidosis and is instead called berylliosis.

Diagnosis typically occurs in adults between age 20 and 50, but rarely can occur in children or the elderly.[1-4] It affects males and females, with a slightly greater prevalence rate in females. Although sarcoidosis has been reported in identical twins, it is not felt to be hereditary. In the US, prevalence rates vary from 1 to 40 per 100,000.[4, 9-10] Race and ethnicity have strong affects on prevalence rates.[9] Worldwide, in Caucasians prevalence rates average 10 per 100,000 with the highest rates in Northern Europe but none as high as found in African-Americans ranging from 35 to 64 cases per 100,000.[4-10] In the United States, prevalence rates range from 2.5 to 7.6 per 100,000 for Caucasian males and from 13.2 to 81.8 per 100,000 for African-American males.[4, 9-10] In New York City (NYC), prevalence rates may be as high as 17 per 100,000 for Caucasians and 64 per 100,000 for African Americans.[10] Without doubt, these published rates underestimate the true prevalence as most individuals are asymptomatic and remain undiagnosed unless chest radiography was performed. In fact, the highest prevalence rates are found in populations receiving mandatory chest radiographs as part of an occupational or tuberculosis screening program.

Because over 90% of sarcoidosis patients have lung involvement and most are asymptomatic, the typical clinical presentation is patients referred for evaluation of an abnormal chest radiograph that suggests sarcoidosis, but may less commonly be due to lymphoma or rarely tuberculosis. Patients may also present with symptoms related to the specific organ(s) involved[17,18], which for

the lung would be shortness of breath with or without cough. Sometimes these symptoms are not related to a specific organ and are termed "constitutional symptoms" such as fatigue, fever, and weight loss (with or without loss of appetite). When symptomatic, the clinical presentation is usually that of insidious onset over months to years but may also be acute in onset. When acute, patients may present with a classic constellation of symptoms called Lofgren's syndrome which includes: fever, swollen lymph nodes within the chest (bilateral hilar and mediastinal adenopathy), erythema nodosum (painful red bumps on the lower anterior legs) and arthritis (multiple joints but most commonly both ankles). Generally, acute disease has a good prognosis with spontaneous resolution being a frequent outcome. Chronic disease is found more often in symptomatic patients with insidious onset and multiorgan involvement. Exacerbations and relapses are more common in patients with chronic sarcoidosis and are typically treated with oral corticosteroids (see treatment section below).

How is the diagnosis of sarcoidosis confirmed? Laboratory test results can support the diagnostic impression but cannot confirm it. Such data includes: elevated lymphocytes in lung lavage fluid, elevated angiotensin converting enzyme (ACE) levels in the blood, positive gallium scan, or anergy (absence of skin sensitization to common allergens). It is generally recommended that patients with sarcoidosis have biopsy confirmation of their diagnosis. Transbronchial lung biopsy is usually the procedure of choice and yields a diagnosis in the majority of cases. Other options for obtaining tissue: biopsy of the mediastinal lymph nodes by mediastinoscopy, bronchoscopy or gastroesophageal endoscopy, video-assisted thoracoscopic lung biopsy, and rarely surgical open-lung biopsy. In some patients who have typical clinical and radiographic features and who have other organ involvement (ex. skin nodules, or eye, sinus or salivary gland symptoms), biopsies can be obtained less invasively from these extra-thoracic organs.

Chest radiographs in sarcoidosis are classified as Stage 0 through Stage IV.[19] It is important to realize that chest radiographic staging does not correspond to the chronologic progression of disease. Patients may present at any stage of radiographic disease. The term Stage 0 is reserved for the rare group who present with only extra-thoracic organ involvement and have a normal chest radiograph. This group has a low likelihood of disease progression. Stage I chest radiographs are the most common and show bilateral hilar and mediastinal adenopathy without obvious lung involvement (Figure 2-6.2). However, the majority of these patients do have microscopic lung involvement with positive diagnostic findings on transbronchial lung biopsies. Also the majority of these patients will demonstrate spontaneous resolution of their disease without relapse. Stage II radiographs show bilateral hilar and mediastinal adenopathy along with lung infiltrates and/or nodules (Figure 2-6.3). Stage III radiographs show lung infiltrates and/or nodules without hilar or mediastinal adenopathy (Figure 2-6.4). Although less likely than in Stage I, spontaneous remission may still be possible in Stage II and III disease. Stage IV radiographs show bilateral lung fibrosis (scarring) mostly in the upper and middle lobes of the lung (Figure 2-6.5). Once fibrosis is present, spontaneous remission can no longer occur and these patients have the worse prognosis.

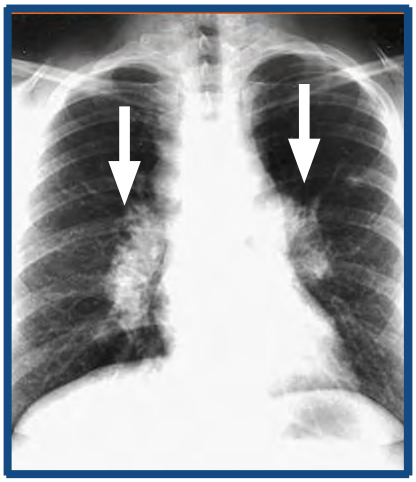

Figure 2-6.2: Chest radiograph of Stage I Sarcoidosis – enlarged lymph nodes (arrows)

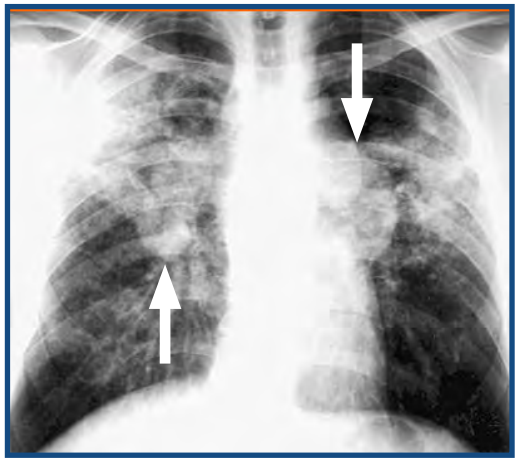

Figure 2-6.3: Chest radiograph of Stage II Sarcoidosis – enlarged lymph nodes (arrow pointing up) and involvement of lung tissue (arrow pointing down)

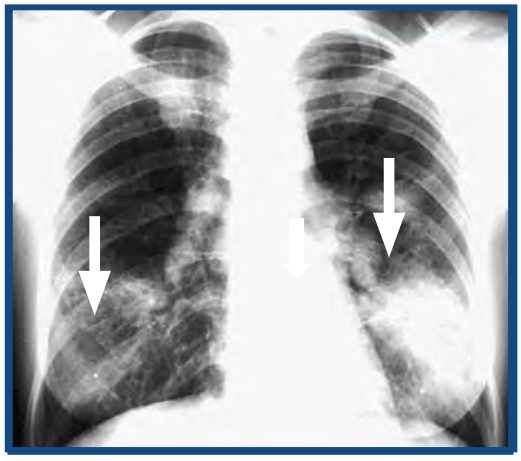

Figure 2-6.4: Chest radiograph of Stage III Sarcoidosis – involvement of lung tissue (arrows) without swollen lymph nodes

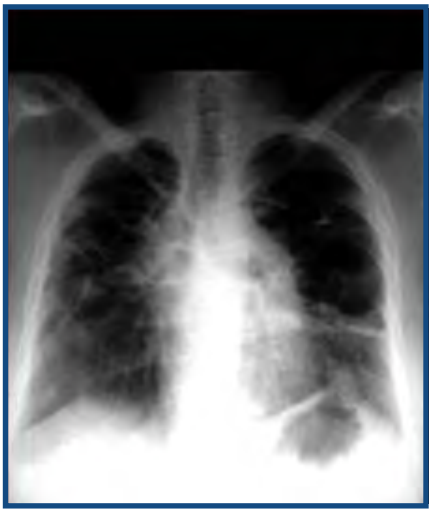

Figure 2-6.5: Chest radiograph showing Stage IV Sarcoidosis with fibrosis and cavities

The most common manifestation of pulmonary sarcoidosis is granulomatous involvement of lung tissue at the alveolar level.[1,17,18] This is where gas exchange occurs and once considerable involvement occurs, there are reductions in lung volumes, and oxygen diffusion from the alveolar membrane to the red blood cells becomes impaired leading to low oxygen levels in the blood (hypoxemia). Endobronchial involvement (granulomas in the airways) may also occur. Patients with endobronchial involvement have intractable cough and may have asthma-like disease with airflow limitation and wheezing. In contrast, necrotizing sarcoidosis is a rare form of the disease and refers to the presence of cavitation on radiographic imaging and necrosis with granulomatous vasculitis on pathology. Patients may be asymptomatic or may have nonspecific symptoms (fever, fatigue, and weight loss) and pulmonary symptoms (shortness of breath, cough and chest pain). Most patients respond to steroids. Other pulmonary manifestations include various forms of pleural disease, including pleural effusion (fluid between the lung and chest wall), pleural thickening, pleural nodules, and pneumothorax (rupture of the lung). High-resolution CT has improved the detection of pleural disease, especially pleural thickening and pleural nodules, which may be found in anywhere from 20 - 75% of patients. Effusions are less common and resolve spontaneously or with steroid therapy. Pneumothorax is an extremely rare complication.

Pulmonary function may be normal, even with stage I, II or III radiographic abnormalities, or may demonstrate restriction or obstruction, with or without abnormal gas exchange (reduction in oxygenation). The most frequent pulmonary function finding is normal function, but when abnormalities occur, they typically show a restrictive physiology with reduced lung volumes (the vital capacity and total lung capacity) and reduced gas exchange (diffusing capacity and oxygen saturation). In general, gas exchange abnormalities provide the best indication for the need for treatment (see below).

Although the lung is the most common site of involvement, it is not uncommon for other organs to be involved and in fact confidence in the diagnosis of sarcoidosis increases when extra-pulmonary involvement is found.[17,18] Skin involvement, occurs in about a quarter of patients, with the most common lesion being erythema nodosum on the anterior surface of the lower legs.

Other skin findings may occur and when necessary skin involvement can be proven by a skin punch biopsy done by a dermatologist. Eye involvement occurs in 10 - 80% of sarcoidosis patients. The most common presentation is uveitis and typical symptoms include pain, redness, photophobia (avoidance of light), and lacrimation (increased tears). Other eye problems include conjunctivitis, hemorrhage, cataracts, glaucoma, and retinal ischemia. Eye findings may be confused with another autoimmune disease – Sjogren's syndrome. Annual ophthalmologic evaluation is recommended as blindness is a rare but preventable complication.

Clinically significant cardiac involvement is rare but is difficult to diagnose. Unfortunately, the diagnosis is commonly made when a patient presents with sudden death from ventricular arrhythmias or complete heart block and this appears to have been the case in a recent National Institute for Occupational Safety and Health (NIOSH) fire fatality investigation.[20] For this reason, we recommend a cardiac evaluation in every patient, especially fire fighters, after sarcoidosis is first diagnosed. For fire fighters, we believe this should include an electrocardiogram and imaging at rest and stress. Electrocardiograms may show evidence of electrical conduction abnormalities and arrhythmias. Echocardiogram imaging may show evidence for cardiomyopathy (enlarged heart with abnormal function), dilation, decreased ejection fraction, or wall motion abnormalities. Radionuclide imaging studies (thallium, gallium, or technetium) and cardiac MRI may be even more accurate at revealing abnormalities.

Other organs are even less commonly involved but when inflamed may present with salivary and parotid gland enlargement, chronic rhinosinusitis, extra-thoracic adenopathy (cervical, axillary, epitrochlear, and inguinal areas), liver enlargement (hepatomegaly), spleen enlargement (splenomegaly), anemia, or arthritis. Neurologic involvement (central or peripheral) occurs in less than 10% of patients and if symptomatic may present with headaches, fatigue, unilateral facial nerve paralysis or muscle weakness. Endocrine or hormonal abnormalities are rare and may involve any endocrine gland, especially the pituitary gland. Abnormal calcium metabolism may result from increased vitamin D activation producing elevated calcium levels in the blood (hypercalcemia) and urine (hypercalcuria). Untreated, elevated calcium levels may lead to renal stones and eventually renal failure.

The clinical impact of sarcoidosis depends on which organs are involved and the extent of the granulomatous inflammation. Once the diagnosis is confirmed the patient should be evaluated as to the extent and severity of disease and then followed at regular intervals. Symptoms should prompt evaluation of the relevant organ(s) and treatment would be based on the severity of that involvement. Even if asymptomatic, all sarcoid patients should have their lungs, eyes, heart and calcium levels evaluated at the time of initial diagnosis and probably annually thereafter. This evaluation should include chest imaging (radiographs or CT), pulmonary function tests (flow rates, volumes, diffusion and oxygen levels), eye exam by an ophthalmologist, electrocardiogram (with cardiac imaging initially and when clinically indicated), and calcium levels (blood and urine).

Treatment of sarcoidosis is indicated when organ dysfunction is clinically significant.[1] Oral corticosteroids are first-line therapy. Inhaled corticosteroids

have little effect unless there are asthma-like symptoms. In sarcoidosis, oral corticosteroids are used to improve function of the involved organ (assessed by pulmonary function tests and oxygen levels) thereby, providing symptom relief and an improved quality of life while possibly preventing disease progression. However, these goals must be balanced by the potential for serious side effects from the long-term use of corticosteroids and the lack of certainty that disease progression can be influenced over the long-term. For this reason, it is not recommended to treat asymptomatic patients with minimal organ involvement (ex. patients with Stage 1 or Stage II radiographic sarcoid and normal pulmonary function tests). Indications for treatment with oral corticosteroids would include lung involvement with impaired gas exchange (reduced diffusion and hypoxemia), eye disease that has failed to improve with topical treatment, cardiac involvement (e.g., cardiomyopathy or serious arrhythmias), elevated calcium levels (blood or urine) with recurrent kidney stones or renal insufficiency; disfiguring skin lesions, severe platelet deficiency with bleeding, severe liver insufficiency, and/or incapacitating bone, muscle or neurologic involvement. A typical starting dose is 40 mg of prednisone, or its equivalent, daily or on alternate days. Patients are followed carefully and those with objective improvement begin to gradually and slowly taper or reduce their corticosteroid dose over the next 6 to 12 months to as low a level as tolerated without return of symptoms or organ dysfunction. Many patients will have a good clinical response and objective measures of improved organ function, allowing corticosteroids to be discontinued. Unfortunately, some have relapses requiring repeat corticosteroid treatment. In some patients, either during initial treatment or re-treatment with corticosteroids, side effects are intolerable or treatment response is inadequate. These patients qualify for second-line immunosuppressive drugs. Hydroxychloroquine is a first-line or second-line drug used when sarcoidosis is the cause of isolated skin, bone or calcium problems. Methotrexate is a second-line drug used alone or as a steroid-sparing agent. It may take up to six months to demonstrate a treatment effect. Recently, a new class of medication (TNF antagonists) has been used in patients unresponsive to steroids and methotrexate. Rarely, (approximately 1% of patients) develop severe life-threatening pulmonary disease (severe hypoxemia and pulmonary hypertension) despite aggressive use of immunosuppressive medications and may be candidates for lung transplantation.

Is the prevalence of sarcoidosis increased in fire fighters? Occupational clusters of sarcoidosis are not unknown and have been reported in nurses,[21] United States Navy enlisted men serving on aircraft carriers,[22,23,24] teachers,[25] automobile manufacturers,[25] retail industry workers,[25] and as previously mentioned beryllium workers.[16] In 1993, Kern was the first to report a cluster of three cases in fire fighters from Rhode Island.[26] In 1996, Prezant and co-workers reported an increased rate of sarcoidosis in fire fighters from the Fire Department City of New York (FDNY), the largest fire department in the world employing nearly 11,500 fire fighters and fire officers.[27] In 2006, using this previously published prevalence rate as a baseline, Prezant and coworkers reported an even higher rate of sarcoidosis in FDNY fire fighters exposed to World Trade Center Dust.[28]

Case ascertainment for the identification of FDNY fire fighters with sarcoidosis involved five pathways.[27,28] First, a chart review of all currently employed FDNY fire fighters was completed to identify fire fighters with sarcoidosis

prior to the start of our prospective study in 1985. Second, beginning in 1985, all FDNY fire fighters with signs or symptoms of pulmonary disease were referred to a pulmonary specialist at the FDNY Bureau of Health Services for prospective evaluation, database collection and when indicated, treatment. Third, all chest radiographs taken at FDNY were prospectively reviewed. This review was accomplished as follows: (a) all films were routinely interpreted by a board-certified radiologist without knowledge that a study was underway; and (b) if the radiographic findings as evaluated by the radiologist were abnormal, the chest radiograph was reviewed by our board-certified pulmonologist, who was aware that a pulmonary surveillance study (for all lung disease, not just sarcoidosis) was underway. FDNY fire fighters have a chest radiograph as part of their FDNY pre-employment evaluation and then on an average three-year cycle as part of their FDNY IAFF wellness medical evaluation. Fourth, all disability leave and retirement applications were reviewed for sarcoidosis cases. Finally, health and safety representatives of the unions representing FDNY fire fighters were told of this initiative and of our interest in evaluating fire fighters with sarcoidosis. In 1995 an additional group of FDNY Emergency Medical Services (EMS) healthcare workers (emergency medical technicians and paramedics) were included in the study. In 2001, disease surveillance for sarcoidosis continued under the auspices of the FDNY World Trade Center (WTC) Monitoring and Treatment Program.

Inclusion in this study required biopsy proven pathologic evidence of sterile non-caseating granulomas compatible with the diagnosis of sarcoidosis and no clinical or radiographic evidence of sarcoidosis prior to FDNY employment. To ensure the latter, an independent radiologist, without knowledge of the study or diagnosis in question, reviewed the pre-employment chest radiographs in suspected cases. Prior to 9/11/01, one fire fighter and one EMS HCW refused a biopsy and were excluded from the study. After 9/11/01, none refused biopsy. Pre- and post-9/11/01, the majority of biopsies were obtained by mediastinoscopy of intra-thoracic lymph nodes. Three cases suspected of occurring prior to FDNY employment were excluded from study.

Between 9/11/1985 and 9/10/2001, 22 FDNY fire fighters were diagnosed with granulomatous disease consistent with the diagnosis of sarcoidosis (Figure 2-6.6).[27,28] All 22 were male, one was African-American, one was an ex-smoker and none were EMS workers. The average number of new cases was two per year with a range of zero to five per year and the average annual incidence rate for FDNY rescue workers (fire fighters and EMS) was 14 cases per 100,000. 76% of the cases had Stage 0 or Stage 1 radiographic imaging. Although, shortness of breath on exertion was the most common symptom, (nearly 50% of the cases) it was mild and most had normal pulmonary functions. None had evidence for asthma or airway hyperreactivity on bronchodilator testing and cold air challenge testing, and only one had abnormal gas exchange with a reduced diffusion of oxygen. Three patients (14%) were treated with oral corticosteroids; two cases with shortness of breath and abnormal pulmonary function, and one case with joint aches and normal pulmonary function. After 12 to 18 months, all three fire fighters were off medication, asymptomatic, and returned to full fire fighter duties without further exacerbations.

After the WTC (between 09/11/01 and 09/11/06), 26 WTC-exposed FDNY rescue workers were diagnosed with granulomatous disease consistent with

the diagnosis of sarcoidosis (see Figure 2-6.6). One was female, two were African-American, two were ex-smokers and three were EMS workers. All 26 arrived at the WTC site within the first three days of the collapse. Thirteen patients presented in the first year post-WTC (9/11/01 to 9/10/02), one in the second year (2003), four in the third year (2004), four in the fourth year (2005) and four in the fifth year. Incidence rates were 86/100,000 exposed workers during the first 12 months post-WTC and then averaged 22/100,000 in the years thereafter as compared to 14/100,000 during the 15 years pre-WTC.[27,28] The annual incidence rate of sarcoidosis among FDNY rescue workers significantly increased in the five years post-WTC. Nearly identical increases in incidence rates were seen in patients whose diagnostic evaluation was initiated due to an abnormal chest radiograph as compared to those initiated due to symptoms. Although chest radiograph screening increased in the years immediately post-WTC, statistical analysis demonstrates that the increased incidence of sarcoidosis post-WTC did not result from the relative increase in the number of screening chest radiographs.

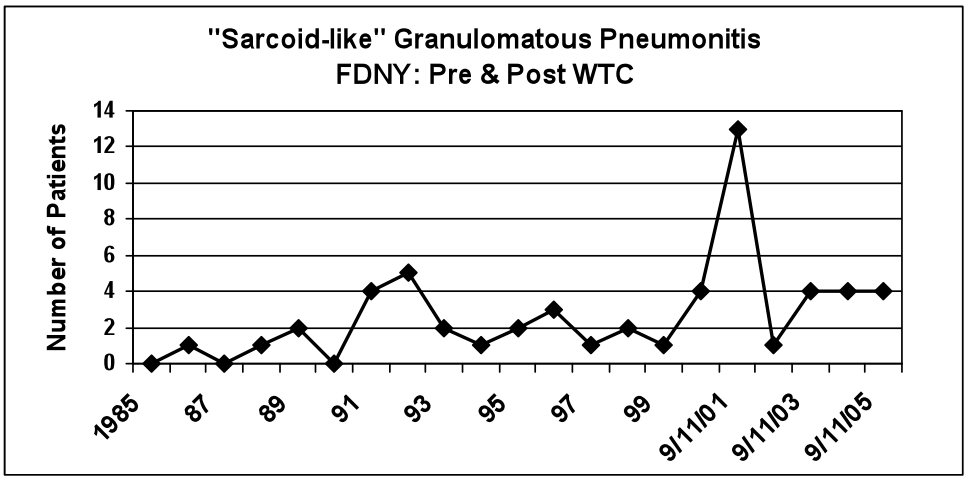

Figure 2-6.6: The number of cases of biopsy proven World Trade Center Sarcoid-like Granulomatous Pulmonary Disease (WTC-SLGPD) in the 5 years since 9/11/01 as compared to pre-WTC cases of sarcoidosis or SLGPD starting from 1985 in rescue workers from the Fire Department of the City of New York (FDNY).

After the WTC, the presentation shifted towards greater radiographic and clinical findings. Only 35% presented with Stage 0 or Stage I sarcoidosis on chest radiographic imaging. Asthma-like symptoms were now common, with nearly 70% reporting cough, shortness of breath, chest tightness and/or wheezing exacerbated by exercise/irritant exposure or improved by bronchodilators. Pulmonary functions confirmed reversible airways obstruction in at least a third of these cases. New-onset airway obstruction was evident on spirometry in four (15%) patients, two of whom had a bronchodilator response. Airway hyperreactivity was assessed in 21 of 26 patients by either methacholine or cold air challenge and positive results were found in eight (38%). Although the incidence rate for sarcoidosis returned to almost pre-9/11 levels after the first year, asthma rates remained similarly high in both those diagnosed within the first year post-WTC and those diagnosed in years two through five. What remained similar to pre-9/11 was that gas exchange abnormalities remained rare with abnormal diffusion of oxygen evident in only two patients (8%).

After the WTC, eight patients (31%) were treated with oral corticosteroids. During this study, 22 patients were diagnosed within the first four years post-

WTC and therefore had follow-up for at least one year. Pulmonary function improved in the two patients with abnormally low diffusion of oxygen (both treated with oral corticosteroids) and remained stable in the other 24 patients. Chest imaging abnormalities remained unchanged in 12 (two received oral corticosteroids), improved in four (two received oral corticosteroids), and resolved in six patients (two received oral corticosteroids). All 18 patients with asthma by any criteria were treated with inhaled steroids and bronchodilators, with subjective improvements in symptoms.

Increased incidence of sarcoidosis or of a sarcoid-like granulomatous pulmonary granulomatous disorder (SLGPD) within a large population shortly after experiencing an intense environmental inhalation exposure of any type has, to our knowledge, never been described. All 26 patients were present during the first 72 hours post-WTC collapse when respirable dust concentrations were at their highest. During this time period, most patients reported no mask use or "minimal" use of a "dust" or N95 mask and no patient reported wearing a P-100 respirator. That such an intense exposure post-WTC could shortly thereafter induce a pulmonary granulomatous reaction has previously been reported for a single case only.[29] Several additional cases of sarcoidosis or SLGPD have been observed in the WTC workers and volunteers cohort (non-FDNY) followed by the Mt. Sinai Medical Center – World Trade Center Clinical Consortium (personal communication, R. Herbert, MD) as well as in the NYC Department of Health's WTC Registry.

Should these post-9/11/01 cases be classified as sarcoidosis, inhalation induced SLGPD or hypersensitivity pneumonitis? None of our cases reported acute systemic symptoms (weight loss, fever, etc.) or exposures (ex. birds) typical of hypersensitivity pneumonitis. Nor were chest CT and biopsy findings typical of hypersensitivity pneumonitis. Bilateral hilar adenopathy is a rare finding in hypersensitivity pneumonitis. Over 400 substances have been identified in airborne and settled samples of WTC dust, many of which have been previously reported to be associated with sarcoidosis.[11-16] Future tests are planned to determine if beryllium sensitivity was present but it may be too late to determine the exact chemical, element or mixture responsible. Regardless, we believe that there is clear epidemiologic evidence for an association between sarcoidosis or SLGPD and firefighting and WTC dust exposure. These results will hopefully add new insight into the etiology of sarcoidosis as well as providing increased attention to the need for improved respiratory protection and surveillance following environmental/occupational exposures.

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Chapter 2-7
Pulmonary Fibrosis and Interstitial Lung Disease

By Dr. Robert Kaner, MD

PULMONARY FIBROSIS

Pulmonary fibrosis refers to a variety of conditions that result in scarring in the gas exchanging regions in the lungs.[1,2] There are a number of inhaled environmental agents that can cause pulmonary fibrosis; which is the end result of chronic lung inflammation. In addition, there are lung diseases of unknown cause that result in pulmonary fibrosis. While epidemiologic studies have not shown an increased incidence of pulmonary fibrosis in fire fighters, this topic is of interest to fire fighters because of their potential to inhale smoke as well as industrial substances such as insulation particles and chemicals that may become airborne during fires and explosions. The key concept is that environmental exposure to potentially-fibrogenic substances can largely be prevented through the appropriate use of properly fitting respirators.

In order to understand how and where pulmonary fibrosis occurs, it is necessary to describe some basic facts about the organization of the lung. The lung is composed of a number of different types of structures that serve different functions. Inhaled substances pass through the upper airway, vocal cords and larynx prior to traveling through the branching tubes that make up the bronchial tree. The airways terminate in the tiniest passages that lead into the alveoli, the gas exchanging units of the lung. In the alveoli, the pulmonary capillaries (the smallest caliber blood vessels) run directly adjacent to the alveolar air sacs, allowing for the efficient exchange of oxygen and carbon dioxide between blood and air. Scar tissue can form in the walls of the alveoli or in the airspaces of the alveoli or both. The extremely thin space in between the alveolar wall and the capillary is called the interstitium. This interstitial space becomes dramatically widened by inflammatory cells and the deposition of scar tissue, hence the broad category of this class of lung problems is termed 'interstitial lung disease'.

Major Categories of Interstitial Lung Disease and Pulmonary Fibrosis

The major environmental agents that are implicated in occupational pulmonary fibrosis include inhalation of industrial dusts such as asbestos fibers, silica (from sandblasting) and coal dust from mining. Many other substances have been linked to the development of pulmonary fibrosis in humans and animal models including fiberglass, mica and industrial dusts from refining of organic

products like cotton. The key characteristic shared by all particles that can cause pulmonary fibrosis is the size of the particles. If the particles are larger than three microns in length they tend to deposit in the nose, throat and large airways of the lung. Smaller particles are increasingly likely to be deposited in the terminal airways or alveoli, where they can cause inflammation and subsequent scarring, leading to interstitial lung disease and fibrosis. In general, single short exposures are much less likely to cause fibrosis than repeated daily exposures over years. Of asbestos workers developing asbestosis (interstitial lung disease due to asbestos) half have had >20 years of exposure. However, many cases have occurred in workers with <10 years of exposure. The prevalence of asbestosis in asbestos-exposed workers worldwide ranges from 3% to >20% depending upon if they were engaged in the manufacture of cement products containing asbestos, mining and milling of asbestos (highest prevalence) or manufacture of asbestos fiber or rope. In the US, common occupational exposures occurred in shipyard workers who sprayed asbestos insulation on the surfaces of the holds of ships in naval shipyards, as well as those working in the same work environment. Other occupational exposures included grinding brake linings, which formerly contained asbestos and may still be present in old and replacement brake pads and clutch plates. The particles must be airborne in order to cause disease, so intact insulation that is not degraded in some way does not represent a true risk of asbestos exposure until the integrity of the sealed substance is compromised during maintenance or removal activities that lead to the airborne release of asbestos fibers. Of note, fibers that are brought home on the surface of clothing can become airborne again when the clothing is handled, leading to exposure of family members. Asbestosis is of particular concern to fire fighters due to their potential exposure to insulation containing asbestos that was used in residential homes. Asbestos can still be found in floor and ceiling tiles, shingles, flashing and siding, pipe cement, plasters and joint compounds, all of which could become damaged and airborne during a fire. For further information on the health consequences of asbestos exposure, see the Chapter on Asbestos-Related Lung Disease.

Another common type of interstitial lung disease that can progress to pulmonary fibrosis is a condition termed hypersensitivity pneumonitis or extrinsic allergic alveolitis. This disease is mediated by an immunologic response in the lung to an inhaled organic antigen. Hundreds of types of organic antigens have been implicated. The most common types are due to ongoing exposure to birds such as parakeets or pigeons (bird fancier's lung). The offending antigens are proteins present in the bird droppings that become aerosolized. Another common cause of hypersensitivity pneumonitis is exposure to mold, as in moldy hay (farmer's lung).

There are other types of chronic inflammatory lung disease of unknown cause that sometimes lead to fibrosis such as sarcoidosis. Sarcoidosis causes a specific pattern of inflammation that the pathologist recognizes as a granuloma, composed of activated macrophages (also called epithelioid giant cells) surrounded by lymphocytes in a spherical configuration. This disease is characterized by spontaneous remissions and exacerbations. A small minority of individuals with sarcoidosis will progress to irreversible pulmonary fibrosis. See the Chapter on Sarcoidosis for further information on this subject.

There are systemic connective tissue diseases associated with pulmonary fibrosis, such as rheumatoid arthritis and scleroderma. Usually the joint or skin disease is present for a long time before lung involvement occurs, but rarely, the lung disease can be the initial manifestation of these systemic disorders. These generally have a somewhat better prognosis than idiopathic pulmonary fibrosis, a condition of unknown cause.

Pulmonary fibrosis can also occur as a complication of certain types of chemotherapy prescribed for cancer treatment. The best known example is bleomycin, a drug used to treat lymphoma and testicular cancer. This drug reproducibly causes pulmonary fibrosis in certain strains of laboratory mice, so is used as a standard animal model for research on pulmonary fibrosis. Another commonly-used cancer treatment, carmustine (BCNU), used to treat brain tumors can cause pulmonary fibrosis as late as decades after it is administered. Interstitial lung disease, which may be a consequence of prior chemotherapy, radiotherapy, graft versus host disease and acute lung injury, is also a complication of hematopoietic (bone marrow) transplantation.

Another commonly-employed cancer treatment, external beam radiation therapy, can cause radiation pneumonitis and fibrosis in a minority of individuals. The acute symptoms may begin within several weeks following radiation to the chest for treatment of lung cancer, breast cancer or lymphoma. Fibrosis may occur months to years later.

The remaining types of interstitial lung disease are termed 'idiopathic', meaning having no known cause. The most common types of idiopathic interstitial lung disease are termed idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. Another common disorder is termed cryptogenic organizing pneumonia. The reason that an accurate diagnosis of the specific type of interstitial lung disease should be made is that the prognosis and potential for response to treatment as well as the dose and duration of treatment recommended is dependent upon the specific diagnosis.

Cryptogenic organizing pneumonia is an inflammatory disorder that follows a viral infection and a variety of other acute insults to the lung. Its importance is that it may often be confused with bacterial pneumonia, but responds readily to treatment with systemic steroids.

In contrast, idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia are generally diseases of much longer duration where symptoms may occur for months to years prior to a diagnosis. Of note, in a small minority of cases, idiopathic pulmonary fibrosis occurs in families. The genetics of the predisposition to develop idiopathic pulmonary fibrosis in both the familial and non-familial forms are only beginning to be understood.

Symptoms of Pulmonary Fibrosis

The main symptoms of pulmonary fibrosis are shortness of breath and frequent cough. The shortness of breath is usually only with exertion until the disease is very advanced. The cough is usually dry, without production of sputum. A minority of individuals will develop clubbing, a specific change in the soft tissue structure of the distal parts of the fingers that leads to widening of the end of the finger just after the last finger joint and a change in the angle that the nail-bed makes with surface of the finger. None of the symptoms and

signs are specific for interstitial lung disease and/or pulmonary fibrosis, so a careful diagnosis is necessary to distinguish these from other types of medical problems that can affect the chest. Swelling of the feet and legs may occur in advanced pulmonary fibrosis as explained below.

Individuals with chronic interstitial lung disease and pulmonary fibrosis typically have symptoms for months to years before a diagnosis is made. Patients with this disease generally report a very gradual onset and progression of shortness of breath noted when exerting themselves. Sometime the interstitial disease is discovered accidentally when imaging of the chest is done for another reason. Often the individual is admitted to the hospital for "pneumonia" and only in retrospect is it apparent that interstitial lung disease is the underlying problem.

A very small minority of individuals will present with an acute illness lasting for only a few weeks with rapidly progressive, interstitial lung disease. Biopsy of the lungs of these individuals shows a pattern that the pathologist calls diffuse alveolar damage which is the morphologic equivalent of acute lung injury or adult respiratory distress syndrome with or without evidence of a more chronic background process of interstitial lung disease. Usually no underlying cause for this illness is determined, which is then termed acute interstitial pneumonia. The disease has a significant mortality, particularly in individuals who develop respiratory failure of sufficient degree to require mechanical ventilation.

Individuals with idiopathic pulmonary fibrosis are also susceptible to acute lung injury superimposed upon their underlying pattern of inflammation and scarring. This acute lung injury has been termed acute exacerbation of idiopathic pulmonary fibrosis. Its cause is unknown. Radiographically it appears a pattern of new ground glass opacities superimposed upon a background of chronic interstitial changes and pulmonary fibrosis. In this context, 'ground glass' does NOT mean actual inhaled glass. Rather, it is a radiology term based on the visual impression that the chest image is hazy as if the glass screen in which they view the chest film has lots of scratches or grindings on it. A ground glass appearance is actually the result of non-specific inflammation of the lung tissues.

Hypersensitivity pneumonitis may present early in the course as acute attacks of cough and shortness of breath that occur within several hours after acute exposure to the inhaled antigen, which gradually resolve over time. A clue to the diagnosis is that the symptoms may disappear when the individual is removed from the offending antigen, as when taking a prolonged trip, only to recur on returning home. Symptoms linked to a specific place such as work, with improvement or worsening when away from work, may also provide a clue to the diagnosis. Hypersensitivity pneumonitis that has progressed to advanced fibrosis can be difficult to distinguish from idiopathic pulmonary fibrosis.

Physiologic Consequences of Interstitial Lung Disease and Pulmonary Fibrosis

The interstitial and intra-alveolar inflammation and scarring directly impairs the lungs' ability to oxygenate the red blood cells. As a result, the oxygen saturation may drop, particularly with exercise. Exercise-induced shortness of breath occurs as a result of the impairment of gas exchange and the increased

demands placed upon the heart, since a compensatory increase in heart rate will occur at much lower levels of exercise than in individuals with normal lungs. Oxygenation of the blood may remain normal at rest until the disease is far advanced. Some types of exercise are more demanding in this regard than others. Stair and hill climbing, particularly while carrying heavy objects, are often the first noticeable symptoms of the disease.

When pulmonary fibrosis progresses to an advanced stage, pulmonary hypertension may develop. This means the pressure in the system of blood vessels supplied by blood flow from the right-side of the heart to the vessels in the lungs may increase, particularly during exercise. If the average pulmonary arterial pressure exceeds 30 mm Hg (35 mm Hg with exercise), then pulmonary hypertension is said to be present. As pulmonary hypertension progresses, it can lead to right-sided heart enlargement and right heart failure. One of the major symptoms of right heart failure is swelling of the feet, ankles and legs. A large study sponsored by National Institutes of Health (NIH) is underway to address the issue of whether treating pulmonary hypertension in idiopathic pulmonary fibrosis will result in improvement in exercise capacity.

If the fibrosis progresses to a point where respiratory failure occurs, death is the usual outcome.

Diagnosis of Pulmonary Fibrosis

The key elements of diagnosis of pulmonary fibrosis are the history, physical examination, pulmonary function tests and chest CT scan and lung biopsy.[3] The chest CT should preferably be done with high resolution imaging techniques including inspiratory and expiratory views. Intravenous contrast does not aid in the diagnosis of interstitial lung disease, but can be very useful for diagnosis of pulmonary emboli.[3] The high resolution chest CT has become the gold standard imaging study to aid in the diagnosis of interstitial lung disease and pulmonary fibrosis and is mandatory in nearly all cases (Figure 2-7.1).

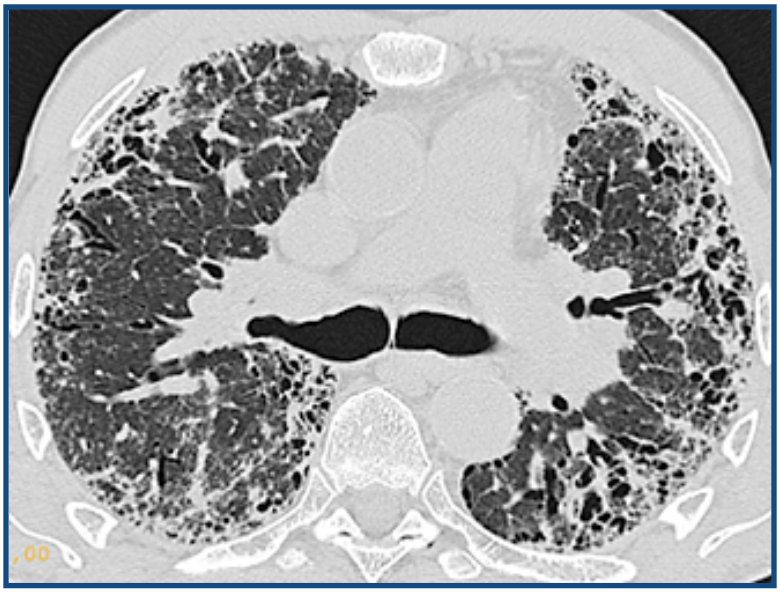

Figure 2-7.1: Pulmonary Fibrosis

Certain features of the high-resolution chest CT may support a specific diagnosis of interstitial lung disease or suggest alternatives. The overall pattern of disease is very important in the classification. Certain diseases such as sarcoidosis and hypersensitivity pneumonitis tend to have the abnormalities distributed in a pattern that corresponds to bronchovascular bundles, the conglomeration of airways and attendant blood vessels and lymphatics. Hypersensitivity pneumonitis often is skewed toward a more upper-lobe distribution. In sharp contrast, idiopathic pulmonary fibrosis has a characteristic basilar (lower lung) distribution of disease. Pulmonary fibrosis appears on the CT scan as 'reticular', a type of abnormality characterized as increased relatively linear thin white lines. Active inflammation tends to cause a more dense and coarse increase in radiodensity appearing as nonlinear patchy areas of increased white attenuation on the chest CT which may fill in alveolar spaces completely and can be referred to as 'ground glass opacities'. Ground glass opacities are characteristically seen in hypersensitivity pneumonitis, nonspecific interstitial pneumonia and during the acute exacerbation phase of idiopathic pulmonary fibrosis. More dense consolidation is often indicative of infection or cryptogenic organizing pneumonia. Advanced disease may be described as honeycombing due to its resemblance to the internal wax structure of a beehive. This finding when pronounced may add to the probability of the underlying disease process being idiopathic pulmonary fibrosis. Another finding known as traction bronchiectasis refers to the enlargement of airways in the periphery of the lung that are being tethered open by the centripetal forces exerted when extensive scarring occurs in the substance of the lung tissue.

Radionuclide scanning with isotopes such as radioactively tagged gallium can be useful to demonstrate active lung inflammation. Gallium is injected into the patient's vein, after which a scan of the chest is done to assess the distribution of the gallium within the lung. Areas of inflammation "light up" on the scan; but this test lacks specificity.

Pulmonary function tests show a restrictive pattern, which means that measured lung volumes and rates of airflow from the lung on forced expiration are both reduced. The diffusing capacity, a test measuring the ability of gases to transfer from the atmosphere into the bloodstream, is usually reduced, even prior to the development of restriction.

In the majority of cases, a surgical lung biopsy is required to obtain sufficient lung tissue so that a specific diagnosis may be rendered.[3] Generally this biopsy requires general anesthesia and can be obtained via video-assisted thoracoscopy, where three tiny incisions are made in the chest wall, through which the thoracic surgeon can insert a fiberoptic camera and tools to perform the biopsies (Figure 2-7.2). The procedure is safe for most people but can sometimes be obviated if the chest CT is diagnostic for a specific entity such as what is known as usual interstitial pneumonia. It is often not recommended to individuals who have increased risk for surgical procedures due to other medical conditions.

Specific pathological findings are seen in the surgical lung biopsy specimens obtained from individuals with idiopathic interstitial lung diseases. Cryptogenic organizing pneumonia shows marked inflammation in the alveolar spaces along with plugs of fresh fibrous connective tissue extending into the lumen of small airways. Usual interstitial pneumonia, the histologic correlate of

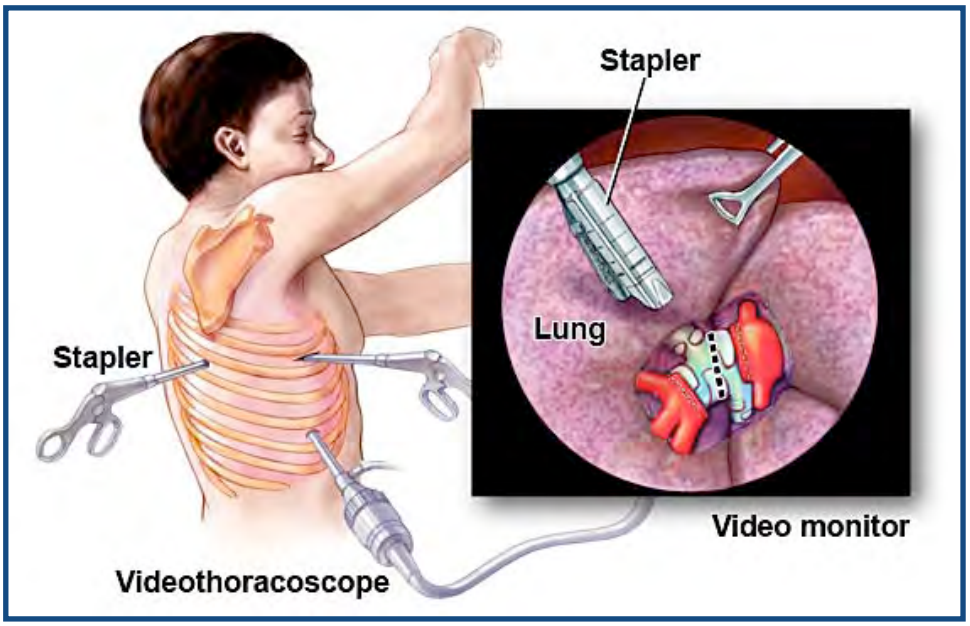

Figure 2-7.2: Video-assisted thoracoscopic surgery (VATS)

idiopathic pulmonary fibrosis, is characterized by dense fibrosis that has a subpleural distribution. In the subpleural region, a distinctive finding known as fibroblastic foci composed of ball-like structures of accumulating fibroblasts and myofibroblasts, the fibrosis-producing cells, are frequently present. There are typically very localized areas of very diseased lung immediately adjacent to relatively normal-appearing lung, a feature pathologists describe as temporal heterogeneity. There is microscopic honeycombing corresponding to the honeycomb change visible on high resolution chest CT. In contrast, the distribution of disease is much more uniform in nonspecific interstitial pneumonia. It also lacks the temporal heterogeneity characteristic of usual interstitial pneumonia. The degree of inflammation in nonspecific interstitial pneumonia tends to be more pronounced, although subtypes without much inflammation have also been described.

Fiberoptic bronchoscopy, a procedure performed by medical pulmonary physicians with the patient under moderate sedation, generally cannot provide an adequate amount of tissue for diagnosis of interstitial lung disease. However, there are important exceptions which include sarcoidosis, where the yield of transbronchial biopsy is over 90%. Sometimes hypersensitivity pneumonitis can be diagnosed via transbronchial biopsy. Bronchoscopy is a good tool for the diagnosis of many lung infections and is often used first when infection is suspected to avoid the need for general anesthesia and surgery.

In short, the definitive diagnosis of interstitial lung disease depends on a multidisciplinary approach between clinicians, radiologists and pathologists who have expertise in these types of disorders, working together to consider all of the relevant information to come to a diagnostic conclusion.

Prognosis

The prognosis in interstitial lung disease and pulmonary fibrosis depends upon an accurate diagnosis of the underlying disease process. The prognosis is different for the fiber and dust-induced fibrosis as opposed to the interstitial

lung diseases without a known cause. Within the lung diseases without a known cause, the prognosis is different in idiopathic pulmonary fibrosis as compared with nonspecific interstitial pneumonia. Individuals with idiopathic pulmonary fibrosis have a survival rate of three to five years, whereas the survival rate in nonspecific interstitial pneumonia is > 10 years. Connective tissue disease-related interstitial lung disease also tends to have a better prognosis than the idiopathic types.

Certain findings are known to correlate with a worse prognosis. Severe pulmonary function test abnormalities, particularly if progressive, carry a worse prognosis, regardless of the underlying cause. The development of right-sided heart failure indicates far advanced disease. Oxygenation generally worsens as the disease progresses.

Available Treatment

The treatment of interstitial lung disease and pulmonary fibrosis depends upon the specific diagnosis.[4] For idiopathic interstitial lung diseases and those due to connective tissue diseases, if treatment is recommended, it usually includes systemic steroids such as prednisone. There is no evidence that inhaled medications have any significant effects in these disorders. Idiopathic pulmonary fibrosis in particular has no proven therapy and for which there is no FDA-approved drug. Anti-inflammatory immunosuppressive drugs such as azathioprine (Imuran®), cyclophosphamide (Cytoxan®) or mycophenolate mofetil (Cellcept®) are often added to or substituted for prednisone. These drugs have numerous significant side effects, not the least of which is increased susceptibility to infection. Any decision to begin any such supportive treatment must balance the potential benefit against the potential side effects of these medications.

A large prospective randomized trial of an antioxidant N-acetylcysteine (NAC) is about to begin under sponsorship of the NIH. This study will compare treatment with NAC with and without concomitant prednisone and azathioprine therapy and will include a control group with all placebos. This study will follow up on a European study showing better preservation of lung function in individuals with idiopathic pulmonary fibrosis (IPF) treated with the combination of prednisone, azathioprine and NAC compared with prednisone and azathioprine alone. The rationale for the use of NAC, is that it is metabolized in the body to glutathione, an important antioxidant that is depleted in the epithelial lining fluid of individuals with IPF. Oxygen-free radicals and their metabolites may exacerbate the injury to the alveolar epithelial cells that is part of the current understanding of IPF pathophysiology. It is expected that this study will determine the standard of care for newly diagnosed IPF.

In contrast, nonspecific interstitial pneumonia generally responds favorably to prednisone therapy. After the initial response, the medication dose is tapered over the course of months. If the disease worsens, the steroid dose is increased. The immunosuppressive drugs may be added as steroid-sparing agents in individuals intolerant of prednisone. Fibrosis due to hypersensitivity pneumonitis is best treated by removal of the individual from exposure to the offending antigen. A short course of prednisone is often helpful in treating shortness of breath and/or cough.

Chemotherapy-induced pulmonary toxicity is usually treated with steroids

if the individual is symptomatic with shortness of breath or cough. The steroids are tapered over the course of weeks to months. If fibrosis is discovered years after chemotherapy, treatment is ineffective.

For occupational and environmentally-induced fibrotic lung diseases due to inorganic dusts such as asbestos, there is no effective treatment; however supportive therapy that can be offered to individuals affected by these lung diseases Supplemental oxygen is prescribed for individuals whose oxygen saturation is below 88% either at rest or with exercise. While it does not alter prognosis, it can relieve symptoms and improve exercise tolerance.

Pulmonary rehabilitation, including dieting where weight loss is indicated, is recommended for individuals with significant exercise limitation, as it positively impacts performance regardless of the nature of the underlying lung process. It is mandatory for individuals being considered for lung transplantation.

For individuals with any type of interstitial lung disease or pulmonary fibrosis whose disease progresses to the advanced stage, lung transplantation may be the best option for those who qualify. Idiopathic pulmonary fibrosis is now the most common indication for which lung transplant is performed. Since the pre-transplant evaluation is very extensive and time consuming and donor lungs are in short supply, individuals who may require transplant in the future are encouraged to begin the evaluation process long before the transplant becomes necessary.

Prevention of Pulmonary Fibrosis

Pulmonary fibrosis due to occupational or environmental exposures is clearly preventable via the use of appropriate precautions such as the use of respirators when these agents are airborne at significant concentrations. During the fighting of an actual fire, the self-contained breathing apparatus (SCBA) worn by most fire fighters, if functioning and worn properly, will constitute adequate protection. In the absence of a SCBA, the minimal protection required when there is the possibility of environmental dust exposure is a NIOSH certified P-100 disposable filtering facepiece respirator (99.9% filtration of 0.3 micron particles) (Figure 2-7.3) or a NIOSH-certified respirator with a higher level of respiratory protection, including a full-facepiece or half-facepiece air purifying respirator (APR) (Figure 2-7.4) or powered air-purifying respirator (PAPR) with a HEPA filter/canister (Figure 2-7.5).

Figure 2-7.3: NIOSH-Certified P-100 Filtering Facepiece Respirator

Figure 2-7.4: NIOSH-Certified APR with a HEPA Filter

Figure 2-7.5: NIOSH-Certified PAPR

An APR or PAPR will not protect against gases and chemicals unless it is fitted with cartridge(s) or canister specifically designed and approved for this purpose. Further, a P-100 respirator provides the highest levels of particulate or aerosol protection as compared to other filtering facepiece respirators such as the N-95 or N-99. Additionally, the P-100 is a disposable respirator and should be properly disposed of after each use where an exposure occurred. The P-100 must have seal-enhancing elastomeric components (e.g. rubber or plastic respirator-to-face seals) and must be equipped with two or more adjustable suspension straps. Without these components, it is very difficult to obtain and/or maintain a face seal so as to protect the wearer.

Respirators that do not properly seal or do not fit will offer no respiratory protection. All respirator use must be administered as part of a comprehensive Respiratory Protection Program (RPP), according to the Occupational Safety and Health Administration (OSHA). The RPP contains mandatory provisions for training respirator users, selecting and maintaining respirator equipment, conducting fit checks and conducting fit tests.

Increased Risk to Fire Fighters

Increased occupational risk of interstitial lung disease and pulmonary fibrosis in fire fighters has not been demonstrated in large epidemiologic studies involving thousands of fire fighters, the largest of which studied over 10,000 individuals. These findings have been confirmed by large independent studies in several different countries. Two studies have reported an increased incidence of sarcoidosis in fire fighters pre- and post-World Trade Center (WTC).[5,6] Whether this represents a true occupational risk of fire fighters has not been definitively established. However, there is concern that fire fighters and rescue workers in certain types of large disasters may be at risk for interstitial lung disease.

Relationship to World Trade Center Exposure

Concern exists about the potential for the development of pulmonary fibrosis in those individuals that were exposed at the WTC on and after September 11, 2001. This is due to the possibility that there may have been asbestos in the air during the first three days following the disaster; the increased level of particles in the air small enough to reach the airspaces of the lung; and the measurement of various building materials known to be associated with pulmonary fibrosis, especially with the abnormal alkalinity of these particles. To date, while many other types of respiratory abnormalities have been documented, no cases of pulmonary fibrosis have yet been reported in the peer-reviewed medical literature, but several have been noted anecdotally in the lay-press. There have been several case reports of hypersensitivity-like disease. This does not preclude the possibility that cases of pulmonary fibrosis may be identified in the future. Whether or not this occurs, first responders must be prepared to reduce the possibility of significant environmental exposure to inhaled fibrosis-inducing agents by properly wearing appropriately selected respiratory protection during firefighting or rescue efforts.

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Chapter 2-8
Pulmonary Vascular Diseases

By Dr. Alpana Chandra MD, Dr. Amgad Abdu MD, and Dr. Andrew Berman, MD

The two sides of the heart have distinct functions. The right side of the heart receives venous blood from the body and then pumps it into the pulmonary circulation to pick up oxygen from the lungs. The oxygenated blood then drains into the left sided chambers of the heart that pump it through the body with each heart beat, providing energy to the organs of the body. Pressure in the left side of the heart is routinely measured as one's blood pressure, and when it is elevated, we refer to this as systemic hypertension. When resistance in the pulmonary circulation circuit rises, pressure on the right side of the heart can rise and when this occurs, pulmonary hypertension results. In another condition known as pulmonary embolism, one or more blood clots travel to the lung where they eventually stop and cut off blood flow to part of the pulmonary circulation. These two diseases of the pulmonary vasculature will be the focus of this chapter. In addition, fluid accumulation in the air spaces of the lung, or pulmonary edema, will also be discussed.

PULMONARY HYPERTENSION (PH)

The pulmonary circulation is ordinarily a low resistance circuit between the left and right chambers of the heart. However, diseases involving the pulmonary vasculature can cause an increase in resistance in this circuit leading to an increase in pressure of the pulmonary artery, the large blood vessel conducting blood from the right side of the heart to the lungs. Pulmonary hypertension is defined as a clinical condition characterized by persistent elevation in the pressure of the main pulmonary artery. While less common than systemic hypertension, PH is a life-threatening disorder. Despite our increasing understanding of this condition, its cause remains unknown.

Pathology

The blood supply for the right lung and the left lung mostly comes from the pulmonary artery which branches into two large arteries supplying the respective lungs. Inside the lung, each pulmonary artery accompanies the appropriate bronchus or airway and continues to divide into smaller branches down to the level of small arterioles and finally capillaries, which are positioned around the air sac or alveolus. Gas exchange takes place here such that oxygen is transferred from the air in the alveolus to the blood in the capillary. The oxygenated blood then passes into the post capillary venules, which join up to form larger veins that finally form the pulmonary veins draining into the left chambers of the

heart. Pulmonary hypertension is the result of pathology or injury in any of these areas, and is often characterized by excessive muscularization of the small arteries (medial hypertrophy), scarring, inflammation and narrowing of the blood vessels (vasoconstriction).[1] In some cases there might also be blockage of these small arterioles with blood clots.

Epidemiology

PH affects over 25 million individuals worldwide and causes premature disability and death for many.[2] It is a deadly disease and the estimated median survival from the time of diagnosis is about 2.8 years. Time to death however varies widely among patients, with some dying within months of diagnosis and others living with the condition for decades. Underlying etiology may influence survival as those with PH related to congenital heart disease may live longer than patients with other underlying etiologies.

Etiology

This condition was previously designated as Primary Pulmonary Hypertension (PPH) in the absence of any demonstrable cause, and as secondary pulmonary hypertension, if otherwise. It is not surprising that as our diagnostic capabilities have increased, many cases of pulmonary hypertension originally designated as 'primary' are now considered "secondary". Infrequently, pulmonary hypertension has also been found to run in families. The standard classification of pulmonary hypertension is now etiology-based, and is reviewed in Table 2-8.1.

Idiopathic (or "unknown cause") pulmonary arterial hypertension (IPAH) is most commonly a disease of young adults with a peak incidence in the third and fourth decades of life. It is also more common in women as compared to men, especially in women of childbearing age. IPAH can only be diagnosed after all other causes are excluded.

Pulmonary hypertension can result from heart disease. If the left side of the heart is not functioning optimally, the system can essentially get backed-up. Pressure can build up in the pulmonary circulation due to troubles pumping the blood out of the left heart chambers, which occurs in a condition called congestive heart failure. Certain types of congenital heart disease can also result in PH.

Pulmonary hypertension often occurs in the setting of chronic lung disease. Patients with emphysema/COPD or pulmonary fibrosis may develop elevated right heart pressures due to periods of low oxygen. Similarly, patients with sleep apnea can develop PH due to the fall in oxygen that occurs when patients stop breathing during sleep.

Occlusion in the pulmonary vessels due to chronic thrombotic/embolic disease is another category and is usually due to blood clots but may also be caused by tumor cells. The incidence of PH due to chronic thrombotic/embolic disease is approximately three to four percent after acute pulmonary embolism.

Standard Classification of Pulmonary Hypertension
I - Pulmonary Artery Hypertension
• Idiopathic Pulmonary Artery Hypertension (IPAH) • Familial Pulmonary Artery Hypertension (FPAH) • Collagenital systemic to pulmonary shunts (large, small, repaired or nonrepaired)) • Portal hypertension • HIV infection • Drugs and toxins • Other (glycogen storage disease, gaucher disease, hereditary hemorrhagic teleangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
II - Associated with significant venous or capillary involvement
• Pulmonary veno-occlusive disease • Pulmonary capillary hemangiomatosis • Pulmonary venous hypertension • Left-sided atrial or ventricular heart disease • Left-sided valvular heart disease
III - Pulmonary hypertension associated with hypoxemia
• COPD • Interstitial lung disease • Sleep-disordered breathing • Alveolar hypoventilation disorders • Chronic exposure to high altitude
IV - PH due to chronic thrombotic and/or embolic disease
• Thromboembolic obstruction of proximal pulmonary arteries • Thromboembolic obstruction of distal pulmonary arteries • Pulmonary embolism (tumor, parasites, foreign material)
V - Miscellaneous
• Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Table 2-8.1: Standard Classification of Pulmonary Hypertension

PH can also result from diseases outside the lung. Autoimmune disorders, specifically collagen vascular diseases, are associated with the development of PH. Such diseases include scleroderma, systemic lupus erythematosis (also referred to as SLE or "lupus") and rheumatoid arthritis. In patients with liver cirrhosis, 2 - 10% may develop a form of PH indistinguishable from IPAH pathologically. Since the 1980s, increasing numbers of cases of pulmonary hypertension associated with HIV have been reported in literature, although a cause and effect relationship has not been perfectly established.

Pulmonary hypertension can also be a complication of certain drugs or dietary supplements. The relationship between drug ingestion and development of pulmonary hypertension was first raised in the late 1960s when there was an epidemic of unexplained pulmonary hypertension in the users of an appetite

suppressant drug, amironex fumarate, reported out of Switzerland, Austria and Germany. Some commonly used diabetes medications, which have since been withdrawn from the market, have also been linked with causing the disease. In 1981 severe pulmonary hypertension developed in a large number of people in Spain who ingested rapeseed oil intended for industrial use but which had been sold as cooking oil. More recently, chronic pulmonary hypertension has been associated with the use of products containing L-tryptophan, a common dietary supplement.

Signs and Symptoms

Signs and symptoms of PH are non-specific and are frequently attributed to other diseases that can lead to a delay in diagnosis. The most common symptom is shortness of breath with exertion. Chest pain and easy fatigability are also commonly reported. Ten percent of patients, more often women, might also report a painful, bluish discoloration of their fingertips (Raynaud's phenomenon). Infrequently patients report hoarseness of voice or blood streaked sputum. Fainting and leg swelling may develop later on in the course of the disease. The mean time between onset of symptoms and diagnosis is 27 months.

On physical examination, the usual second sound of the heart beat is louder than the first, due to the loud closure of the pulmonic valve in the setting of elevated right heart pressures. A murmur may be heard along the border of the chest bone during systole or contraction phase of the heart. As the disease progresses, signs of heart failure like liver enlargement and fluid retention may occur.

Classification

The degree of symptoms and functional abilities determines the functional class of the disease, which has been outlined by the World Health Organization. Class I patients do not have symptoms or limitations of activity. Class II patients are comfortable at rest, but are slightly limited in physical activity, and may experience dyspnea or fatigue, chest pain, or near syncope. Class III patients are marked limited in their ability to perform physical activity. Like Class II patients, they are comfortable at rest, but now experience symptoms at less than ordinary activity. Class IV patients are unable to perform any physical activity without experiencing symptoms, and may have shortness of breath at rest.

Diagnostic Testing

A variety of diagnostic tests may be incorporated into the evaluation of a patient with PH. Although not a very sensitive test, a simple electrocardiogram (ECG) may be suggestive of pulmonary hypertension and/or reveal underlying changes seen in patients with coronary artery disease that may be associated with decreased function of the left side of the heart. A chest x-ray might reveal a prominent main pulmonary artery and enlargement of the hilar vessels, and may also reveal a pulmonary condition that may cause pulmonary hypertension. Alternatively, a normal chest x-ray may be helpful to rule out other lung diseases that can present in a similar manner. Pulmonary function testing may aid in the evaluation of a specific cause of pulmonary hypertension, such as severe emphysema. Ventilation and perfusion imaging and angiography (described

in the next section) might be required to rule out the presence of blood clots in the lung which can cause pulmonary hypertension.

Echocardiography is a useful noninvasive test to screen for the presence of pulmonary hypertension and in most cases can determine the severity of the disease reasonably accurately. Right heart catheterization, however, is the gold standard for determining the presence and severity of pulmonary hypertension. This is when a catheter is introduced from the groin or the neck vein and passed through the chambers of the right heart into the pulmonary artery. A mean pulmonary artery pressure of greater than 25 mm Hg at rest or 30 mm Hg during exercise is considered to be consistent with pulmonary hypertension. Measured pressures determine disease severity and can predict mortality. It is usually an outpatient procedure performed under local anesthesia. An algorithm for the diagnostic workup of PH is shown in Figure 2-8.1.

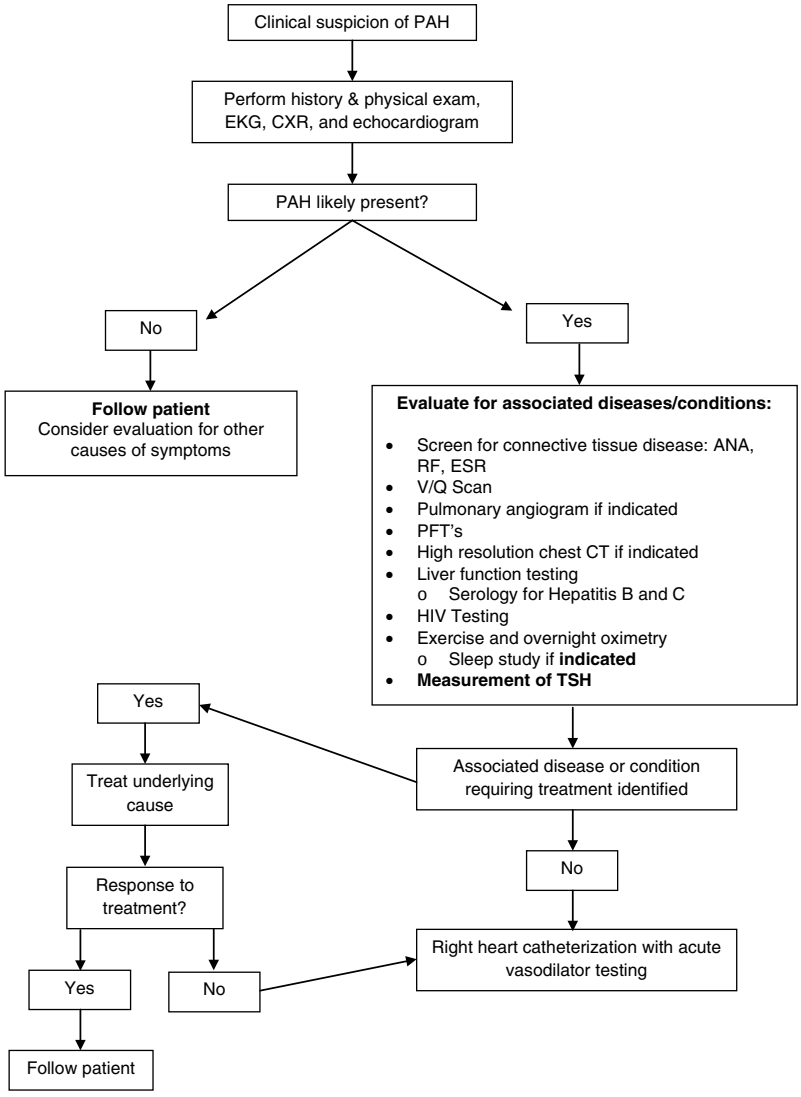

Figure 2-8.1: Algorithm for diagnostic workup of pulmonary hypertension.

MEDICAL MANAGEMENT

General Measures

Although there is no cure for this disease, there have been considerable developments in the last two decades in managing patients with PH.[3] Since physical activity can increase pulmonary artery pressures significantly, it is advisable that patients refrain from heavy exercise or any activity that causes chest pain or fainting. Patients are advised to be careful about medications they take for other illnesses, such as certain decongestants. Patients who wish to become pregnant should be seen by a high risk obstetrics physician as well as one who specializes in pulmonary hypertension, as labor can potentially lead to life threatening strain on the heart, and can cause abrupt deterioration of the disease. Safe and effective methods of contraception should always be discussed. Flying in non-pressurized airplanes and being at high altitudes can cause worsening of the disease by decreasing the amount of oxygen available. In these situations, supplemental oxygen should be used.

Specific Measures

Patients with pulmonary hypertension may be prescribed blood thinning medications by their physicians. Warfarin (brand name “coumadin”) is the most common such agent to be prescribed and has been shown in some patients to prolong life. Patients should be told not to overuse non-steroidal anti-inflammatory drugs (NSAIDS) if they are on a blood thinner, and should also be educated about medications that might interact with this blood thinner. Due to the risk of hemorrhage, however, the decision to initiate treatment is made by the treating provider after careful evaluation of the suitability of a particular patient. Supplemental oxygen therapy is also commonly prescribed, and may also have long term benefits, especially in patients with co-existing lung diseases.

As the disease progresses, the heart continues to fail, and patients may begin to retain fluid as evidenced by swollen feet and weight gain. Diuretics or “water pills” are useful to alleviate this swelling and may lead to less shortness of breath. In some cases, medications like digoxin might be useful to improve the contractility of the failing heart.

Calcium channel blockers like cardizem and nifedipine were the first class of drugs used to treat this disorder. These agents are beneficial in a small fraction of patients with pulmonary hypertension who demonstrate "reversibility" of their elevated pulmonary artery pressures during right heart cathetrizations. Systemic hypotension (low blood pressure) can limit the use of these drugs.

The mainstay of therapy is now selective pulmonary vasodilator therapy. These medications fall into three main categories: prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors. Each class of medication focuses on different parts of the pathway leading to PH. The prostocyclin drugs were the first studied and are effective, though their use can be limited by the way these drugs need to be administered. While originally an indwelling intravenous delivery system was needed, there are now medications in this class that can be given subcutaneously or via a special inhaler used several times throughout the day. Endothelin receptor antagonists and phosphodiesterase inhibitors are gaining acceptance rapidly,

at least in part due to their availability in pill form. Combination regimens of these medications are also now being studied.

Patients treated with these classes of drugs are usually under the supervision of a pulmonary hypertension specialist. Treatment of this disease is life-long, involving close monitoring. For patients who continue to deteriorate on optimum medical therapy, heart-lung transplantation or lung transplantation is an option. Hopefully, as our experience with the disease and its management increase, we can continue to significantly impact on the quality of life and survival of patients with PH.

PULMONARY EMBOLISM

A blood clot, or thrombus, in the pulmonary circulation is called a pulmonary embolism (PE). Most of the blood clots in the lungs are a result of propagation or dislodging of clots formed in the deep veins of the legs, arms or pelvis.[4] A thrombus in any large deep vein is referred to as a deep venous thrombosis, or DVT. The obstruction of blood flow in the pulmonary circulation can cause shortness of breath and even death, depending on the size and number of blood clots. Untreated recurrent small pulmonary embolisms over time can lead to pulmonary hypertension, discussed earlier in this chapter. Treatment centers on blood thinning to prevent the formation of future clots.

Epidemiology

The National Heart, Lung, and Blood Institute (NHLBI) reports there are at least 100,000 cases of PE occurring each year in the United States. PE is the third most common cause of death in hospitalized patients. If left untreated, about 30 percent of patients who have PE will die. Most of those who die do so within the first few hours of the event.[5] These numbers are likely underestimates of the true incidence, as signs and symptoms are nonspecific and may masquerade as other illnesses and therefore, not be recognized.[6]

Risk Factors

The major risk factors for blood clot formation include significantly-reduced blood flow, injury to the lining of blood vessels and certain conditions that may promote clot formation. Reduced blood flow is the most common and can result from immobility, which can be due to severe medical illness, hip and knee surgery, broken limbs, or even long periods of travel in a car or airplane. There are also genetic factors that predispose individuals for DVTs, often due to either too little or too much of a protein involved in clot formation. Common deficiencies involve Factor V Leiden, protein S and C, and anti- thrombin III. Increased Factor VIII and elevated homocysteine levels are also associated with clot formation.[7]

The risk for PE in patients presenting with a suspicion for the disease can be calculated using a simple patient-based assessment tool. Patients with significant points need further work up to diagnose or exclude PE. One such point system is known as the Modified Wells Criteria: clinical assessment for PE[8,9],in which certain clinical risk factors obtained via initial history and physical examination are assigned points. The point assignment is characterized in Table 2-8.2.

Clinical Risk Factors	Points
Clinical symptoms of deep venous thrombosis (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than PE	3.0
Heart rate > 100	1.5
Immobilization > 3 days or surgery in prior month	1.5
Previous DVT/ PE	1.5
Hemoptysis (coughing up blood)	1.0
Malignancy	1.0

Table 2-8.2: Clinical Risk Factors

If a patient accumulates four or less points and has a blood test with low D-dimer (a break down product of clots, which will be discussed later), then PE is unlikely. However, if the patient has more than four points on initial evaluation, then further work up is warranted.

Clinical Presentation

The clinical presentation of PE is often non-specific and variable. Signs and symptoms may be related to the initial site of DVT, such as lower extremity swelling, tenderness or pain. Once a clot travels to the lung and occludes a segment of the pulmonary circulation, signs and symptoms may be related to the heart, lung, or systemic signs such low grade fever or hypotension. The most often reported signs and symptoms are shown in Table 2-8.3 and patients can present with none or many of these findings.[7]

Circulatory collapse, or shock, is associated with massive PE and occurs with a frequency of about eight percent.[6] Clinically, the patient may present with fainting in the setting of low blood pressure. Unexplained anxiety is also a relatively-common presenting symptom.

Signs and Symptoms	*% of Patients*
Shortness of breath	70%
Increased Respiratory Rate	70%
Chest pain	65%
Rapid Heart Rate	37%
Cough	37%
Blood streaked sputum	15%

Table 2-8.3: Signs and Symptoms of Pulmonary Embolisms

Diagnostic Tests

Once the diagnosis of DVT or PE is entertained, further diagnostic tests are performed.[8] Chest x-rays can be normal or abnormal, and therefore cannot be used to make this diagnosis. They may be helpful however when an alternative diagnosis is found such as pneumonia, heart failure or a rib fracture. ECG changes are common, but are also non-specific. Echocardiograms may show elevated pressure in the right side of the heart (i.e., pulmonary hypertension) due to an occluded pulmonary circulation, though this can also be seen in a number of conditions including heart failure, severe emphysema and sleep apnea, as discussed earlier. Arterial blood gases can also be normal, especially in younger patients.

Evaluation for DVT

Duplex ultrasound of the lower extremities may reveal a clot in the deep veins, even without lower extremity swelling. When this is found, it is more likely that the chest imaging studies described below will show a PE. Since both a DVT and a PE are treated similarly with blood thinners, a diagnosis of a DVT may avoid further testing. In the absence of a DVT, however, a PE may still have occurred, and perhaps the presence of a clot in the pulmonary circulation and not the lower extremities signifies that the clot dislodged and propagated. Since this test is relatively quick, portable, accurate, and relies on sound waves, and is therefore non-invasive, it is a common first approach to the diagnosis of PE. Its usefulness is limited however in patients with severe obesity or lower extremity edema.

D-dimer Concentration

A D-dimer assay is a blood test which looks for enzymatic break down products of clots. It is often positive in many conditions and is therefore non-specific. However, it is rarely negative (< 5 % of patients) in patients who have a documented DVT or PE. In a low risk patient, a negative D-dimer may help exclude PE from the differential diagnosis.[9]

Ventilation-Perfusion (V/Q) Scan

The V/Q scan was previously the most common diagnostic test for PE and has been well-studied. Interpretation is based on the probability of the patient having a PE and is determined by comparing the blood flow and the air flow in regions of the lung. A high probability study would show no blood flow to a region that is aerated. A normal V/Q scan would show intact blood flow and aeration and essentially rules out a clinically significant PE. Unfortunately, most scans are neither normal nor high probability. In addition, as many as 40% of patients with a low probability study but with a high clinical likelihood for PE, turn out to have this diagnosis.

Spiral CT or CT Angiogram

CT pulmonary angiogram is an accurate, invasive test that is commonly used to diagnose PE. It involves injection of contrast dye through an intravenous line followed by CT scan of the chest. The dye will fill up the pulmonary vessels, and PE would be seen as filling defects (see Figure 2-8.2). The dye may occasionally cause renal insufficiency and should not be used in patients

with renal failure. In many patients, a negative duplex ultrasound of the lower extremities and a negative spiral CT rules out PE.[9] Another advantage of this test is that it permits visualization of the entire lung, which may lead to an alternative diagnosis when a PE is not identified.

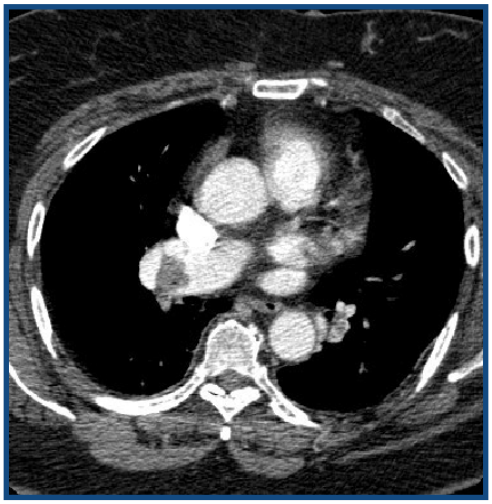

Figure 2-8.2: Filling Defects in Pulmonary Vessels

Pulmonary Angiogram

Pulmonary angiogram is considered the gold standard to diagnose PE. In this test, a catheter is inserted into a blood vessel in the groin or arm and then passed into the blood vessels of the lung. Injection of contrast dye then permits direct imaging of the pulmonary circulation. A negative pulmonary angiogram rules out PE. This test, however, is invasive, requires experienced support staff and has a small risk of serious complications such as bleeding and arrhythmias, and therefore is not commonly performed.

MANAGEMENT

PE is a potentially life-threatening disease and a high index of suspicion needs to be maintained in patients at risk or with suggestive symptoms. Management is in general, supportive, where the patient receives blood thinners to prevent the formation of new clots and the extension of existing clots.

General Measures

Supplemental oxygen is often given, especially if the oxygen saturation level is low. If the patient has low blood pressure, intravenous fluids are given. Patients are often monitored for irregular heart beats.

Specific Measures

Anticoagulation therapy with blood thinning agents is the initial treatment of patients with PE. For the most part, it should be initiated in all patients except those who have active internal bleeding. If no contraindication exists, heparin is started followed by long-term therapy with coumadin. The duration of therapy is decided based on assessment of risk versus benefit. For patients who are diagnosed for the first time with PE, blood thinning treatment commonly lasts for six months, while those with recurrent PE may be treated for the rest of

their life. The most common side effect of blood thinners is bleeding. This can be reduced by close monitoring of blood tests to keep the blood thin enough but not too thin.

Filters placed in the superior or inferior vena cava, the major veins returning blood from the upper and lower parts of the body, respectively, can prevent clot dissemination to the lungs. They should be considered as a therapeutic modality in patients who either have a contraindication to the use of blood thinners or who have PE despite appropriate and adequate therapy with blood thinners.

Prognosis

Without treatment, PE has 30% mortality from recurrent emboli. With proper therapy, the mortality is reduced to two to eight percent.[6]

PULMONARY EDEMA

Pulmonary edema signifies abnormal accumulation of fluid in the air sacs of the lungs. This occurs when there is (1) an increased pressure in the blood vessels of the lungs (cardiogenic pulmonary edema), or (2) an increase in the leakiness of these blood vessels (non cardiogenic pulmonary edema) or (3) some combination of the two. As fluid fills the lungs, oxygen cannot be absorbed and the patient develops low oxygen levels.

Cardiogenic pulmonary edema is due to heart failure, which means the heart is not able to pump out enough of the blood it is receiving from the lungs and the system backs up. This can result from weakness in the left ventricle which can occur after a heart attack. Heart valves that don't open wide enough or are too leaky can also cause fluid to accumulate. High pressure in the right side of the heart (pulmonary hypertension) can also lead to pulmonary edema.

Non-cardiogenic pulmonary edema occurs when fluid builds up but the heart is functioning normally. This can occur as a result of lung infections, aspiration, near-drowning, high-altitude, or smoke inhalation, to name a few. Pulmonary edema due to toxic gas inhalation will be discussed separately at the end of this chapter.

Patients with pulmonary edema complain of extreme shortness of breath similar to suffocating, which is worse when lying flat. They are often quite anxious. The physical exam in patients with pulmonary edema is nonspecific. Patients have a high respiratory rate. Some are coughing with frothy, blood tinged, sputum. Lung exam often reveals crackles, though occasionally wheezing is also heard.

The diagnosis of pulmonary edema is made by combining the clinical presentation and physical exam with a good medical history. It is confirmed by the chest x-ray which shows bilateral patchy haziness, often accompanied by a collection of fluid (pleural effusion). Measurement of impaired gas exchange can be performed using noninvasive pulse oximetry or invasive arterial blood sampling. In some situations hemodynamic monitoring can be performed by catheterization of the heart.

Pulmonary Edema Associated with Inhalation of Foreign Material

Pulmonary edema can occur as a result of toxic gas and smoke inhalation. This may occur during exposure to chemicals during building or vehicular fires or industrial accidents. Pulmonary edema in cases of toxic gas or smoke inhalation is due to lung injury which is thought to begin with chemical burns to the upper and lower airways. The incidence is thought to increase with the extent of burns. Two thirds of patients with more than 70% burns will also have inhalational injury. Inhalation injury adds significantly to the mortality in patients with burns. In one large cohort, the mortality rate was 29% when inhalation injury was present and only two percent in its absence.[10]

The diagnosis of inhalational injury is made by reported history of exposure, physical exam, and testing. Carbon monoxide is frequently inhaled during fires, and its levels in the blood can serve as a diagnostic marker of the extent of exposure. The severity of the inhalational injury can be estimated by fiberoptic examination of the airways.

The simplest and best treatment for smoke inhalation is termination of exposure as soon as possible and then administration of 100% oxygen. Specific antidotes like sodium nitrite and thiosulfate may or may not be needed. Hyperbaric oxygen is also recommended although data proving its superiority is scarce. Patients with severe lung injury or upper airway edema may require intubation and mechanical ventilation. The efficacy of antibiotics and corticosteroids is not proven.[11] The administration of diuretics should be avoided.[12]

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Chapter 2-9
Fire Fighters and Lung Cancer

By Dr. Adrienne Flowers, MD and Dr. Melissa McDiarmid, MD

THE FIRE FIGHTING ENVIRONMENT

The toxic environments in which fire service members live and work have long been suspected to have an adverse effect on fire fighter health. Virtually every hazard class can be found in the fire fighting environment including physical hazards, such as ionizing radiation, biologic agents, musculoskeletal hazards and the psycho-social stress of responding to life-threatening emergencies.[1] Chemical hazards, primarily the toxic products of combustion[2,3,4] have been of particular concern as threats to health, especially when considering the work-relatedness of cancer development.

Known or presumed carcinogens (cancer-causing agents) have been found in the fire fighting environment and include: benzene, formaldehyde, acrolein, perchloroethylene, cadmium, and some of the polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene and chrysene.[3] Asbestos exposure during overhaul operations has long been raised as a risk[5,6] and the exposure to diesel exhaust at the fire house has also been flagged as potentially hazardous.[7]

There is evidence to support the belief that some of these hazards could cause respiratory disease through an inhalation exposure route. Health studies over the last 30 years have consistently shown excesses of non-malignant respiratory disease in fire service members.[8,9,10,11,12] Less consistent however, have been links between firefighting and malignancies of the lung.[12,13,,14] The following limitations of fire fighter health studies make the evaluation of lung cancer risk due to exposures received during firefighting activities very difficult. First, there is a general lack of detailed historic smoking information among fire fighters. Smoking is a primary cause of lung cancer and this lack of information makes it impossible to separate the contribution of work exposures and smoking in the development of lung cancer (Figure 2-9.1). Second, because lung cancer can take many decades to develop, insufficient years of observation can result in under identification of deaths. For example, if the study period is not of sufficient length, fire fighters who develop and die from lung cancer late in life, long after the typical 20-year fire fighter career span, may not be identified. The onset of lung cancer relatively late in life, long after fire service retirement would then elude researchers trying to link the diagnosis to work which ended several decades earlier. None the less, there are biologically plausible reasons to be concerned about lung cancer development from fire fighting work, especially among the more senior members who worked prior to regular use of self-contained breathing apparatus (SCBA).

This chapter will provide an overview of lung cancer, its types, how it presents and is diagnosed, classified and treated and what is known about its work-

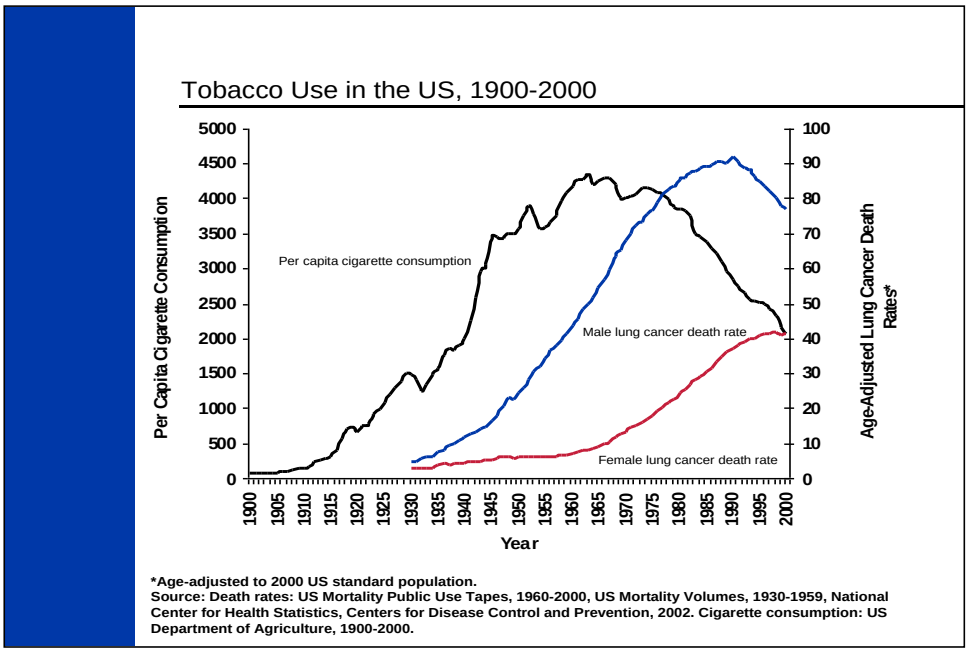


Figure 2-9.1: Tobacco Use and Lung Cancer in the United States

relatedness among other occupations and exposed groups. Some prevention strategies applicable to fire service members will also be described.

LUNG CANCER EPIDEMIOLOGY

Although lung cancer is the second most common type of cancer diagnosed in both men and women (second to prostate cancer in men and breast cancer in women), it ranks first as the cause of cancer deaths annually in both genders.[15] In fact, it accounts for more deaths annually than breast, prostate and colon cancer combined.[15] According to the National Cancer Institute, the estimated numbers of new cases and deaths from lung cancer in the United States in 2008 was 215,020 and 161,840, respectively. It typically occurs in people older than 50 years. Based on reports from cases between 2001-2005, the median age at diagnosis is 74 years and the number of new cases increases with age.[16] Lung cancer is rare in people less than 45 years old.[15] Because of the high mortality rate, survival statistics for lung cancer patients are quite poor with only 15% of patients achieving the five-year survival mark.[15]

A person's risk of developing lung cancer, like any cancer, is dependent on two types of factors: (1) host factors involving a person's genetic make up that ultimately influence susceptibility to cancer-causing agents and (2) environmental factors which include not only risks from exposure to the external environment such as contaminated air or workplace hazards, but also substances found in the diet or acquired through social habits such as smoking.[17]

In addition to the genetic host factors that influence lung cancer risk, there are other personal health factors that must be considered. For example, people with a history of chronic obstructive pulmonary disease also have an increased risk of developing lung cancer. As the obstruction on the pulmonary function test (PFT) worsens, so does the risk of lung cancer.[18] It remains controversial whether a medical history of other previous lung diseases may also predispose to certain types of lung cancer.[19]

That the principal risk factor for lung cancer development is cigarette smoking is undisputed. About 90% of all lung cancer in the United States is estimated to be attributable to cigarette smoking[20] which is thought to increase the risk of lung cancer development by 20-fold, compared to those who never smoked. In addition, secondhand smoke, or smoke from other people's cigarettes, increases the risk of lung cancer in non-smokers. Public health experts state that current lung cancer statistics describe an "epidemic" that can be traced to the 1930s and reflect the increase in cigarette smoking at that time and which continued rise into the 1980s for men and which still continues to rise in women.

While most of the studies on smoking and lung cancer have focused on cigarette smoking because the prevalence of such smoking was so high after World War II, exposure from pipes and cigar smoking is also thought also to raise the risk of lung cancer.[21]

There are many other environmental causes of lung cancer. In fact, lung cancer has been the most thoroughly studied of cancers regarding environmental causes, perhaps because of the obvious inhalation exposure route making deposition of cancer- causing agents directly into the lung, a plausible scenario for initiating a cancer. Table 2-9.1, displays a list of currently-recognized environmental causes of lung cancer.[15,17,21]

The occupational hazards which contribute to lung cancer risk include the polycyclic aromatic hydrocarbons which derive from coal products and energy production and from combustion of these products. Other chemicals including some metals are known lung carcinogens as is asbestos and diesel exhaust, which, as mentioned above are encountered in the fire service. Studies of cancer risk by occupational group tend to reinforce these observations about agents which increase lung cancer risk, as seen in Table 2-9.2.[22,23,24] It would be fairly easy to map the substances which are known to increase lung cancer risk from Table 2-9.1 to the occupations where they are encountered in Table 2-9.2.

LUNG CANCER

There are two main categories of lung cancer: Non-small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). As their appearance may be similar on chest x-ray or CT scan, the only certain way to distinguish between them is to examine specimens under a microscope. Each has different sub-classes within the main categories that are based on the cell type in the lung that is growing abnormally.

Non Small Cell Lung Cancer

NSCLC is a broad category which encompasses all types of cancer that are not SCLC. This classification accounts for approximately 80% of lung cancer cases.[15]

This main category is further subdivided into seven classes of lung cancer based on the type of lung cell that is affected. This can be determined by the appearance of the cell under a microscope. Among this group of seven classes of NSCLC, the three most prevalent are adenocarcinoma, squamous cell, and large cell cancer, in that order.

Environmental Causes of Lung Cancer
Smoking -- Active
Smoking -- Passive (Second-hand exposure)
Smoking -- Marijuana
Diet (Low Fruit & Vegetable Consumption)
Air Pollution
Coal Cooking fires -- indoor exposures -- developing world
Coke Oven Emissions (Benzo (a) pyrene)
Soots
Shale Oil
Arsenic
Chromium
Nickel
Beryllium
Cadmium
Vinyl Chloride
Mustard Gas
Chloromethyl ether
Diesel exhaust
Silica (crystalline)
Asbestos
Radiation
Low LET (linear energy transfer – e.g. x-rays and gamma rays)
High LET (e.g. neutrons, radon)

Table 2-9.1: Environmental Causes of Lung Cancer (Adapted from Alberg and Samet, 2003;[17] ACS, 2008;[15] IARC, 2009[21])

Selected Occupations at Increased Risk of Lung Cancer Development
Coal Gasification Workers
Coal Tar Distillation Workers
Coke Oven Workers
Fire Fighters
Insulators
Metal and Machining Workers
Miners and Quarry Workers
Painters
Pavers and Roofers
Rubber Workers

Table 2-9.2: Selected Occupations at Increased Risk of Lung Cancer Development (Adapted from IARC, 2009;[22] MacArthur et al., 2008;[36] Bruske-Hohlfeld et al., 2000[24])

- **Adenocarcinoma** is the most common form of NSCLC. This type of cancer is responsible for about 40% of all types of lung cancer.[15] In the lung, these cancers typically form on the peripheral of the lung.[25] Due to hormonal differences or other as yet unknown reasons, this is the form of lung cancer that is most frequently diagnosed in women.

- **Squamous Cell Carcinoma** makes up about 25 - 30% of all lung cancers and is slow growing. It usually takes three to four years to become evident on a chest x-ray. It tends to arise more centrally in the lung; therefore on presentation, there may be obstruction of bronchi with post-obstructive pneumonia.[25]
- **Large Cell Cancer** is a less commonly-occurring type of cancer representing about 10 - 15% of lung tumors.[15,25]

Clinical Presentation and Symptoms of NSCLC

Because there are no screening protocols considered beneficial for large-scale population testing for lung cancer (i.e., testing of asymptomatic people for early detection), lung cancer is usually diagnosed when a patient presents to their physician with symptoms and a chest radiograph (x-ray) is obtained (Figure 2-9.2). Almost 90% of people have symptoms at the time of diagnosis. Most in fact have at least two symptoms at diagnosis.[26] The most common symptoms reported are cough and generalized systemic complaints that include weakness, fatigue or anorexia (inability to eat). Other symptoms that may be present at the time of diagnosis include: dyspnea (shortness of breath), chest pain, bloody sputum (phlegm), and pneumonia. Some patients will present with a change in the shape of their nail beds called clubbing. Others may present with elevated blood calcium levels.

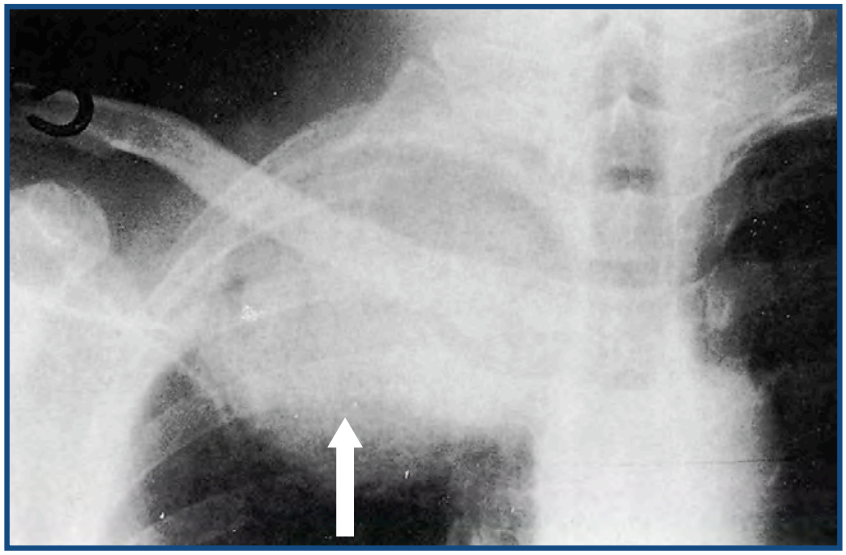


Figure 2-9.2: Lung Mass (arrow) Subsequently Identified as Non Small Cell Lung Cancer on Biopsy

Symptoms may occur that reflect the impact of the tumor behaving as a mass in the chest and pressing on other structures such as nerves or airways that could manifest as hoarseness, trouble swallowing, stridor (difficulty breathing in with resulting noise heard over the trachea [air-pipe] in the neck) or cough. Symptoms resulting from compression of major blood vessels such as facial or upper body swelling (superior vena cava syndrome) and lightheadedness may sometimes occur. Symptoms may occur from spread of the tumor to outside the chest (metastasis) to other organs. Examples include: bone pain from bone involvement; fatigue from brain and/or liver involvement, headaches and/or seizures from brain involvement and paralysis from spinal cord involvement.

Figure 2-9.3 depicts the frequency of commonly-occurring symptoms reported by lung cancer patients at time of presentation.

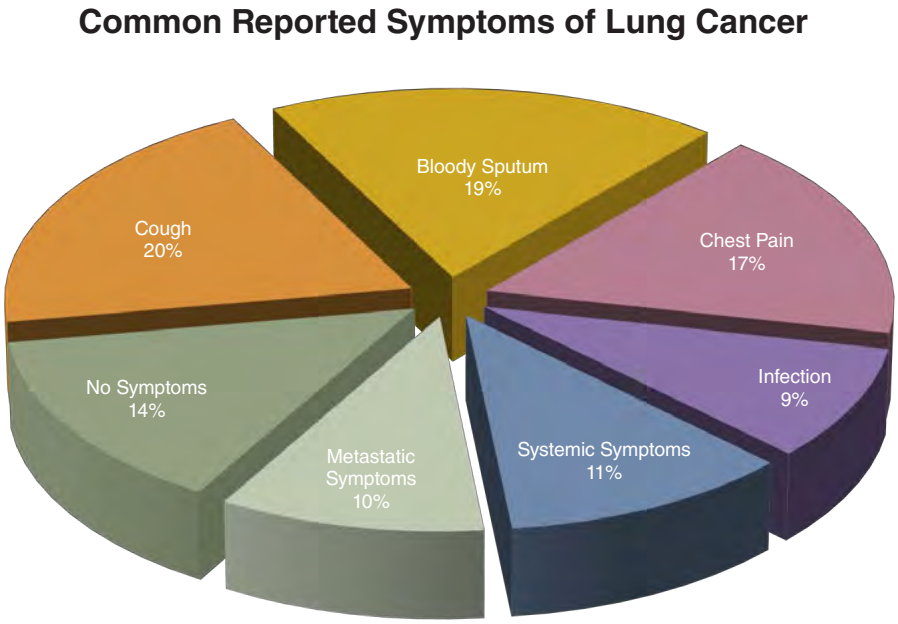


Figure 2-9.3: Most Common Symptoms at the Time of Presentation: (Adapted from Buccheri, 2004)[26]

Diagnosis

The diagnosis of lung cancer is usually determined after a patient presents to the doctor with symptoms as described above. The process will begin with a thorough health history and physical examination. The history focuses on risk factors for cancer including cigarette smoking, environmental or occupational exposure to carcinogens and family history of lung cancer. Imaging of the chest is an important component of the diagnostic assessment. Most clinicians will start with a chest radiograph (x-ray) to determine if a lung mass (tumor) is present (see Figure 2-9.2). A normal chest x-ray can rule out this diagnosis in many instances: however, in some cases cancer can be missed. For example, a review of primary care records in England revealed that 10% of patients diagnosed with lung cancer had a chest x-ray interpreted as normal within the year prior to their diagnosis.[19] This is especially true if the tumor was less than 1 cm or 10 mm in diameter or if it is hidden behind a normal chest structure such as a bone or lymph node.

If an abnormality is seen on a chest x-ray, this can be further evaluated by Computed Tomography (CT) scanning. In addition to confirming abnormalities on chest x-rays, CT imaging may also find abnormalities that may not be visible on a chest x-ray, such as very small nodules less than 1 cm in diameter and swollen lymph nodes. Figure 2-9.4 depicts the diagnostic steps which are taken to evaluate a patient for lung cancer.

Tissue Biopsy

Once a mass has been identified, diagnosis is made by tissue biopsy or aspirate of the abnormal tissue. There are different types of procedures to obtain this biopsy material and the most appropriate procedure or approach depends

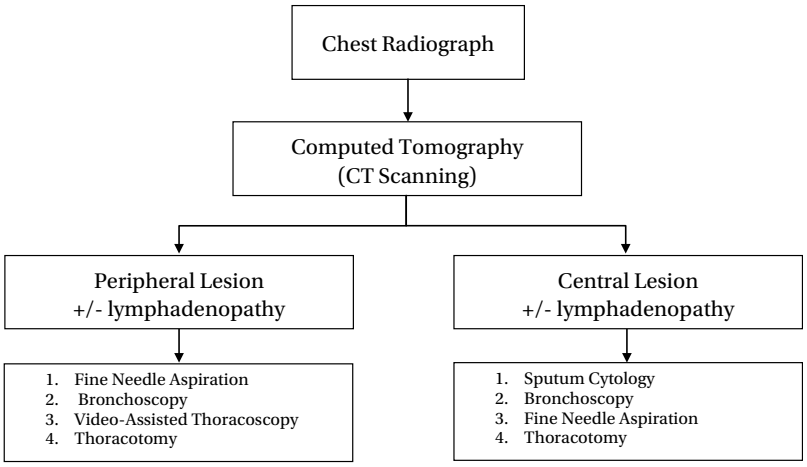


Figure 2-9.4: Diagnostic Protocol for Lung Cancer Patients: (Adapted from Davita,200525 and National Comprehensive Cancer Network (NCCN)[27])

on numerous factors including: the location of the tumor, the likelihood that metastasis has already occurred, how ill the patient is, local expertise and patient preference. Choices include bronchoscopy, transthoracic needle, mediastinoscopy, video-assisted thoracoscopy and occasionally, open lung thoracotomy. These procedures are often performed by pulmonologists (lung doctors), invasive radiologists, or thoracic (chest) surgeons to obtain biopsy specimens and confirm involvement of tissues and lymph nodes that are seen on CT scan and other imaging studies.[28] A description of these approaches is detailed below.

- **Bronchoscopy** is a procedure to view airways directly. A flexible scope is inserted into the airway through the mouth or nose. Through the scope, a tissue biopsy or other specimens (brushing or washings for cells) are obtained from a tumor in the airway (Figure 2-9.5) or from a tumor in the lung. New techniques coupling bronchoscopy and ultrasound guidance

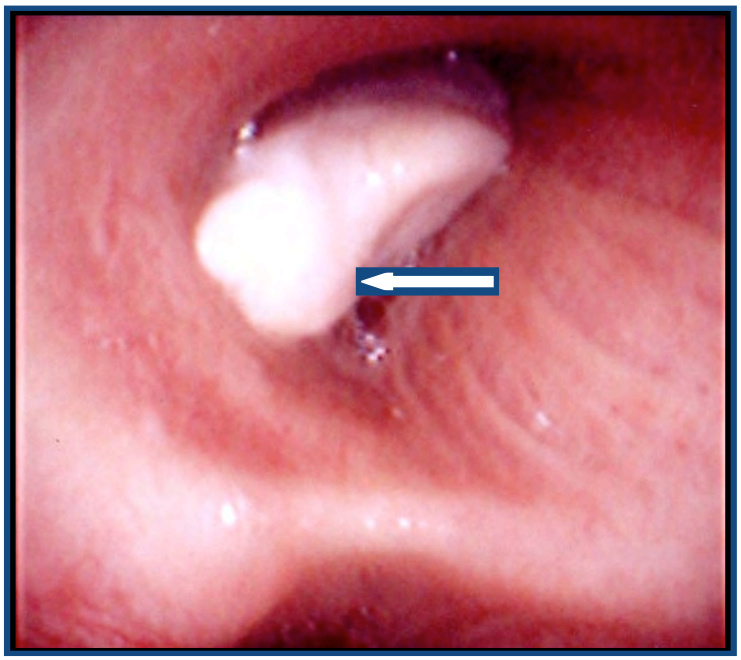


Figure 2-9.5: Tumor Mass within a Bronchus or Airway (arrow) that was Visualized and then Biopsied through a Bronchoscope.

are allowing even small lung nodules and lymph nodes to be sampled. Local anesthesia and mild sedation is provided, so that the bronchoscopy is only mildly uncomfortable. This procedure does not require an overnight hospital stay.

- **Transthoracic Needle Biopsy or Aspirate** is a procedure to sample peripheral lung nodules or masses. No incision is required. Rather, a needle is passed through the chest and then with X-ray guidance is directed into the nodule or mass to obtain the tissue sample. Local anesthesia is provided and mild sedation is available if needed. This procedure does not require an overnight hospital stay.
- **Mediastinoscopy** is a procedure to examine and sample the lymph nodes inside the center of the chest. In this procedure a small incision (about 2 inches) is made at the base of the neck and a scope is passed into the middle of the chest. Biopsy samples can be obtained from these centrally located lymph nodes but not from the airway or lungs. This procedure is done under general anesthesia and typically does not require an overnight hospital stay.
- **Video-Assisted Thorascopic Surgery (VATS) or Open Lung Thoracotomy** is a procedure to sample and/or remove lymph nodes, lung nodules and other evidence of cancer in the chest. This procedure is done under general anesthesia and will require a hospital stay for several days or longer.

Staging of NSCLC

Staging of the disease refers to determining the extent of the cancer in the body. This includes how large the tumor is and whether there is evidence for metastasis (cancer spread) to other areas including lymph nodes within the chest or to distal organs outside the chest. One of the best indicators of the extent of cancer is involvement of the lymph nodes. Lymph nodes are tiny glands that help the body fight infection but are often the first areas for tumor metastasis. Staging for NSCLC, in contrast to SCLC, is critically important because although metastasis is far too common, it is not the presumption. The prognosis and treatment will depend on the stage or extent of disease at the time of diagnosis.

Staging is done by radiographic imaging of the body. All patients should receive a chest CT that includes imaging to assess abdominal organs that are common sites of metastasis – the liver and adrenal glands. Any patient with neurologic symptoms should also have a magnetic resonance imaging (MRI) of the head and spinal cord to evaluate for metastasis to the brain or spine. A positron emission tomography (PET) scan is now becoming the test of choice for staging of non-neurologic organs (for details see chapter on chest imaging).

Cancer is divided into five main stages: zero, one, two, three and four. The most commonly used staging classification system, the Tumor Nodal and Metastasis (TNM) system, grades tumors on the basis of tumor size and location and the consequences thereof such as local invasion, partial lung collapse, or obstructive pneumonia (T), the presence and location of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The overall stage of the tumor is determined by the combination of the TNM score,

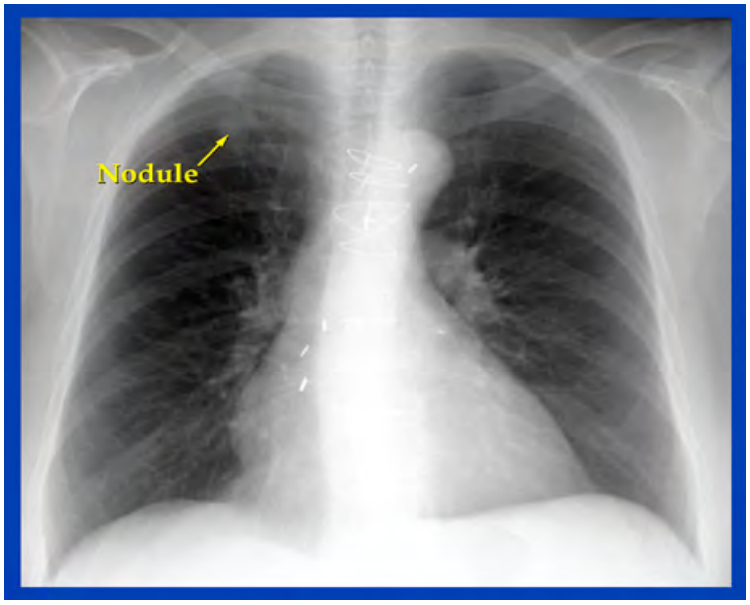
which defines the extent of disease, and is used to determine the prognosis and treatment. An A and B subgroup is applied to stages to separate those within a stage who have certain findings associated with a better or worse prognosis. Overall, the earlier the stage, the easier to treat and the better the prognosis. When diagnostic techniques and/or treatments are developed and impact on survival, the staging system is revised. Although there are complexities in the staging system that are beyond the scope of this chapter, the basic criteria for classification are as follows:

- **Stage 0** also known as carcinoma in situ is a very early stage of cancer where the cells are not yet invading. Stage 0 disease would not be evident on chest x-ray or CT. Rarely, if ever do we make the diagnosis of lung cancer at Stage 0 , but it is our hope that newer screening techniques will be developed to achieve this.
- **Stage I** is early disease where the tumor is only on one side of the lung; is not greater than 3 cm in diameter; and does not involve the chest wall, pleura (the skin between the lung and chest wall), lymph nodes or main airway. Figure 2-9.6 shows a chest x-ray and CT scan of stage I lung cancer.
- **Stage II** is a tumor on one side of the chest that is either not greater than 3 cm in diameter but involves chest lymph nodes on the same side close to the tumor, or is greater than 3 cm in diameter without lymph node involvement or the inner surface of the pleura. Figure 2-9.7 shows a chest x-ray and CT scan of stage II lung cancer.
- **Stage III** is a tumor of any size that involves chest lymph nodes distant from the tumor (same or opposite side), or diaphragm, main airways, or the outer surface of the pleura or pericardium (lining between lung and heart). Figure 2-9.8 shows a chest x-ray and CT scan of stage III lung cancer.
- **Stage IV** is metastastatic cancer, where the disease has spread to other organs in the body. Lung cancer most commonly spreads to the other lung, or pleural fluid (between lung and chest wall), chest wall, bone, brain, liver, and/or adrenal glands.[25] Figure 2-9.9 shows a chest x-ray and CT scan of stage IV lung cancer based on metastasis to the liver.

Prognosis

The higher the stage, the more advanced the cancer and poorer the prognosis. The percentage of patients who live at least five years after being diagnosed is termed the five-year survival rate. For patients diagnosed with stage I lung cancer, the five-year survival rate is 56%, though rates are higher for the A subgroup (73%). This relatively favorable survival substantially decreases as the disease spreads. The five-year survival rate for stage IV is 2%.[29]

There are certain factors, called prognostic factors that may predict a better outcome of treatment and prognosis for a given stage of disease. Good prognostic factors at the time of diagnosis include early staging at the time of diagnosis, the patient's good general functional ability called "performance status" which includes daily activities as well as function assessed by pulmonary and cardiac tests and either no weight loss or weight loss of less than 5% at the onset of disease.



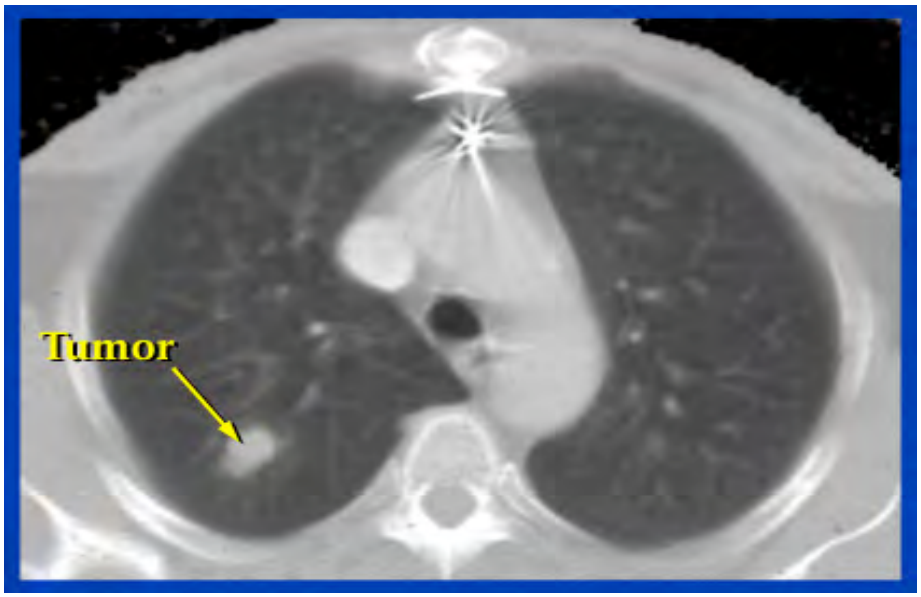
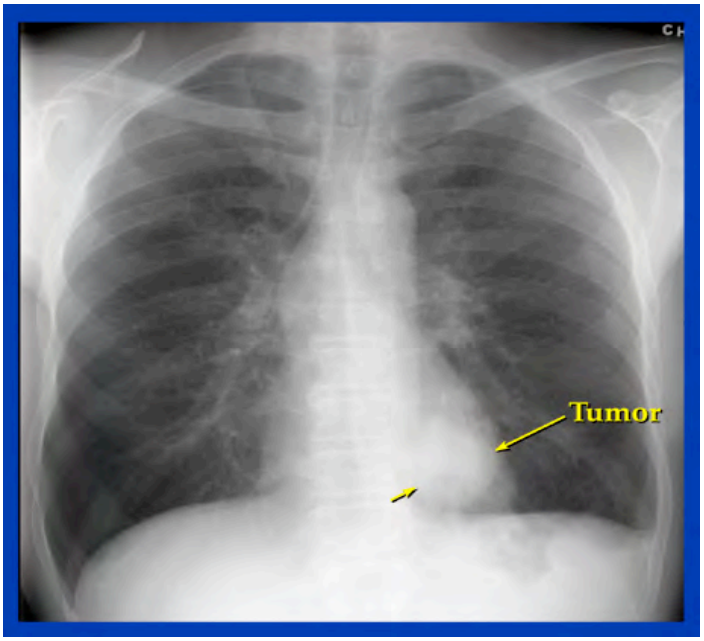


Figure 2-9.6: Chest X-ray and CT Scan Showing a Nodule (less than 3 cm in diameter) without Spread to Adjacent Structures (Stage I disease).

Treatment of NSCLC

Treatment is based on the staging at the time of diagnosis. The treatment of cancer has become a field involving multiple "modalities", or types of interventions. Based on the type and extent of disease, a therapeutic plan is designed by a pulmonologist, thoracic surgeon, medical oncologist who may administer chemotherapy and a radiation oncologist who may administer radiation therapy. In latter stages of disease, pain or palliative physicians are an important addition to this process.

Unfortunately, 75% of all lung cancer (NSCLC and SCLC) present with either regional or metastatic disease at the time of diagnosis.[29] For this reason, very few patients have disease that is amenable to cure by surgical resection alone;



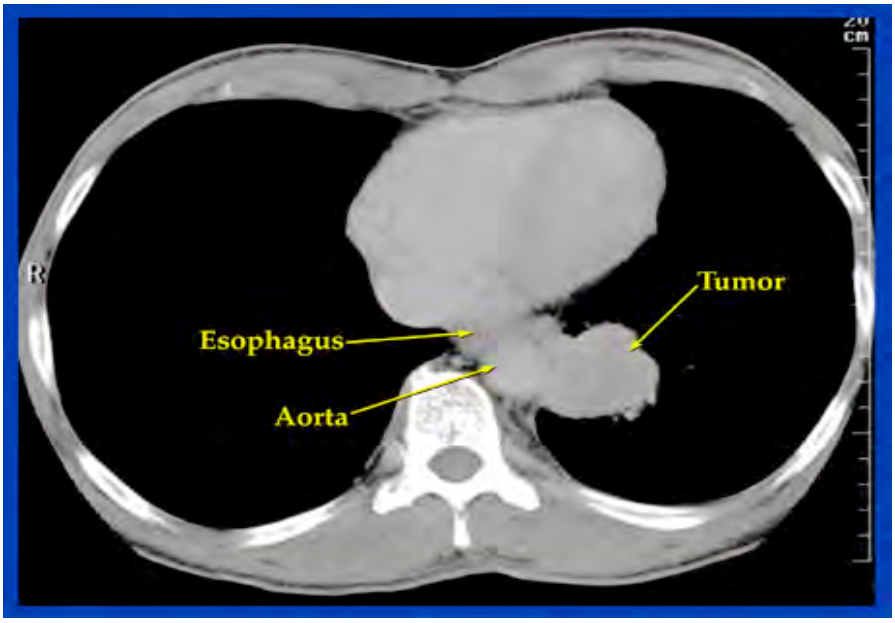


Figure 2-9.7: Chest X-ray and CT Scan Showing a Nodule (greater than 3 cm in diameter) without Spread to Adjacent Structures (Stage II disease).

however, for patients that present with localized disease, Stage I-II, surgical resection vs. surgical resection with low-dose chemotherapy is the current approach. Treatment decisions for some stage II and all stage III through IV disease are far more complex. There are no standard treatment regimens for NSCLC and each decision to treat must be made on an individual basis. The three modalities of treatment are outlined below.

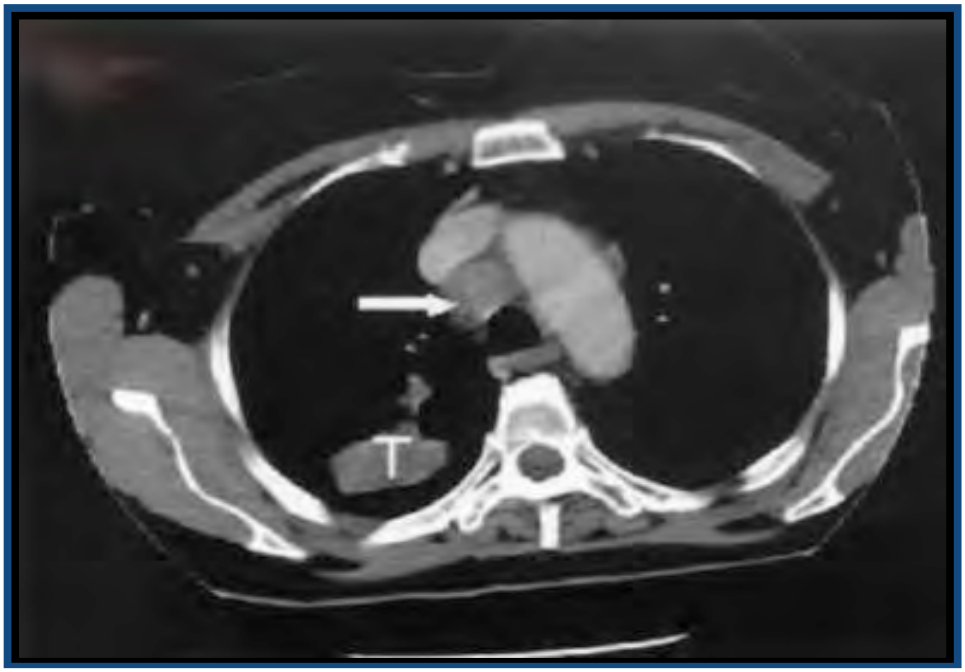


Figure 2-9.8: Chest CT Scan Showing a Tumor with Lymph Node (arrow) Involvement in a Location that Defines this as Stage III Disease.

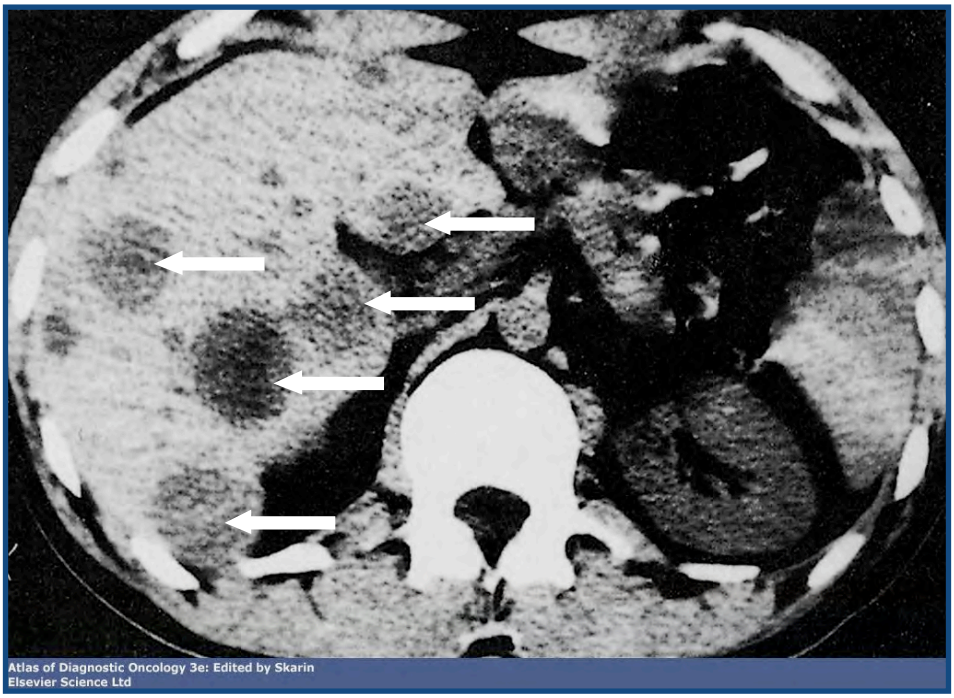


Figure 2-9.9: CT Scan Showing Metastasis to the Liver (larger ones identified by arrows) Thereby Defining this as Stage IV Disease.

- **Surgical Resection** remains the mainstay of treatment for Stage I and Stage II NSCLC. It involves complete removal of the tumor. Depending on location and size of the tumor, the surgical approach can be performed by video assisted thoracoscopic surgery or by open lung thoracotomy. In general, when possible, the entire lobe of the lung where the cancer is found is removed (lobectomy). However, in certain patients removal

of a cone-shape piece of lung, or wedge resection may be performed. For carefully selected patients with Stage III disease, surgery may also be considered (usually those with negative mediastinal lymph nodes). Some patients with stage IV disease may benefit from surgical resection of an isolated metastasis (e.g., to the brain or adrenal gland) to improve functional status but this does not improve survival.

- **Chemotherapy** is the mainstay of treatment for more advanced NSCLC. This involves the use of medications designed to kill cancerous cells in the body. As opposed to patients with Stage I NSCLC, those with Stage II disease who have undergone surgical resection, and who then receive adjuvant chemotherapy (treatment that is given as an add-on to the primary surgical treatment) have improved survival versus surgery alone. For patients with stage III disease, a combined modality approach using chemotherapy and radiation therapy is generally preferred. Patients with stage IV disease are generally treated with systemic therapy and/or palliative care. Side effects of chemotherapy vary depending upon the regimen used. There are many drugs for the oncologist to consider, and treatment choices (involving the selection and number of agents) are individualized to the patient. As new research is accepted and mainstreamed into general clinical practice, chemotherapy recommendations will change.
- **Radiation Therapy** is often used in conjunction with chemotherapy in patients with an advanced stage of NSCLC. In those patients with early stage disease but who are not candidates for surgery (due to advanced age or coexisting medical problems), stereotactic body radiation therapy (SBRT), a technique that utilizes precisely-targeted radiation to a tumor, may also be an option. The goal of radiation therapy is to target x-ray beams directly at cancer cells while minimizing damage to adjacent tissue. Radiation therapy, when successful, shrinks the size of the tumor. For extensive disease, radiation helps to alleviate symptoms (e.g. pain) associated with the cancer burden. Radiation therapy to the brain may also help treat or prevent further metastasis.

Small Cell Lung Cancer

Annually, SCLC now represents about 15% of all lung cancers.[29] In 2008, approximately 32,000 new cases were diagnosed in the United States. This type of cancer is on the decrease from a peak in 1986 when it represented 18% of all lung cancers.

SCLC has many environmental risk factors. This cancer is almost always associated with cigarette smoking.[1] As many as 98% of patients with SCLC have a history of smoking.[28] For smokers, the risk of developing SCLC is 25 times higher than non-smokers. The same observations have been seen with cigars and pipes.[1] There is also concern that cigarettes with menthol may have higher levels of cancer because menthol allows for more inhalation of the cigarette smoke.

Other environmental exposures that raise the risk for SCLC include: bischloromethyl ether, vinyl chloride, asbestos, radon and exposure to therapeutic radiation. It is also important to note that developed countries have higher incidences of SCLC, suggesting that air pollution exacerbates the development of SCLC.

Certain types of SCLC can secrete biologically-active antibodies, hormones and proteins. When these tumors secrete these biologically-active substances, the condition is called a "paraneoplastic syndrome". Most common paraneoplastic syndromes include the Syndrome of Inappropriate Antidiuretic Hormone (SIADH), Cushing's, Lambert- Eaton syndrome and paraneoplastic encephalomyelitis. These syndromes can cause a variety of symptoms depending on the substance released.

Clinical Presentation and Symptoms

The symptoms at the time of presentation are very similar to those of NSCLC including: cough, shortness of breath, hoarseness, chest pain or bloody sputum. These tumors tend to be closer to the bronchial tree or the airways and may present with an obstructive pneumonia.

In contrast to NSCLC, this tumor has a more rapid doubling time and earlier development of metastasis. Seventy-five percent of cases have metastasis at the time of diagnosis.[28] The most common sites of metastasis are the liver, bone, bone marrow, adrenal glands and brain. Symptoms reflect metastatic organ involvement with bone pain due to bone involvement, fatigue and jaundice from liver involvement, and fatigue, headaches or seizures from brain involvement.

In addition, the SCLCs may secrete circulating proteins, hormones and antibodies. Symptoms from these circulating factors may include: increased thirst, bone pain, rashes, nail bed changes, and/or neurologic abnormalities.

Diagnosis

The diagnostic pathway for SCLC is similar to NSCLC.

Staging

The staging pathway for SCLC is not as complex as for NSCLC and is shown in Figure 2-9.10. SCLC has two stages – limited and extensive. The limited stage refers to disease that is confined to one side of the chest and may be encompassed within a tolerable radiation field. Everyone with SCLC should have a full body CT (chest/abdomen/pelvis) and an MRI of the brain. Some centers are now doing a PET scan as well or instead of a full body CT. Approximately 30 - 40% of patients with SCLC have limited disease at the time of diagnosis. Extensive stage disease is more common and extends beyond that one side of the lung and may include collections of fluid around in the lungs and around the heart caused by cancer cells.

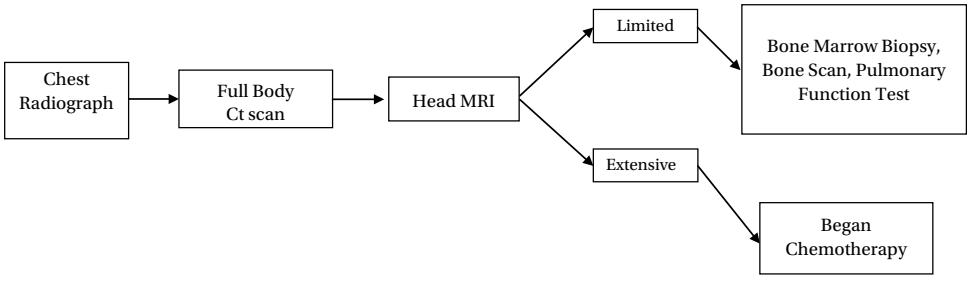


Figure 2-9.10: Algorithm for Staging Small Cell Lung Cancer (adapted from NCCN Data).

Prognosis

As was true with NSCLC, pre-treatment factors predict how well patients do with treatment. Again, the extent of the disease is the strongest prognostic factor. The more limited the disease at the time of diagnosis, the better the outcome. Other factors associated with a better prognosis include age less than 55 years, female gender, and higher functional status (the ability of the patient to carry out daily life activities). Poor prognostic factors include age 70 years or older, current tobacco use and an elevated lactate dehydrogenase (LDH) level in the blood. The latter is an indicator of more bulky and extensive disease.

Without treatment, the prognosis for metastatic SCLC is very poor with a median survival of five to eight weeks. Treatment with combined chemotherapy and radiation therapy achieves a response rate of 80% but three-year survival even for limited disease is only 14 - 20%.

Treatment

Even for limited disease, microscopic metastasis not evident at the time of diagnosis precludes a surgical cure. Chemotherapy is the mainstay of treatment for SCLC. However, for patients with "very limited disease" (ex. single small lung nodule without lymph node involvement or any evidence of metastasis), some have improved survival rates with surgical resection followed by chemotherapy. Some studies suggest a five-year survival rate of 50 - 80% after surgical resection of a limited stage SCLC nodule.

In contrast to NSCLC, SCLC is very sensitive to chemotherapy and radiation therapy. Chemotherapy combined with radiation achieves a response rate of 80% and a complete response rate in 40% of patients. The types of chemotherapy drugs used are beyond the scope of this chapter. The addition of radiation therapy can further improve response rates by about 75% and survival rates by about 5%. Radiation therapy is most effective when given early on and during the chemotherapy. For extensive disease radiation helps to alleviate symptoms (e.g. pain) associated with the cancer burden. Radiation therapy to the brain may also help treat or prevent metastasis.

SCREENING FOR LUNG CANCER

Screening is a medical term for a non-invasive test that can be used in asymptomatic persons for the early identification of disease at a stage when successful treatment is still possible. Examples of this are the Pap smear for cervical cancer, colonoscopy for colon cancer, mammography for breast cancer and the prostate screening antigen (PSA) for prostate cancer. Numerous studies have shown that chest radiographs and sputum cytology, either alone or in combination are not useful tests for screening high-risk populations such as tobacco smokers. Lung cancers were identified, but in most cases were found at an advanced stage that precluded successful treatment.

Recently, a study using chest CT scans for the screening of lung cancer in tobacco smokers produced promising results,[30] though this type of screening cannot be recommended until large scale studies are completed. In 2007, based on a review of the data available, the American College of Chest

Physicians Guidelines for the Diagnosis and Management of Lung Cancer concluded that "for high-risk populations, no screening modality has been shown to alter mortality outcomes." The American College of Chest Physicians guidelines recommends that, "individuals undergo chest CT screening only when it is administered as a component of a well-designed clinical trial with appropriate human subjects' protections." [31] These guidelines will be updated depending on the results from a multi-center study on the effectiveness of serial CT scanning in reducing the death rate from lung cancer.

It is also important for patients participating in this type of investigational Chest CT screening to first be aware that 20 - 40% of the population has small (<5 mm nodule) or intermediate size lung nodule (5 to 7 mm nodule). Rarely are these size nodules cancerous, but they are too small to biopsy. Therefore, they must be followed with repeat CT scans, usually for one to two years. This can be anxiety provoking to the patient but current technology provides no other alternatives.

PREVENTION

Because the overwhelming cause of the total lung cancer burden in the United States is smoking (at about 90%), it follows that not smoking is the best prevention practice to avoid this disease. It is also good news for smokers that smoking cessation is beneficial to your health at any age and will result in a decreased risk of lung cancer development compared to people who continue to smoke.[32] It is important to encourage family members and co-workers who still smoke to stop, not only to protect themselves, but others (including you) who they live and work with from second-hand smoke. Modern tobacco cessation programs use combination drug and behavioral modification modalities to achieve exceptional strong cessation rates ranging anywhere from 30 - 40%.[33] For further details, see the separate chapter on tobacco cessation.

Another important prevention practice to avoid exposure to cancer-causing agents generally is to be vigilant about use of SCBA. This is true not only during the active stages of fire suppression, but also during overhaul when some chemicals of combustion may be present at concentrations as high or even higher than during the active firefighting phase.[34]

Adherence to NFPA requirements regarding use of diesel exhaust capture devices to achieve point source exhaust control in the fire house will also minimize preventable exposure to this lung carcinogen.

While firefighting is a known "high-hazard" occupation which places fire service members in situations threatening to both life and health, these strategies described above will go a long way to protect members from exposure to cancer causing agents and other health hazards encountered in the work environment.

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Chapter 2-10
Asbestos-Related Lung Diseases

By Dr. Stephen Levin, MD

INTRODUCTION

In the course of their work, fire fighters may have recurrent exposure to asbestos dust, especially during the overhaul phase of a fire response when, although respiratory protection is required, self-contained breathing apparatus (SCBA) is infrequently worn. Insulation and other asbestos-containing materials are often disturbed when buildings undergo spontaneous collapse or demolition during firefighting, with asbestos fibers remaining airborne long after fire fighters have ceased using their SCBAs at the site.

From 1890 to 1970, some 25 million tons of asbestos were used in the United States, approximately two-thirds of which were used in the construction industry. The natural resistance of asbestos to heat and acid, its tensile strength, and its remarkable thermal, electrical and sound insulating properties have led to its use in over 3,000 applications, including floor tiles, boiler and pipe insulation, roofing materials, brake linings, and cement pipes. More than 40,000 tons of fireproofing material, containing 10- 20% asbestos by weight, was sprayed annually in high-rise buildings in the period from 1960 to 1969. Much of this material remains in buildings, factories, and homes. When fires occur in these structures, fire fighters disturb asbestos-containing materials and are at risk for exposure to asbestos dust, especially because fire fighters do not regularly wear respiratory protection during the overhaul phase of fire response. Measurements of asbestos fiber concentrations in the air during overhaul have been shown to exceed OSHA's short-term exposure limits.[1]

Evidence that such exposures to asbestos have health consequences for fire fighters can be found in studies that have looked at abnormalities on chest x-rays consistent with asbestos-related scarring. New York City fire fighters, assigned 25 or more years earlier to ladder companies situated near large office and factory buildings, warehouses or poor residential areas with frequent fires, underwent examination with chest x-rays interpreted by "B-readers" who have certified expertise in recognizing asbestos-related changes. Among fire fighters who had no known exposure to asbestos outside of their work as fire fighters, 13% had lung tissue abnormalities and/or changes in the lining of the lungs typical of asbestos-related scarring[1], compared with a rate of x-ray abnormality of only two percent among adult males examined in general population surveys.[3]

Increased lung cancer rates among fire fighters have been reported in some studies,[4] although not consistently.[5] Evaluating the available data on lung cancer among fire fighters is difficult because of their lower prevalence of tobacco

use. Cases of mesothelioma, a type of cancer caused in the great majority of cases by exposure to asbestos, have been reported among fire fighters with no history of exposure to asbestos other than during firefighting.

WHAT IS ASBESTOS?

The term 'asbestos' refers to a group of six, naturally-occurring fibrous mineral silicates of magnesium and iron that form in host rock. Asbestos-containing ore is mined, crushed, and milled to obtain the fibrous material, which is then processed further into finer fibers. There are two main types of asbestos: amphiboles (straight fibers) and serpentines (curly fibers bundled together). The amphiboles that have been used commercially include amosite, anthophyllite, and crocidolite. Other amphiboles (tremolite and actinolite) are not used commercially but are frequently contaminants of other silicates, including vermiculites and talcs. Chrysotile is the only type of serpentine asbestos in commercial use and represents 95% of all asbestos imported into the United States and incorporated into commercial products (Figure 2-10.1).

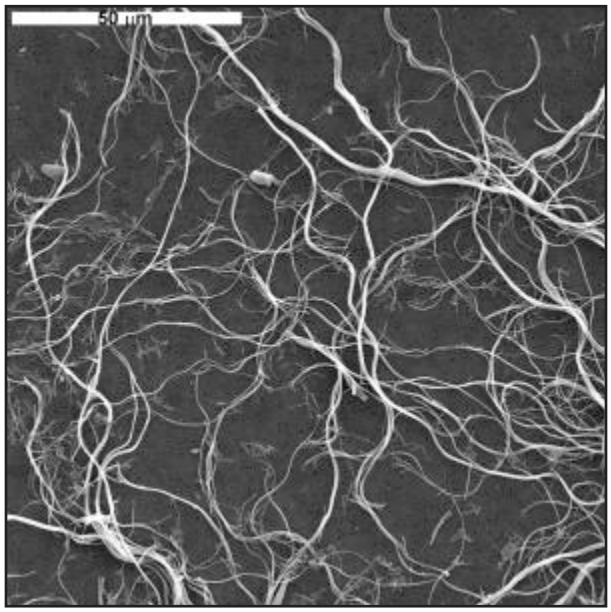

Figure 2-10.1: Chrysotile Asbestos Fibers.

The Diseases Caused by Asbestos

The inhalation of asbestos fiber is recognized as a cause of both non-malignant (i.e., non-cancerous) lung diseases, including asbestosis (scarring of the lung tissue), pleural scarring (scarring of the lining of the lung and/or the chest wall) and benign pleural effusions (fluid in the space between the lung and the chest wall). Exposure to asbestos dust also causes lung cancer and diffuse malignant mesothelioma, a cancer of the lining of the lung (pleural mesothelioma) and the lining of the organs in the abdomen (peritoneal mesothelioma). Exposure at high concentrations among asbestos insulators and other occupational groups has also been associated with increased rates of cancer of the gastrointestinal tract, kidney, pancreas, and larynx. It's possible to develop asbestos-related scarring of the lung and not develop an asbestos-related cancer, and asbestos-related lung cancer and mesothelioma can occur in the absence of lung scarring.

All types of asbestos fiber are associated with the development of asbestos-related scarring and cancers. There has been considerable debate about whether chrysotile asbestos is a cause of mesothelioma and whether it is as potent as the amphibole fibers in causing this specific cancer. In the United States to date, exposure to asbestos is regulated without distinction as to fiber type. Fire fighters should be protected against the inhalation of asbestos dust of any type.

How Asbestos Causes Disease

Asbestos-related disease, with the exception of asbestos "warts" in the skin, results from inhaling asbestos fibers into the upper airways and the lung. Swallowing asbestos fibers has not been consistently shown to cause digestive tract cancer. Animal experimental studies of long-term, high-level ingestion of asbestos fibers have failed to demonstrate a reproducible effect on the likelihood of developing cancer. There is, however, epidemiological evidence from human population studies that indicates that swallowing asbestos fibers can cause human disease. Communities exposed to asbestos-contaminated drinking water have been found in some studies to have excesses of cancer of the stomach and pancreas.

When asbestos-containing materials in place are disturbed, asbestos fibers of varying diameters and lengths can be suspended in the air. Once airborne, fine asbestos fibers remain in the air for many hours even when the air appears relatively still. Air movement created by wind or human activity easily re-suspends asbestos fibers that may have settled on surfaces. When they are inhaled, the larger asbestos fibers are deposited in the nose and upper airway. Fibers with diameters in the range of 0.5 to 5 μm can penetrate deep into the recesses of the lung and deposit at the branching of the finest airways, the alveolar ducts (see Chapter on the Anatomy of the Lung). Asbestos fibers that reach the airways are to a limited extent cleared by the mucociliary escalator, the continuous movement of mucus and trapped particles from the airways in the lung to the back of the throat (usually to be swallowed un-consciously). This movement is driven by the action of microscopic hair-like structures (cilia) projecting from the inner lining of the airways into the mucus layer. The fibers that remain in the airways are transported into the lung's interstitial tissue – the space between the alveoli (where gas exchange occurs and oxygen is absorbed) and the surrounding capillaries. The presence of these fibers then attracts macrophages (specialized scavenger cells) that attempt to engulf the fibers and dissolve them with digestive enzymes. The macrophages are themselves killed by the asbestos fibers and disintegrate, releasing enzymes and DNA-damaging oxygen free radicals into the surrounding tissue, damaging the cells lining the small airways, and initiating inflammation and the scarring process. Over time, there is an accumulation of interstitial macrophages, white blood cells, fibroblasts (cells that deposit scar tissue) and scar tissue itself. This fibrotic or scarring process progresses, usually slowly over years, in some cases leading to stiff, small lungs with impaired ability to oxygenate the blood. The scarring can continue to worsen even after the inhalation of asbestos fiber has stopped, since many fibers persist in the lung and continue to cause new scar formation and to increase the risk for asbestos-related cancers. Ongoing exposure will result in an increasing accumulation of fiber in the lung, thereby increasing the risk for asbestos-related scarring and cancers.

The mechanism by which asbestos causes cancer is still not fully understood. The genetic changes, many of them already identified, caused by a cell's exposure to asbestos (or to gene-modifying agents carried by the asbestos fiber to the cell) are now being investigated with the genetic research tools developed in recent years.

Asbestos fibers that are swallowed up by macrophages may become coated with an iron-containing material, forming an *asbestos body* or *ferruginous body*. Only a small proportion (about one percent) of fibers becomes coated, so this cannot be considered an effective protective mechanism. There is evidence that amphiboles cause the formation of asbestos bodies more readily than chrysotile. The presence of asbestos bodies in lung tissue, fluid washed from the lungs (bronchoalveolar lavage fluid), or in sputum, has been used as a marker of exposure, although individuals appear to vary considerably in how likely they are to form these structures. The finding of abnormally high asbestos body concentrations in sputum, bronchoalveolar lavage fluid or lung tissue indicates a history of exposure to asbestos in excess of "background" and can support the diagnosis of asbestos-related disease. The absence of asbestos bodies does not rule out that asbestos fibers in the lung may have caused disease. High concentrations of asbestos fibers have been found in the lungs of exposed individuals who have developed scarring or fibrosis, but do not have unusual numbers of asbestos bodies in their lung tissue.

Some asbestos fibers that penetrate into the interstitial lung tissue migrate to the pleural membrane that lines the lung and the chest wall, most likely by lymphatic channels. Some are distributed to other tissues in the body via the lymphatic circulation and via the bloodstream.

HEALTH EFFECTS OF EXPOSURE TO ASBESTOS

Non-Malignant Asbestos-Related Diseases

Pulmonary Asbestosis

Pulmonary asbestosis is the diffuse, interstitial fibrosis (scarring) in the lung tissue caused by the deposition of asbestos fibers of any type in the lung. The fibrosis results in a lung disease that generally becomes evident clinically after 15 to 20 years or more have elapsed from the onset of exposure. While there are biological differences among individuals in susceptibility to the scarring caused by exposure to asbestos, the likelihood of developing asbestosis is related to the cumulative amount of fiber inhaled over time. Such scarring is most commonly seen among workers exposed recurrently on the job and family members exposed repeatedly to take-home dust. However, even short-term exposure (e.g., less than one month), when asbestos fiber concentrations in the air are high enough (e.g., in the manufacture of asbestos-containing products), can result in fatal asbestosis. There is no evidence that single or rare exposures to asbestos dust are associated with the development of scarring lung disease.

The most prominent symptom of asbestosis is the gradual onset of shortness of breath on exertion, with progression over time. Cough, either dry or productive of small amounts of clear sputum, may be present. Chest pain, either sharp or aching in character, occurs in a small proportion of patients with asbestosis.

On physical examination, crackling sounds (rales) on expiration over the base of the lungs and that persist after coughing, may be heard. Clubbing, a rounding of the end of the fingers and a "spooning" of the fingernails may be present when scarring is advanced. The chest x-ray shows small, irregular lines of scarring in the mid and lower lung zones after sufficient fibrosis has accumulated, although the characteristic pathologic findings of interstitial scar formation may be evident on microscopic examination of tissue well before the abnormalities become detectable on the chest x-ray or CT scan. These physical and radiographic findings are not specific for asbestosis and can be found in other fibrotic lung diseases see Chapter on Pulmonary Fibrosis and Interstitial Lung Disease).

Pulmonary function (breathing) test abnormalities (for details see Chapter on Pulmonary Function Tests) demonstrate a restrictive impairment, with a decreased forced vital capacity (FVC) – an inability to inflate the lung with a normal volume of inhaled air, a decreased total lung capacity (TLC) – the total volume of air in the lungs after a deep breath, and a decreased diffusing capacity (D_LCO) – a measure of the lung's ability to transfer oxygen to the blood. Flow rates through the large airways, measured as the forced expiratory volume at 1-second (FEV_1 and FEV_1/FVC ratio) are usually normal, but narrowing of the small airways (decreased FEF_{25-75} values) has been reported to accompany asbestosis. Interestingly, this has also been found among non-smoking workers exposed to asbestos but without chest x-rays evidence of asbestosis, suggesting that asbestos dust may have some mild irritant properties in addition to its ability to cause scarring. Impaired ability to oxygenate the blood as it passes through the lung, due to the accumulation of interstitial scarring, can lead to arterial oxygen desaturation (low oxygen levels in the blood), evident at first only during and immediately after exercise, accounts for much of the shortness of breath on effort experienced by many people with asbestosis.

In individual cases, there is often a poor correlation among the appearance of scarring on the chest x-ray, the degree of shortness of breath and the pulmonary function results. Some patients with marked abnormalities on the chest x-ray may have few symptoms and normal pulmonary function. The converse may also be true, with the severity of symptoms and/or pulmonary function test results seemingly out of proportion to the degree of x-ray abnormality. Studies of groups of exposed workers, however, demonstrate relationships among these effects of the scarring process.

In severe cases of asbestosis, respiratory impairment can lead to death, often when the affected individual develops a chest infection (e.g., pneumonia) that further compromises lung function. When scarring becomes dense and extensive, increased resistance to blood flow through the small arteries in the lung may develop, from obliteration of the network of small arteries and capillaries and from pulmonary capillary constriction caused by low oxygen levels in the alveolar air sacs. This results in pulmonary hypertension and may ultimately cause the muscle of the right ventricle of the heart (which pumps blood through the lungs) to enlarge to overcome the increased resistance to blood flow. If the pulmonary hypertension is severe enough for a sufficient period of time, the right ventricle can fail, a condition known as cor pulmonale, a well-recognized potentially fatal complication of advanced asbestosis.

There are a number of medical conditions that can look like asbestosis, both clinically and radiographically. A list of the most common of these conditions is presented in Table 2-10.1. Most important of the diseases listed are idiopathic pulmonary fibrosis (for details see the chapter on pulmonary fibrosis) and congestive heart failure.

Most Common Conditions Mimicking Pulmonary Asbestosis
Idiopathic pulmonary fibrosis
Congestive heart failure (radiographic appearance)
Hypersensitivity pneumonitis
Scleroderma
Sarcoidosis
"Rheumatoid lung"
Other collagen vascular diseases
Lipoid pneumonia
Desquamative interstitial pneumonia
Other pneumoconioses (dust-related lung scarring)

Table 2-10.1: Common Conditions Mimicking Pulmonary Asbestosis

Pleural Thickening or Asbestos-Related Pleural Fibrosis

Pleural thickening, or asbestos-related pleural fibrosis (scarring of the lining of the lung and/or the chest wall), is the most common consequence of exposure to asbestos in the occupational setting. The scarring can occur in localized areas in separate and discrete plaques (circumscribed pleural thickening) or can occur as a more extensive and diffuse scarring process over the surface of the pleura and involve the costophrenic angle (the angle or gutter made by the chest wall and the diaphragm where they come together) – defined as diffuse pleural thickening. Evidence of pleural scarring usually appears after 20 or more years have elapsed since the onset of exposure to asbestos dust (the latency period), and a latency of 30 to 40 years after exposure begins is not uncommon.

Under the microscope, the plaques appear as deposits of collagen, the protein that is deposited in early scar formation. Circumscribed pleural scarring more commonly involves the parietal pleura (the lining of the chest wall) and often can be found on the surfaces of the diaphragm. Pleural plaques can be found on the visceral pleura (the lining of the lung itself) as well. The pericardium (the lining around the heart) and the pleural surfaces in the center of the chest (the mediastinal pleura) may also be involved. Although non-calcified thickening is more common, calcium deposits in areas of pleural scarring, whether localized or diffused, is frequently evident on the chest x-ray and become more common with increasing time since onset of exposure. Conditions that can cause pleural thickening other than exposure to asbestos are presented in Table 2-10.2.

Conditions Mimicking Asbestos-Related Pleural Thickening	
Discrete or localized	*Diffuse*
Chronic mineral oil aspiration Chest trauma Infectious processes (old TB, pneumonia) Lymphoma Metastatic cancer Mica and talc exposure Myeloma Scleroderma	Chronic beryllium disease Collagen vascular diseases Drug reactions Infection Loculated effusions Mica and talc exposure Sarcoidosis Silicosis Uremia

Table 2-10.2: Conditions Mimicking Asbestos-Related Pleural Thickening)Adapted from Rosenstock and Cullen.[6])

When pleural thickening deforms the underlying lung tissue, *rounded atelectasis* or a *pseudotumor* may develop and prompt concern about the presence of a cancer. These lesions are characteristically less than 2 cm in diameter, and are located next to an area of pleural thickening or fibrosis. Evaluation by comparison with old chest x-rays, or with a CT scan of the chest, will usually reveal the characteristic features of this form of scarring and avoid unnecessary biopsies. Nevertheless, given the increased risk of lung cancer among asbestos-exposed workers, the diagnosis of rounded atelectasis should be made with appropriate caution and biopsy obtained in cases where the radiographic findings are uncertain.

In the past, pleural thickening was thought to represent only a marker of prior exposure to asbestos, without consequence for the individual's health; but pleural thickening, even when circumscribed, has more recently been shown to impair lung function, measured by pulmonary function tests or by exercise testing. Diffuse pleural scarring is associated with restrictive lung disease and impaired gas exchange, even in the absence of asbestosis (interstitial fibrosis). The lung can become entrapped or encased by a thick rind of scar, and in severe cases can cause pulmonary impairment and death. Diffuse pleural thickening is thought to result almost invariably from the occurrence of a pleural effusion, a collection of fluid in the pleural space (see below).

Both asbestosis and asbestos-related pleural fibrosis can be detected with greater sensitivity by CT scanning of the chest, especially by the high-resolution CT scan (HRCT). CT scans have been shown to detect asbestosis and pleural scarring when the chest x-ray appears normal. This technique may be useful in resolving cases that are uncertain on plain chest x-rays. The radiation exposure, time and cost involved in performing a CT scan have decreased as the technology has improved, making the CT scan more accessible as a tool for early detection.

Benign Asbestos-Related Pleural Effusions

Benign asbestos-related pleural effusions, collections of fluid in the pleural space between the lung and the chest wall, may occur within the first 10 years after the onset of exposure and may, therefore, be the first evidence of asbestos-related illness. These effusions can occur once and never recur or can reappear multiple times, on the same or opposite side of the chest. The

diagnosis is made by excluding other causes after examining the pleural fluid and finding that microscopic examination of the cells in the fluid reveals no malignant (cancerous) cells and cultures for bacterial or tuberculosis infection are negative. The fluid is usually reabsorbed spontaneously within several weeks; but thoracentesis (draining the fluid from the chest) for relief of chest pain and/or shortness of breath, and thoracoscopy (inserting a tube with a camera into the chest) to obtain a pleural biopsy for diagnostic purposes, are frequently performed. Many patients with pleural effusions, however, have no symptoms. There is evidence that diffuse pleural thickening (see above) may be the result of benign asbestos-related effusions following their reabsorption.

TREATMENT OF NON-CANCEROUS ASBESTOS-RELATED DISEASE

There is no effective treatment available for asbestosis. Measures used for patients with other forms of interstitial fibrosis, including steroids and anti-inflammatory medications, have not proven effective in controlling the asbestos-related scarring process or its consequences. The decreased blood oxygen levels associated with advanced scarring can be managed in part by the use of supplemental inhaled oxygen, and *cor pulmonale* is treated as for other causes of right heart failure. For patients with impending pulmonary failure due to asbestosis, a last resort option is lung or heart-lung transplantation, although experience with this approach remains limited.

Asbestos-related circumscribed pleural scarring may be associated with a loss of exercise tolerance, but, as with asbestosis, no specific treatment for this condition is available. In cases of extensive, diffuse pleural thickening with entrapment of the lung, stripping of the lining of the lung (*pleurectomy*) may be necessary to permit lung expansion.

Despite the lack of treatments that affect the scarring process itself, individuals with asbestos-related scarring of the lung tissue and/or pleura are advised to maintain an active aerobic exercise program and to avoid obesity in order to preserve and even improve exercise tolerance.

Benign asbestotic pleural effusions are treated as are effusions from other causes, with careful evaluation to rule out the possibility of malignancy by removal of the fluid (*thoracentesis*) and microscopic examination of the cells present. In cases of multiple, recurrent effusions, introduction of an irritant material to fuse the pleural lining of the lung to the pleural lining of the chest wall (*pleurodesis*) has been utilized to prevent further accumulations of fluid.

ASBESTOS-RELATED CANCERS

Lung Cancer

Lung cancer is the most common asbestos-induced malignancy and is the principal cause of death from asbestos in developed countries. Diagnosis of asbestos-related lung cancer generally occurs 20 or more years after onset of exposure. In a large study of the causes of death among heavily exposed asbestos insulators, over 50% of the cancer deaths were due to lung cancer.

Lung cancers associated with asbestos exposure are similar under the microscope to other primary cancers of the lung. All cell types of cancers arising in the airways occur at increased rates. Lung cancers occur with increased frequency in all locations of the lung following exposure to asbestos. Studies of lung cancer distributions by cell type and lobe of origin found no difference in anatomical site or microscopic characteristics between the cancers associated with asbestos exposure and those related to cigarette smoking.

Cigarette Smoking and Exposure to Asbestos

Cigarette smoking and exposure to asbestos dust have been shown to interact in a multiplicative (or synergistic) fashion in causing lung cancer, rather than a simple addition of the risks associated with each exposure. In a large group of heavily exposed asbestos insulators, lung cancer death rates were 5-fold increased for non-smokers and over 50-fold increased for smoking asbestos workers, compared with lung cancer mortality among non-smoking blue collar workers not exposed to asbestos. Lung cancer among blue collar cigarette smokers not exposed to asbestos was 11 times that of non-smokers. Table 2-10.3 summarizes these results.

Interaction between Smoking and Asbestos in Lung Cancer Mortality				
Group	*Exposure to Asbestos*	*Cigarette Smoking*	*Death Rate (per 100,000/yr)*	*Mortality Ratio*
Controls	NO	NO	11.3	1.00
Asbestos Workers	YES	NO	58.4	5.17
Controls	NO	YES	122.6	10.85
Asbestos Workers	YES	YES	601.6	53.24

Table 2-10.3: Interaction Between Smoking and Asbestos in Lung Cancer Mortality[7]

The increase in lung cancer risk is proportionate to the degree of exposure to asbestos and the cigarette smoking "dose." Cessation of smoking among asbestos-exposed workers has been shown to be associated with a decreased risk of lung cancer, although the risk never decreases entirely to the level of never-smokers. The cancers seen in significant excess among asbestos insulators other than lung cancer that have been shown to occur at even higher rates among cigarette-smoking asbestos workers included cancers of the esophagus, mouth and throat, and larynx. Smoking appears to have no influence on the risk of mesothelioma or cancers of the stomach, colon/rectum, and kidney among asbestos-exposed workers.

Smoking has been associated with an increase in lung tissue scarring evident on chest radiographs among men with asbestos exposure. There is little evidence that smoking alone, without exposure to asbestos, can produce the appearance of scarring on the chest x-ray. Cigarette smoking among asbestos workers has been shown to increase the risk of death from asbestosis. Clearly, for any fire fighter who is a current smoker, quitting cigarettes is the most important step one can take to protect their health.

The role of lung scarring in the development of asbestos-associated lung cancer is a subject of considerable debate. Workers exposed to asbestos have been shown to have an increased risk of lung cancer, even when chest x-rays have shown no lung tissue fibrosis. Studies have demonstrated that scarring of the lung tissue may be visible under the microscope in cases of lung cancer where the chest x-ray has been normal. As a practical matter, it is not necessary to demonstrate asbestosis on the chest x-ray or in biopsied tissue in order to attribute a causal role to asbestos in cases of lung cancer.

Treatment of Lung Cancer

Until the past decade, the treatment of lung cancer has been persistently unsuccessful, whether the approach utilized surgery, chemotherapy or radiation – with cure rates of only 5 - 10% in advanced disease. The primary difficulty was that lung cancers were detected at an advanced stage in over two-thirds of the cases, with spread of the tumor to local tissues, lymph nodes or distant organs (for details see the Chapter on Lung Cancer). More recently, there is some evidence that screening for lung cancer with CT scans can identify new tumors at a time when they are still small and have not yet spread to local or distant sites. Cure rates when tumors are found in such early stages may be 70% or greater. In 2007, based on a review of the data available, the American College of Chest Physicians Guidelines for the Diagnosis and Management of Lung Cancer concluded that "for high-risk populations, no screening modality has been shown to alter mortality outcomes." [8] The American College of Chest Physicians recommends that, "individuals undergo chest CT screening only when it is administered as a component of a well-designed clinical trial with appropriate human subjects' protections." [8] These guidelines will be updated depending on the results from a multi-center study on the effectiveness of serial CT scanning in reducing the death rate from lung cancer.[8]

Malignant Mesothelioma

Diffuse malignant mesothelioma is a tumor arising in the cells of the lining of the chest wall and/or lung (the pleura) and the lining of the abdominal organs (the peritoneum). Three microscopic patterns are recognized: epithelial, sarcomatous, and mixed or biphasic, each with its own likelihood of positive response to treatment, with the epithelial type most responsive. The great majority of patients with mesothelioma have a history of exposure to asbestos, and this has led to its description as a "signal neoplasm" because of its rarity in the absence of exposure to asbestos.

Among heavily exposed asbestos insulators, over nine percent of all deaths have been shown to be due to malignant mesotheliomas. In comparison, rates of death from mesothelioma exceeds 10 per million deaths among adults in the U.S. general population. A latency of 20 years or more from the onset of exposure to asbestos is again observed, with most mesothelioma deaths occurring more than 30 years from onset of asbestos work. There is evidence that the risk of developing a mesothelioma appears to increase the longer the individual is from the onset of exposure, prompting special concern for exposures among young children who may inhale asbestos dust brought home on their parents' contaminated work clothing.

Once occurring, diffuse malignant mesotheliomas generally spread rapidly over the surfaces of the chest and abdominal cavities and organs, often with little invasion of the organs involved. Penetration into the ribs and chest wall and spread to local lymph nodes is not uncommon. As the tumor grows more bulky, it can compress the underlying lung, markedly impairing lung function. The disease often presents with chest pain and shortness of breath, frequently due to pleural effusions, which prompt initial medical attention. The diagnosis is made on the basis of microscopic examination of cells separated from pleural fluid or, more commonly, tissue obtained by closed pleural biopsy or by thoracoscopy. Special tissue staining techniques (immunohistological staining) and/or assessment using high magnification electron microscopy is often necessary to establish the diagnosis with certainty.

Treatment of Malignant Mesothelioma

Advances in the treatment of malignant mesotheliomas of the chest and abdomen have occurred in the past 10 years. However, prognosis remains poor with the majority of patients surviving no more than 13 months after diagnosis. Chemotherapy alone with permatrexed (Alimta®) may extend life an average of three months and with a measurable improvement in the quality of life during that time compared with those who are untreated. For some, surgery, accompanied by washes of the chest or abdomen with heated chemotherapy solutions, has resulted in surviving more than five years after diagnosis. Nevertheless, treatment remains ineffective for the great majority of patients, and prevention remains the key approach to mesothelioma from a public health perspective.

PREVENTING ASBESTOS-RELATED DISEASE AMONG FIRE FIGHTERS

Fire fighters are most likely to be exposed to asbestos during overhaul, when asbestos-containing materials are frequently disturbed and when respiratory protection is infrequently worn. The key to preventing asbestos-related scarring and cancer is the use of respirators that will trap the great majority of the fine asbestos fibers before they are inhaled. The IAFF is working on a lighter weight and less bulky SCBA unit that could be more practical for the longer wear necessary during overhaul activities. Fire fighters are advised to wear their SCBA, especially in circumstances where they might be exposed to asbestos: for example, ripping out large areas of insulation that could contain asbestos.

Studies of other asbestos-exposed occupations have demonstrated that family members can be placed at risk for asbestos-related disease when workers bring their dusty work clothing home to be laundered[9], often contaminating the family car in the process. Fire fighters should take appropriate measures to ensure that dust from the fire site is not brought home, especially because young children may be at special risk for mesothelioma decades later, even following relatively low exposure levels.

Given the evidence of asbestos-related disease among fire fighters, consideration should be given to medical screening for asbestos-related scarring and cancers among particular groups of fire fighters whose risk of exposure to asbestos-containing materials is greatest. The IAFF supports

screening through the use of the IAFF's Wellness-Fitness Initiative. Screening exposed fire fighters has multiple benefits. Earlier disease detection may make curative treatment possible for some asbestos-associated cancers. Screening presents an opportunity for education on the health hazards of asbestos and for emphasizing the importance of eliminating further exposure. Prevention of disease can be achieved through the reduction of other risk factors, such as smoking.[10] Screening is a mechanism for fire fighters to gain access to medical care and appropriate follow-up treatment, and the diagnosis of illness related to asbestos exposure helps those affected to obtain medical monitoring and other compensation. Screening also assists in epidemiological surveillance of diseases caused by exposure to asbestos.

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Chapter 2-11
Sleep Apnea Syndrome

By Dr. Jaswinderpal Sandhu MD and Dr. David Appel MD

The word *apnea* in Greek language means "without breath". Sleep apnea is a condition in which a person literally stops breathing repeatedly during sleep, sometimes hundreds of times during a single night. The medical definition of apnea means not breathing for ten seconds, but often in people with sleep apnea syndrome these episodes are longer. Although people wake up gasping for breath, often they are unaware of these apneic episodes. Commonly it is accompanied by habitual snoring and excessive daytime sleepiness. The disordered breathing that arises from these repeated episodes of apneas during sleep when also associated with daytime sleepiness is referred to as *sleep apnea syndrome*. Sleep apnea syndrome may result from obstructive apnea or non-obstructive apnea, but the vast majority of people have Obstructive Sleep Apnea (OSA) which will be the focus of this chapter.

SLEEP

Adult humans spend one third of their time sleeping and most of us need seven to eight hours of sleep everyday. Sleep disorders are very common. Approximately 50% of adults in the United States experience intermittent sleep problems and 20% of adults report chronic sleep disturbance. Sleep disturbances often lead to daytime sleepiness that may interfere with daytime activity and cause serious functional impairment. Normally, daily sleep and wake alternates on a circadian rhythm of approximately 25 hours, also known as the biological clock. During daytime, active humans accumulate sleep factor(s) that promote sleep. Typically there is a midday sleep surge, but the accumulated sleep factor(s) are offset by a circadian wake-sleep mechanism that maintains wakefulness during the day. Sleep ensues when the wake portion of the circadian mechanism is turned off and the accumulated sleep factor(s) become relatively unopposed. This circadian rhythm is initiated and controlled by an area of the brain called the suprachiasmatic nuclei of the hypothalamus, and the light-dark cycle is mediated through the retinohypothalamic tract. Even low intensity light signals reset this rhythm every day so that changes in duration of daylight during different seasons are accommodated accordingly. Along with other various clues, a pineal hormone called melatonin, mostly secreted at night, serves as a trigger for the need to sleep.

Sleep Stages

Humans exist in three states: wakefulness, non-rapid eye movement sleep (NREM), and rapid eye movement (REM) sleep. Surprisingly, NREM sleep and REM sleep are as distinct from each other as NREM and REM sleep are distinct from wake.

Normal nocturnal sleep is divided into NREM and REM sleep. NREM sleep is comprised of four stages: Stage I (light sleep), Stage II, and Stages III-IV (deep slow wave or delta-wave sleep). Normally, people enter sleep via NREM sleep with most Stage III and IV sleep occurring in the first third of the night, fulfilling the first restorative obligation of sleep to offset sleepiness. Typically, every 90-120 minutes a period of REM sleep occurs. In the early portion of sleep these REM sleep periods are short and eventually they become longer as the sleep period progresses, with the longest REM sleep period occurring shortly before the end of sleep and the onset of waking. REM sleep probably is important for the processing of memory.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea occurs when during sleep complete obstruction of the pharyngeal airway results in total cessation of airflow from the nose and mouth despite effort by the respiratory muscles to breathe. When the pharyngeal obstruction is such that the airflow is shallow and not completely reduced the event is termed a *hypopnea.* An apnea-hypopnea index (AHI) is determined by assessing the frequency of apneas and hypopneas per hour of sleep. It is normal for some apnea and hypopnea to occur during sleep. Apnea-hypopnea occurring more frequently than five events per hour is abnormal, however. When associated with sleepiness the condition is termed obstructive sleep apnea syndrome (OSAS). Often apneas are associated with arousals and the number of arousals per hour of sleep is called the arousal index. The frequent sleep fragmentation and arousals produced by OSAS often results in profound daytime sleepiness.

Historical Perspective

Osler and later Burwell[1] used the name "Pickwickian Syndrome" to describe a condition involving obesity, chronic hypoventilation and hypersomnolence, based on the obese Charles Dickens character Joe, in the book, "The Posthumous Papers of the Pickwick Club." Obstructive sleep apnea has also been noticed by bedside observation as early as in 1877. In 1964, an illustration showing an obese, hypersomnolent and myxedematous woman with airflow cessation was published, but the authors did not realize the importance of this observation at that time. Gastaut et al in 1965[2], first described three types of apnea, in a patient with "Pickwickian Syndrome." They also postulated that the excessive sleepiness was due to the repeated arousals with the resumption of breathing that terminated the episodes of apnea.

Epidemiology

Obstructive sleep apnea is an increasingly recognized disorder that affects more than 12 million people in the United States. Studies have shown that OSA is a common disorder and poses a significant public health problem. [3] There has been a 12-fold increase in the annual number of patients diagnosed with OSA between 1990 and 1998.[4] Epidemiological studies have established that approximately four percent of men and two percent of women who are 35 to 65 years of age have OSA.[5,6] OSA has a higher incidence in post-menopausal women and is also more common in women than previously thought.

Risk Factors

Typically a person with sleep apnea is an obese male who snores loudly and may report choking and apnea during sleep. However, many patients do not exhibit this pattern. For example non-obese patients with micrognathia (an abnormally small lower jaw) or retrognathia (a receding chin) may have sleep apnea. Therefore, presence of certain clues in the medical history and physical examination should heighten the suspicion of obstructive sleep apnea.[7] A list of features contributing to sleep apnea syndrome is shown in Table 2-11.1.

Features Contributing to Sleep Apnea Syndrome
• Obesity (increased body mass index)
• Increased neck circumference (men 18+ inches; women 16+ inches)
• Anatomic abnormalities (e.g. retrognathia (receding chin), micrognathia, adenotonsillar hypertrophy, enlarged soft palate and macroglossia)
• Systemic disorders (e.g., hypothyroidism, acromegaly, amyloidosis)
• Down's Syndrome and post-polio syndrome
• Neurological disorders (e.g., Parkinson's disease)
• Smoking
• Alcohol consumption
• Medications (e.g. sedatives, sleeping pills, antihistamines)
• Nasal congestion

Table 2-11.1: Features Contributing to Sleep Apnea Ayndrome

Pathophysiology

The pharynx is the space in the back of the throat behind the tongue (Figure 2-11.1). It must be collapsible during speech and swallowing, but it must remain open during breathing. This complex function is accomplished by a group of muscles that can alter the shape of the pharynx during speaking or swallowing, while keeping it open during breathing. The upper airway muscles actually pull on the pharynx to maintain its open position during breathing.

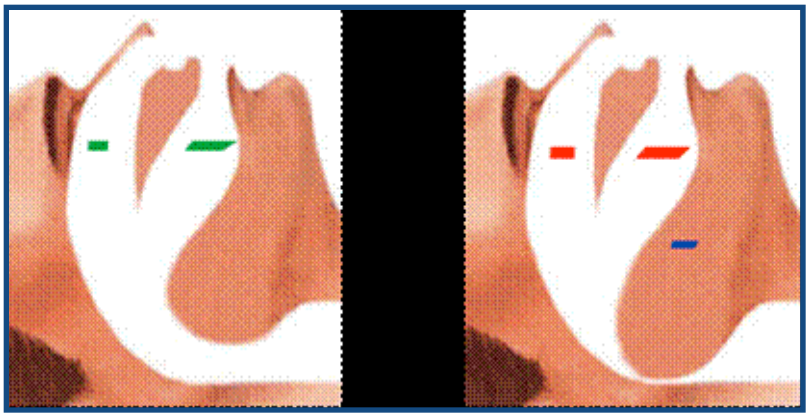

Figure 2-11.1: The panel on the left shows the pharynx during normal breathing. In a patient with OSAS, the airway closes and flow stops, as seen in the panel on the right.

However, during sleep there is general muscular relaxation, including the upper airway respiratory muscles, and in turn the reduced effort of these upper airway muscles leads to narrowing of the pharyngeal space. While awake, breathing is stimulated by both cortical influences (laughing, thinking and speaking) and chemical influences (acid-base changes, carbon dioxide tension, oxygen tension) in the body. In contrast during sleep, breathing is stimulated by chemical influences only.

Typically, people with OSA have a pharyngeal space that is smaller than normal, even when they are awake. This results in increased resistance of airflow in the upper airway. To compensate for this pharyngeal space narrowing, to overcome this increased upper airway resistance, and to maintain a patent upper airway, upper airway muscle activity in people with OSA while they are awake is actually greater than normal.[8] Sleep causes the following physiological changes:

- Upper airway muscles relax
- Reflex activity in the pharynx declines
- The need for chemical stimuli to breathe during NREM sleep increases (increased chemoreceptor set point)
- Surface tension of the upper airway increases

An abnormal pharynx can be kept open in wakefulness by an appropriate compensatory increase in dilator muscle activity,[8] but during sleep upper airway muscle tone declines. Loss of needed compensatory mechanisms imposed by sleep may lead to partial or complete collapse of the upper airway. Partial collapse results in snoring and hypopnea, whereas complete collapse results in episodes of apnea.

During the obstructive apneic episodes the individual continues to try to breathe against the closed upper airway. Carbon dioxide tension increases, oxygen tension decreases and secretion of an increased amount of flight or fight catecholamines (norepinephrine) intensify the effort to breathe. Ultimately this produces an arousal. During the aroused state the upper airway muscles are activated and in turn the pharynx opens. Breathing is restored, but this occurs at the cost of sleep. When the individual resumes sleep the upper airway events described above recur. Thus, a vicious cycle of breathing without sleep and sleeping without breathing is set in motion. Clinical consequences of this disordered breathing during sleep include excessive sleepiness, systemic hypertension, myocardial infarction, heart failure, fatal and non-fatal arrhythmias, stroke, metabolic syndrome and erectile dysfunction. While some of these mechanisms are summarized in Table 2-11.2, the exact mechanisms of how OSA leads to these clinical disorders are many, complex, and beyond the scope of this chapter.

Clinical Manifestations

The cardinal manifestations of OSA are excessive daytime sleepiness and sleep fragmentation caused by habitual snoring and nocturnal gasping.[9] However, a majority of the people with OSA under-report these symptoms and some might be totally unaware of their symptoms. Therefore, a focused history from people as well as their partners who have observed their disturbed sleep behavior can be crucial in identifying persons at risk for sleep apnea. People

with OSA commonly report that their sleep is unrefreshing. They wake feeling tired and often report dry mouth, grogginess, and headaches. They may doze off watching television, reading, at the dinner table, in waiting areas and during conversation. This disorder frequently impairs driving and is a major cause of serious automobile accidents.[10,11] Personality changes, depression and impaired memory may lead to a decline in work quality. Common clinical manifestations of obstructive sleep apnea are listed in Table 2-11.3.

Mechanisms of Different Clinical Disorder Arising from OSA	
Disorders	*Mechanisms*
Cardiovascular and Cerebrovascular disorders	Repeated episodes of negative intrathoracic pressure Increased right and left ventricular afterload Increased level of norepinephrine Increased levels of cytokines: Interleukin 6, 8 and Tumor Necrosis Factor (TNF)-alpha Other inflammatory factors
Metabolic syndrome	Disruption of slow wave sleep Interruption of growth hormone
Erectile dysfunction	Reduced amount of REM sleep; increased pro-inflammatory mediators producing small vessel disease

Table 2-11.2: Mechanisms of Different Clinical Disorders Arising from OSA

Common Clinical Manifestations of Obstructive Sleep Apnea	
Hypertension Myocardial infarction Heart failure Stroke Disrupted sleep Trouble waking up in the morning Dry mouth in the morning Morning headaches Twitching or limb movement	Memory impairment Morning confusion Intellectual impairment Inability to focus Personality changes Irritability Depression Automobile accidents Impotence Night sweats

Table 2-11.3: Common Clinical Manifestations of Obstructive Sleep Apnea

Clearly, OSA has been associated with cardiovascular disease,[12] diabetes mellitus,[13] stroke[14], lipid abnormalities,[15] and pulmonary vascular disease.[16]

Diagnosis

A carefully focused history and physical examination should identify individuals with sleepiness or sleep-breathing disorders.[17] The only way to objectively diagnose OSA, however, is to perform an overnight sleep study (polysomnogram) in a qualified sleep laboratory. Therefore people with reports of daytime sleepiness, loud snoring and choking should be considered for a sleep study.[18]

Typically, polysomnography is a comprehensive overnight study performed in a sleep laboratory by trained technicians who monitor sleep stages, arousals

from sleep, eye movements, breathing effort, airflow, snoring, heart rate and rhythm, body position, limb movements and oxygen saturation (Figure 2-11.2). These measurements enable the diagnosis of both pulmonary and non-pulmonary disorders of sleep.

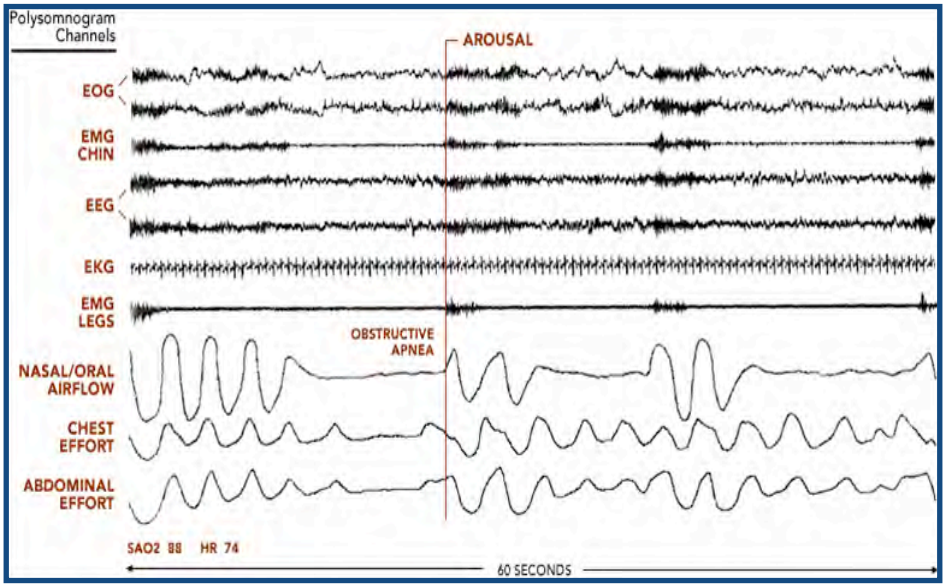

Figure 2-11.2: A polysomnogram of a patient with obstructive sleep apnea. *(Note the lack of flow in the setting of chest and abdominal effort, followed by an arousal.)*

People with OSA often have very rapid sleep onset, but their sleep is interrupted by apnea and is terminated by arousal. This cycle of events is captured on the polysomnogram recording. Soon after the resumption of the breathing, the person resumes sleep and apnea recurs to repeat the cycle. The duration and number of apneas vary among people with OSA. Because respiratory muscles typically lose their tone during REM sleep, OSA is often more severe during this sleep stage. Proper evaluation of the patient should include a sleep sample sufficient to establish the diagnosis and severity of sleep apnea. When moderate or severe sleep apnea is found, a second sleep sample should be obtained during which continuous positive airway pressure (CPAP) is titrated to establish effective CPAP. While mild, OSA may also be treated with CPAP, other treatment such as oral appliances and otolaryngological surgery may be effective. The effectiveness of any treatment of OSA should be validated with overnight sleep studies.

A polysomnogram performed in a sleep laboratory is the gold standard to diagnose obstructive sleep apnea. Because of the relative scarcity of sleep laboratory availability for people with suspected OSA, there is a growing trend for in-home (unattended) sleep studies. We believe, however, that at this time these studies may provide ambiguous or limited information. We further believe that CPAP cannot be accurately titrated during an unattended sleep study. In-home sleep studies may be useful, however, to screen presumed at risk individuals for laboratory sleep studies. To further evaluate patients with sleep apnea and its clinical consequences, the tests often performed are listed in Table 2-11.4. These tests may be obtained to formulate a fuller picture regarding the clinical consequences of OSA in a person with the disorder, but in no way do these tests establish the diagnosis of OSA.

Commonly Used Laboratory Investigations
Complete blood count (polycythemia) Arterial blood gas (obesity hypoventilation syndrome) Electrocardiogram Echocardiogram (right heart failure) Pulmonary function testing (lung volume and saw tooth pattern on flow volume loop) Cephalometrogram

Table 2-11.4: Commonly Used Laboratory Investigations

Treatment of OSA

The goals of treatment of OSAS are to alleviate excessive daytime sleepiness (EDS) and to reduce the frequency of apnea-hypopnea (AHI) to levels not associated with increased cardiovascular and cerebrovascular risk. Attenuation of disruptively intense snoring may have important social implications, however, if the snoring is primary and not associated with OSA, then treatment of such snoring should be decided on its own merits.

Mild OSA (AHI = 6 – 15 events/hour) has not been clearly associated with increased cardiovascular and cerebrovascular risk. Thus, those with mild OSA who lack sleepiness may be best treated with education regarding the causes and risks of OSA, counseling with regard to good sleep hygiene, diet and weight loss, avoidance of alcohol, sedatives, and antihistamines, and possibly use of positional therapy (techniques to avoid sleeping supine).[19] Even for people who lack OSA, regular sleep-wake hours, sufficient sleep hours (most adults require 7 – 8 hours of sleep per day), exposure to sunlight in the early morning, daily exercise (30 – 60 minutes/day but not within two hours of bedtime), limiting caffeine consumption, and completing the evening meal three or four hours before bedtime should be encouraged strongly. Weight loss has been shown to reduce mean AHI.[20,21]

People with mild OSA and coexisting EDS and people with moderate or severe OSA (AHI = 16 – 29 events/hour, and 30 or more events/hour, respectively) with or without EDS need additional treatment specifically directed to attenuating the frequency of apnea and hypopnea. In successfully doing so, sleep becomes less fragmented so that daytime alertness is restored. Furthermore, the apnea-hypopnea-hypoxia associated release of catecholamines and pro-inflammatory mediators is sufficiently attenuated to remove cardiovascular and cerebrovascular risks from OSAS. CPCP, invented by Sullivan in 1981,[22] is the most commonl-prescribed and overall most effective treatment of OSAS and has replaced tracheostomy (now rarely performed for OSAS) as the treatment of choice. Regular CPAP use has been shown to improve quality of life, reduce daytime sleepiness, improve neuropsychiatric function,[23,24] reduce the need for medication to treat hypertension, and reduce the risk for adverse cardiovascular and cerebrovascular events among people with OSAS.[25] With CPAP treatment, positive airway pressure (PAP) is applied to the nose, or nose and mouth, through nasal “pillows”, nasal mask, or full facemask that covers the nose and the mouth. The PAP is transmitted across the nasal and oral cavities to the pharynx. Optimal PAP is determined during an overnight sleep study and it is that PAP that keeps the pharynx open (like an air splint) while the person sleeps in all positions and all sleep stages so that the AHI while using CPAP is < 6 events per hour (Figure 2-11.3).

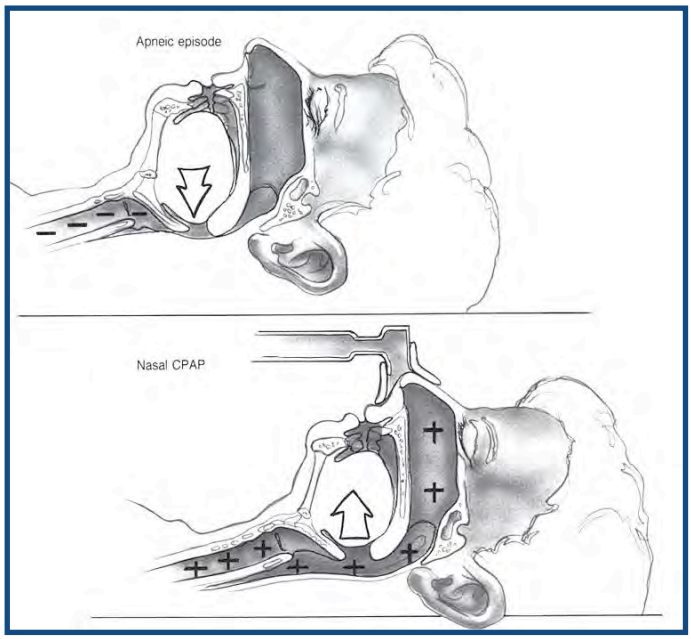

Figure 2-11.3: Effects of nasal CPAP. The top panel shows the occlusion of the upper airway and apnea. The lower panel shows the pneumatic stent properties of CPAP.

There are two varieties of CPAP: (1) CPAP where the positive airway pressure is kept constant throughout both inspiration and expiration (this is termed CPAP) and (2) CPAP where the positive airway pressure is somewhat lower during expiration than during inspiration (this is termed bi-level positive airway pressure or Bi-PAP). The choice of CPAP or Bi-PAP is based on clinical and technical considerations made at the time of the sleep study. Once determined, the needed equipment is prescribed for this person to use at home on a nightly basis. CPAP corrects OSA while the CPAP is being used, but CPAP does not eliminate the underlying tendency for OSA. Thus, CPAP must be used every night throughout the entire sleep period until it can be shown on an overnight sleep study that the affected individual no longer has OSA (e.g., after sufficient weight loss in patients with OSA). Compliance with CPAP use is a major concern. Discomfort from the mask, dry mouth and nose, skin irritation, and claustrophobia are the more common problems contributing to non-compliance with CPAP use while nose bleeds, swallowing of air, and pneumothorax occur much less frequently. Often the reasons for non-compliance with CPAP use are not clear. Early acquisition and application of CPAP following the diagnostic sleep study, patient education, motivation, reassurance, relaxation techniques, and the sense of improved alertness all help to promote compliance with CPAP use. Several studies have shown a majority of patients used CPAP in excess of four hours/night for more than two-thirds of the observed nights.[23]

OSAS treatment other than CPAP may be considered when CPAP is ineffective, the treated individual cannot use the device, or the treated individual prefers an alternative treatment. Alternative treatments include surgical approaches (tracheostomy, uvulopalatopharyngoplasty (UPPP), genioglossal advancement, maxillomandibular advancement, splints) and non-surgical approaches (intra-oral mouthpiece appliances). To date, for almost all people with OSAS, there are no medications that safely, effectively, and reliably correct OSAS.

Tracheostomy was first introduced as a successful treatment for sleep apnea in 1969 and was widely accepted as the treatment of choice. Tracheostomy, performed by ear nose and throat surgeons, involves cutting a hole into the trachea through which a tube is inserted to create a continuously patent airway through which the patient breathes. This bypasses the site of upper airway obstruction that causes OSA. Typically, the individual closes the tracheostomy tube in the day and opens it for sleep at night. Similar to CPAP, sleeping with an open tracheostomy corrects symptoms and morbidity related to OSA, but does not "cure" one of OSA. Even after years of normal sleep and breathing through open tracheostomy, closing the tube results in immediate apnea.[26] Because of the medical and psychosocial morbidity associated with tracheostomy and the invention of CPAP, its use has greatly diminished. Tracheostomy is usually reserved for patients with severe OSA who cannot tolerate CPAP and are not effectively managed by other treatment options.[27,28]

A variety of surgical interventions are used to modify specific sites of upper airway obstruction. The goal of all these procedures has been to create a more capacious pharyngeal space. Tonsillectomy is very effective in children and often the treatment of choice. However, it is usually ineffective in adults. UPPP involves separation of the soft palate from the posterior pharyngeal wall and enlargement of the entire space by removing the tonsils and uvula. Defining a successful operation as one that reduced AHI by 50% one year after surgery, Sher, in his meta-analysis[29], found that in about 40% of patients, UPPP successfully corrected OSAS. Many of the reports in his analysis were anecdotal, however. Importantly, if more stringent criteria for success are applied (AHI = 6 – 10 events/hour), then even fewer people were helped by UPPP. Generally, the procedure is not recommended for people with moderate or severe OSA. This procedure should be performed by otolaryngologists experienced in the treatment of OSAS. Recently, laser uvulopalatopharyngoplasty has been tried for snoring but is not recommended for the treatment of OSA. Genioglossal advancement is performed for obstruction at or below the base of tongue and sometimes also involves resuspension of the hyoid bone.

Mandibluar advancement also known as Le Fort Type I osteotomy and maxillomandibular advancement have been employed in the treatment of sleep apnea. Patients who have craniofacial abnormalities[30,31] and those who have failed genioglossal advancement or uvulopalatopharyngoplasty may benefit from these procedures. Excessive advancement sometimes leads to temporo-manibular joint problems.

Intra-oral mouthpiece appliances have been shown to be effective among people with mild OSA. The American Academy of Sleep Medicine does not recommend their use for moderately severe and severe OSA. They should be crafted by an oral surgeon or dentist with experience in treating OSA. Unfortunately, these mouthpieces do not always correct even mild OSA and there is no reliable way to be completely certain the mouthpiece will correct OSA before it is made. Once made, the individual should undergo an overnight sleep study while using the mouthpiece to assure its efficacy. Some find that sustained use of the mouthpiece overnight to be uncomfortable and temporo-mandibular joint problems from prolonged use have been described.

People with OSAS undergoing surgery with general anesthesia or who are undergoing procedures with use of sedation need special consideration. We suggest the following as cautious and prudent guidelines. When intubation is planned, the patient should be seen by the anesthesiologist well before the planned surgery to determine whether there are problems of intubation related to the patient's crowded pharynx. Following surgery, the patient should be extubated when awake, in a monitored setting, and then should have CPAP applied at a pressure setting previously determined to be effective. CPAP should be administered whenever the patient is sleeping or receiving potentially-sedating medications. Such patients should be observed in a monitored setting over the first 24 to 36 post-operative hours. For those undergoing procedures under sedation, use of CPAP while the patient is sedated is recommended.

CENTRAL SLEEP APNEA

In contrast to OSA, in Central Sleep Apnea (CSA) there is no airflow from the nose or mouth because there is no effort to breathe. While people with OSA may have also some CSA, by itself CSA is relatively less common. Instability of the central respiratory mechanism produces a decrement or transient termination of neural signal output from the respiratory center in the brainstem to the respiratory muscles. This results in the absence of an effort to breathe, absence of airflow from the nose and the mouth (apnea), oxyhemoglobin desaturation, and arousal from sleep.

Typically, people with CSA are men, in their fourth to fifth decade of life, who experience headaches, excessive sleepiness, lethargy, may snore and have hypercapnia. The most common condition associated with CSA is congestive heart failure (CHF) with Cheyne-Stokes breathing.[32] Other conditions associated with CSA include primary dysfunction of the central ventilatory drive (Ondine's curse),[33] metabolic derangement or respiratory muscle disorders, high cervical cord injury, brainstem surgery, birth injuries, bulbar poliomyelitis,[34] encephalitis,[35] brainstem tumors, carotid endarterectomy,[36] Parkinson's disease,[37] hypothyroidism, metabolic alkalosis,[32] respiratory muscle dysfunction due to myasthenia gravis, amyotrophic lateral sclerosis, Guillain-Barre Syndrome and spinal muscle atrophy.

Initially, people with CSA may be thought to have OSA due to the similarity of their clinical manifestations. Definitive diagnosis is made by a sleep study that shows repeated apneas without respiratory efforts. The mainstay of treatment of CSA is treatment of the underlying disorder and avoidance of sedating medications and alcohol. Patients with hypoxemia usually have a good response to nocturnal supplemental oxygen. Others, especially those with CHF and interventricular devices, have been shown to respond to CPAP. Patients with neuromuscular disorders should preferably sleep in an upright position and avoid sleeping in a supine position. In the earlier stages of neuromuscular disease, CPAP may be helpful. However, as the neuromuscular disease progresses and respiratory muscles weaken, often tracheostomy and assisted mechanical ventilation is needed. Some of these people may benefit from diaphragmatic pacing.[38]

MIXED APNEA

Mixed apnea occurs when a central apnea is terminated with an obstructive apnea. The mixed apnea is a manifestation of both abnormalities of central respiratory drive instability and of pharyngeal upper airway occlusion. Functionally, however, mixed apneas are more similar to obstructive apneas. Diagnosis of mixed sleep apnea is made by a sleep study. Nasal CPAP is the most effective treatment option and has been shown to improve quality of life similar to patients with OSA.

UPPER AIRWAY RESISTANCE SYNDROME

Upper airway resistance syndrome (UARS), first described by Guilleminault,[39] is a milder form of disturbed breathing during sleep where increased upper airway resistance in the absence of frank apnea produces frequent arousals and in turn excessive daytime sleepiness. UARS is more common in women. People with excessive sleepiness and disturbed sleep due to UARS are diagnosed and treated similarly to those with OSA.

NARCOLEPSY

It is beyond the scope of this chapter to discuss narcolepsy in depth. A brief description is included here because there is a popular use of the word "narcolepsy" to describe any individual who has excessive daytime sleepiness.[40] While OSAS is a major cause of EDS, many conditions can produce EDS including (but not limited to) narcolepsy, restless leg syndrome, periodic limb movement disorder, insufficient sleep syndrome, and circadian sleep disorders. While narcolepsy causes EDS, EDS is not narcolepsy. Importantly, while narcolepsy and OSAS may coexist in some individuals, most afflicted with narcolepsy do not have OSAS and by far, most afflicted with OSAS do not have narcolepsy.

Narcolepsy is a neurological condition most often resulting from lesions in the posterior hypothalamus where cells that produce the alerting neuro-peptide hypocretin (also called orexin) are in various stages of decay or death. As a result, lower amounts of hypocretin are produced and secreted and proportionally the alerting effects of this peptide are lost. Overnight sleep studies among people with narcolepsy typically show an earlier than usual onset of the first REM sleep period and highly-fragmented sleep from spontaneous arousals. Of interest, narcolepsy is a REM sleep dissociative condition where during wakeful states intrusions of REM sleep occur. Fragmentation of the major sleep period and REM sleep intrusion into the wakeful state account for the clinical features which include excessive daytime sleepiness, memory impairment, dissociative behaviors (i.e., disruptions of aspects of consciousness, identity, memory, motor behavior, or environmental awareness), hypnogogic or hypnopompic hallucinations (visual, tactile, auditory, or other sensory events that occur at the transition from wakefulness to sleep (hypnagogic) or from sleep to wakefulness (hypnopompic)), sleep paralysis (a period of inability to perform voluntary movements either at sleep onset or upon awakening), and cataplexy (condition in which a person suddenly feels weak and collapses at moments of strong emotion). While any sleep-depriving condition may produce EDS, hypnogogic hallucinations, sleep paralysis, and with rare exceptions, cataplexy occur exclusively in narcolepsy. Narcolepsy may exist

with or without cataplexy. The condition occurs equally in men and women. In the United States, one out of 2,000 people are affected.[41,42,43]

Typically, the illness first occurs most often in early teens and late in the third decade of life. There is a genetic association with human leukocyte antigens HLA DR2 and DQ1, however, this association is less strong among African-Americans. The diagnosis is made from a carefully-obtained medical history and is supported by the results of overnight sleep studies followed by a multi-sleep latency testing. The sleep study shows early onset to the first REM sleep period, fragmentation of sleep by spontaneous arousals, and absence of other sleep fragmenting phenomena such as apnea or periodic limb movements. A mean sleep latency of less than eight minutes and two sleep onset REM periods is seen on a multi-sleep latency test. In some cases, measurement of hypocretin-orexin levels in the cerebrospinal fluid is helpful. The condition is treated medically with sleep hygiene techniques that include sufficient hours of sleep (major sleep period), regularly timed naps, medications to promote alertness, and medications that promote sleep consolidation and inhibit cataplexy. The illness is chronic and education, counseling, and supportive measures are often crucial.

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Chapter 2-12
Cough

By Dr. Peter V. Dicpinigaitis MD

Cough is the most common complaint for which patients in the United States seek medical attention.[1] An estimated two billion dollars are spent annually on prescription and over-the-counter (OTC) cough remedies in the United States alone. Fortunately, cough is usually a temporary and self-limited condition. When cough lingers, however, it becomes a troubling problem for the patient and may indicate a more serious underlying condition that requires medical attention. The importance of cough as a clinical problem is reflected in the fact that recently, three major organizations of pulmonary physicians have published guidelines on the management of cough.[2,3,4]

Cough is classified according to its duration (Table 2-12.1). Acute cough refers to a cough present for three weeks or less. If a cough persists for greater than three but less than eight weeks, it is termed subacute. Chronic cough refers to a cough that has been present for greater than eight weeks.[2,3] This distinction is quite important because the various types of cough have different underlying causes.

Classification of Cough by Duration	
Acute	< 3 Weeks
Subacute	3 - 8 Weeks
Chronic	> 8 Weeks

Table 2-12.1: Classification of Cough by Duration

Although we typically consider cough an annoying symptom, it is important to realize that cough is an important defense mechanism. An intact cough reflex effectively clears secretions out of the lungs, and prevents foreign objects from entering the airways.

MECHANISM OF COUGH

The upper and lower respiratory tract are lined with receptors that, when stimulated by a variety of different triggers, can cause cough. The two main types of receptors that induce cough are the rapidly adapting pulmonary stretch receptors, or RARs, and the C-fibers.[5] When these receptors are stimulated, they send impulses to the brain that produce cough. The nature of the communication between the receptors in the respiratory tract and the brain remains poorly understood.

More recently, a specific type of receptor, called the TRPV1 (transient receptor potential vanilloid 1), has been discovered.[6] The TRPV1 is likely one of multiple types of receptors important in causing cough. An active area of current research is the discovery of antagonists (blockers) of the TRPV1 receptor that might be effective future drugs for the treatment of cough.

ACUTE COUGH

As mentioned above, a cough lasting less than three weeks is termed an acute cough. Most cases of acute cough are caused by viral upper respiratory tract infections (URI), i.e., the common cold. Acute cough due to URI is usually self-limited, lasting for only a few days. It is typically non-productive (dry) or is accompanied by small amounts of clear phlegm. Although acute cough due to the common cold is usually short-lived, many individuals seek OTC remedies at their pharmacy to help suppress this annoying symptom. Unfortunately, there is very little scientific evidence that many of the commonly-used cough and cold products sold worldwide are actually effective against cough due to the common cold. In fact, the recent cough management guidelines published by the American College of Chest Physicians (ACCP) recommend that individuals not rush to treat an acute cough, since the cough is usually temporary and few products commercially available have ever been shown to be effective.[2]

The only therapy for cough due to the common cold that has been demonstrated to be effective in adequately-performed clinical studies is a combination of an older-generation antihistamine (such as chlorpheniramine or brompheniramine) and a decongestant (such as pseudoephedrine). One potential drawback of the so-called older-generation antihistamines is that they may cause sedation (drowsiness). The newer-generation antihistamines, such as loratidine (Claritin), cetirizine (Zyrtec), and fexofenadine (Allegra) are less likely to cause sedation and may be useful in relieving allergy symptoms, but they are ineffective in suppressing cough.[2,7] Thus, if relief from an acute cough due to URI is desired for fire fighters and other emergency responders, a combination of an older-generation antihistamine and decongestant is recommended.[2] An important exception to this statement is for acute cough in children. Because these medications have not been shown to be effective against cough in children, and because they can cause side effects that may lead to dangerous behavior in children, such as drowsiness induced by the antihistamines, or hyperexcitability due to pseudoephedrine, the 2006 ACCP guidelines do not recommend the use of any medications to treat acute cough due to the common cold in children.[2]

The previous discussion of acute cough has focused on cough due to URI (common cold). However, it is important to understand that the sudden onset of cough can represent a serious underlying condition that requires immediate medical attention. For example, if the cough is productive, meaning that sputum (phlegm) is produced, especially if the sputum is yellow, green, or blood-streaked, a bacterial bronchitis may be present that would require antibiotic therapy. If these symptoms were associated with high fever, chest pain on breathing in, or significant illness, pneumonia would need to be excluded. Any significant amount of blood produced with coughing requires emergent medical attention, as this could indicate a serious underlying process such as bacterial infection (pneumonia), tuberculosis (TB) or lung cancer. The production of pink, frothy sputum in the setting of shortness of breath and/or chest pain could indicate pulmonary edema (lungs filling up with fluid) that is a sign of heart failure.

Acute Cough and OTC Cough and Cold Products

The ACCP cough guidelines, published in January, 2006 caused a great deal of controversy and gained significant media attention because of their statement that most OTC cough and cold preparations are ineffective against acute cough due to the common cold. There are several likely explanations for the guidelines' conclusion, which was based on a thorough review of the medical literature. Firstly, the guidelines evaluated only studies that were performed in a scientifically rigorous manner. Many of the OTC cough and cold preparations currently available were approved decades ago when criteria for approval of new medications were less stringent and pharmaceutical companies were not obligated to perform and publish exhaustive and meticulous clinical trials.

Secondly, studies of potential therapies for acute cough are difficult to perform. Since acute cough due to the common cold typically resolves spontaneously within a few days, it is challenging to design a study that could demonstrate a drug to be more effective than a placebo. For statistical reasons, a very large number of subjects would need to be evaluated, thus necessitating lengthy and expensive trials. Further complicating matters is the fact that there has been a strong placebo response noted in cough trials.[8] Many studies of cough syrups, for example, have used a placebo syrup to compare to the study drug. However, previous research has shown that a sweet, thick syrup, without any medication, can have a cough suppressing effect (demulcent effect).[8]

Another likely explanation for the failure of some cough medications to show efficacy in clinical trials is that they may contain insufficient amounts of the cough-suppressing (antitussive) agent. For example, dextromethorphan is a non-narcotic opioid drug that is a component of hundreds of cough and cold preparations sold worldwide. Studies have shown that dextromethorphan, at doses of 30 mg or more, is an effective cough suppressant.[9] However, many of the commonly-used cough preparations contain significantly less than 30 mg of dextromethorphan per recommended dose.

SUBACUTE COUGH

When cough persists beyond three weeks (but less than eight weeks) it is termed a subacute cough. Most cases of subacute cough are likely the result of acute cough due to viral URI (common cold) failing to resolve. Why this so-called postviral (or postinfectious) cough lingers in a subgroup of individuals is not well understood. It is probably due to severe irritation of the cough receptors by the initial viral infection of the airways, and subsequent inability of the inflamed area to heal because of persistent coughing that continues to irritate the lining of the respiratory tract.

Subacute, postviral cough has proven to be a difficult condition to treat. For severe cough, a 1-2 week course of oral steroid therapy (with prednisone, for example) is often effective.[10] However, there are few studies evaluating whether inhaled steroids, which are associated with significantly less side effects than oral steroids, are useful for this type of cough.[2,10] Over-the-counter cough and cold remedies tend to be ineffective for subacute, postviral cough.

Another potential cause of subacute cough is pertussis, or whooping cough.[2] Recently, whooping cough has re-emerged as a significant medical issue in the non-pediatric population. Indeed, in 2004, 27% of reported cases of whooping

cough occurred in adults and adolescents. This rise in the incidence of whooping cough is likely due to the waning of immunity that was acquired by adults who had infection prior to the availability of the pertussis vaccine in the 1950s, and, the waning of immunity provided by vaccines that were administered more than a decade previously. Therefore, the ACCP cough guidelines recommend that adults receive the newly available acellular vaccine for protection against this infection.[2] The cough due to pertussis can take the form of violent episodes associated with vomiting, but the characteristic "whooping" sound is in fact present in only a minority of patients.

Some cases of subacute cough will persist beyond eight weeks and therefore will fulfill the definition of chronic cough. A discussion of chronic cough follows below.

CHRONIC COUGH

Chronic cough is the result of one or more underlying conditions persistently stimulating the cough receptors that line the upper and lower respiratory tract. Chronic cough is a serious issue not only because it exposes an underlying illness, but also because of its effect on an individual's quality of life. For example, chronic cough may result in physical problems such as difficulty sleeping, chest pain, throat soreness, exhaustion and, especially in women, urinary incontinence. Many patients who have suffered from chronic cough for months or years become socially isolated, afraid to go out in public for fear of a severe coughing attack drawing unwanted attention. Further worsening the situation is the effect that an individual's chronic cough can have on spouses, family members and coworkers. It is not surprising, therefore, that a recent study demonstrated a very high incidence of symptoms of depression among patients presenting to a specialized cough center for evaluation and treatment.[11]

Causes of Chronic Cough

Multiple studies have shown that in patients who are nonsmokers and who do not have an active pulmonary process demonstrated on chest x-ray, the vast majority of cases of chronic cough are due to one or more of the following conditions:

- Postnasal drip syndrome (PNDS), renamed upper airway cough syndrome(UACS)
- Asthma
- Non-asthmatic eosinophilic bronchitis (EB)
- Gastroesophageal reflux disease (GERD)

Often, more than one of these conditions may be present simultaneously, so a partial response to a particular treatment may indicate that only one of multiple underlying causes of cough have been addressed.

Postnasal Drip Syndrome (PNDS)

Multiple studies performed in the United States have shown PNDS to be the most common cause of chronic cough.[2] PNDS is not a disease but a response to one of many possible stimuli, including viral URI (common cold), allergies,

and sinus infection. Cough may result from the inciting inflammatory process stimulating cough receptors in the upper airway, or from mucus "dripping" down into the back of the throat and mechanically inducing cough. PNDS has recently been renamed upper airway cough syndrome (UACS) to better describe what is likely a multifaceted condition or variety of processes.[2]

The most effective treatment for chronic cough due to UACS is the combination of an older-generation antihistamine (such as chlorpheniramine or brompheniramine) and a decongestant (such as pseudoephedrine).[2] This therapy was also discussed under acute cough due to the common cold. Other treatments that may be effective for chronic cough due to UACS include nasal steroids, nasal ipratropium (Atrovent), and nasal cromolyn. As is the case for acute cough due to the common cold, the newer-generation, non-sedating antihistamines are not effective for UACS-induced cough.

Asthma

Studies have shown that asthma may account for approximately 25% of cases of chronic cough in adults.[2] Cough likely results from the inflammatory stimulation of cough receptors that line the airways. Asthma may be suggested as the cause of chronic cough if the typical associated symptoms of shortness of breath and/or wheezing are present. However, in a subgroup of asthmatics, cough is the sole symptom. This condition is termed cough-variant asthma.

The treatment of chronic cough due to asthma is identical to that of the typical form of the disease: inhaled bronchodilators and inhaled steroids. Studies have shown, however, that up to eight weeks of therapy with an inhaled steroid may be required for resolution of cough.[12] The newest class of asthma drugs, the leukotriene receptor antagonists (LTRAs), have been shown to be particularly effective in cough-variant asthma.[13] Since asthma is a disease of chronic airway inflammation, chronic anti-inflammatory therapy is required to prevent the permanent changes of untreated airway inflammation. Recent evidence suggests that cough-variant asthma should also be treated with chronic anti-inflammatory therapy to prevent irreversible changes.[14]

Non-Asthmatic Eosinophilic Bronchitis (EB)

Only during the past two decades has the condition of non-asthmatic EB been identified and appreciated as an important cause of chronic cough.[15] The airway changes of EB are similar to those of asthma: there is an infiltration of inflammatory cells called eosinophils. Eosinophilic bronchitis differs from asthma in that there is no demonstrable reversibility of airway obstruction with inhaled bronchodilators, and there is no hyperresponsiveenss to methacholine, both of which are hallmarks of asthma. However, chronic cough due to EB responds very well to inhaled steroids and thus, it is likely that some cases of EB are misdiagnosed as asthma. Although the prevalence of chronic cough due to EB has not been formally investigated in the United Staes, two European studies have shown the incidence of EB among patients presenting for evaluation of chronic cough to be about 12%.[16,17]

Gastroesophageal Reflux Disease (GERD)

Multiple prospective studies have shown that GERD is among the most common causes of chronic cough.[2] Chronic cough due to GERD may be difficult to diagnose because more than half of patients with GERD-induced cough do not display the typical symptoms of GERD such as heartburn.[2] Thus, a high index of suspicion must be maintained when evaluating a patient with chronic cough.

Cough due to reflux may result from multiple mechanisms. The mere presence of acid refluxing from the stomach into the distal esophagus may stimulate nerve endings to trigger an esophageal-tracheobronchial reflex resulting in cough. Alternatively (or, additionally), acid may travel further up the esophagus and penetrate the upper airway (larynx) to stimulate cough receptors. This phenomenon has been termed laryngopharyngeal reflux (LPR) and may be very important in terms of reflux-induced cough.

Once the diagnosis of GERD-induced cough is suspected, aggressive medical therapy is required. Often, patients with chronic cough due to GERD need higher doses of medication and longer duration of therapy than patients with typical GERD symptoms (i.e., heartburn) without cough. For example, high-dose therapy with twice-daily proton-pump inhibitors (PPIs; very strong acid-suppressing medications such as Protonix®, Nexium®, Aciphex® and Prevacid®) for at least two months is often required. In some patients, cough persists even though refluxing stomach acid is completely eliminated by the PPI medication. In this subgroup of patients, cough may be due to the reflux of non-acid material into the esophagus. In such cases, additional treatment in the form of prokinetic therapy is required with medications such as metaclopramide. The prokinetic agent limits the reflux of gastric contents into the esophagus and works together with the acid suppressing medication.

When maximal medical therapy is inadequate to control chronic cough due to GERD, surgical intervention may be considered. A procedure called a laporoscopic Nissen fundoplication surgically tightens the junction between the stomach and esophagus to prevent reflux. Unfortunately, the procedure has not proven to be completely effective since some patients achieve only a partial or temporary response.[18]

It is important to realize that, in addition to taking medication, lifestyle measures are essential in treating GERD. Suggestions that GERD patients should follow in an attempt to minimize reflux, and hopefully improve cough, are as follows:

- Sleep with head elevated (2-3 pillows)
- Do not eat within 2 hours of bedtime
- Avoid foods/beverages that worsen GERD
  - Alcohol
  - Caffeine (coffee, tea, cola drinks)
  - Chocolate
  - Peppermint
  - Spicy foods
  - Fatty foods

OTHER SPECIFIC ISSUES RELEVANT TO CHRONIC COUGH

Cigarette Smoking

Chronic cough in a cigarette smoker may be due to any of the causes discussed previously, however, smoking itself must be excluded as a cause of cough. Anecdotal experience suggests that cough due to smoking will resolve or significantly improve within four weeks of quitting. If cough does not resolve after four weeks of abstinence from tobacco, other causes need to be evaluated. A chest x-ray and pulmonary function tests (PFTs) should be performed to exclude evidence of infection, cancer, or chronic obstructive lung disease (chronic bronchitis, emphysema).

Interestingly, research studies have shown that smokers have a diminished cough reflex sensitivity compared to nonsmokers.[19] In other words, it is more difficult to experimentally induce cough in a smoker compared to a nonsmoker. This is probably due to chronic cigarette smoke-induced desensitization of cough receptors lining the respiratory tract. Furthermore, after as little as two weeks of smoking cessation, the cough reflex becomes measurably more sensitive, even in subjects who had been smoking for many years.[20] Because cough is an important protective reflex, these recent findings are significant in that they reveal another potential adverse consequence of smoking. Indeed, cigarette smoke-induced suppression of the cough reflex might explain why smokers are more inclined to suffer respiratory tract infections compared to nonsmokers.[20]

Gender

Multiple studies have shown that women have a more sensitive cough reflex than men, i.e., it is easier to experimentally cause cough in women. This has been shown in studies of healthy subjects[21,22] and in patients with chronic cough.[23] These findings likely explain why the majority of patients seeking treatment in specialized cough centers are women.[2,23]

Medications Taken for Other Reasons

A group of medications known as the angiotensin converting-enzyme (ACE) inhibitors are commonly used to treat hypertension and congestive heart failure. This is the only class of drugs known to cause cough, and does so in 5 - 20% of patients taking these medications.[2] The cough is typically associated with a dry, tickling sensation in the throat. Cough may occur within hours of the first dose of the ACE inhibitor, or may ccur months to years later. The only uniformly successful treatment for ACE inhibitor-induced cough is to stop the medication. In most patients, cough will resolve within one week, although in a subgroup of individuals, the cough may linger for several months. Fortunately, an alternative class of drugs, the angiotensin receptor blockers (ARBs), is available and is not associated with cough.

WORLD TRADE CENTER COUGH

Immediately after the collapse of the World Trade Center on September 11, 2001, members of the New York City Fire Department and other rescue workers were exposed to high concentrations of dust and ash that spread throughout the area. Within several months of the attack, it was observed that many of those exposed developed a persistent cough, eventually termed "World Trade Center cough."[24] As these exposed workers continued to be followed and evaluated over time, it was established that World Trade Center cough was likely a result of various conditions induced by the inhalation of toxic materials, including damage to the upper airways and sinuses (chronic rhinosinusitis); GERD (see discussion above); and damage to the lower airways inducing an asthma-like condition known as reactive airways dysfunction syndrome (RADS).[25] Treatment is aimed at the suspected underlying conditions in a given patient, including inhaled nasal steroids and decongestants for rhinosinusitis; acid-suppressing medications and dietary modifications for GERD (see discussion above); and inhaled bronchodilators and steroids for asthma-like symptoms.[25]

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Chapter 3-1
Inhalation Lung Injury from Smoke, Particulates, Gases and Chemicals

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INHALATION RESPIRATORY ILLNESSES FROM AEROSOLIZED PARTICULATES

Nearly all types of disasters (i.e., fire, building collapse, explosion, volcano, earthquake, hurricane, flood, etc.) liberate high concentrations of aerosolized particulate matter. Classically particles larger than 3 microns in diameter are thought to be deposited in the upper airway with the potential for causing or worsening rhinitis, sinusitis, pharyngitis and tracheitis[1,2], while only particles less than 3 microns in diameter are respirable with the potential for causing or worsening asthma, COPD, bronchiectasis, bronchiolitis and acute pneumonitis (when inhaled over a long period of time and in significant concentrations, particles of this size can cause chronic pulmonary disease, such as pneumoconiosis).[3,4] These assumptions are based on controlled laboratory studies where the overall concentration of particles is limited. However, in the setting of a man-made or natural disaster, dust clouds are generated with high concentrations of airborne particulates over a wide size distribution. The increased minute ventilation required for evacuation and subsequent rescue or recovery (i.e., "fight or flight") efforts strongly favors mouth breathing and the large concentration of aerosolized dust overwhelms or impairs nasal and upper airway clearance mechanisms resulting in large particle penetration to the depth of the small airways and alveoli.[4] In addition to the acute and chronic inflammatory effects of particulate matter on the airways[5], these exposures are complicated by simultaneous exposures to the incomplete products of combustion that are liberated during disasters such as fires, building collapses, explosions and volcanoes and inhaled either as inhaled fumes, vapors and gases or as coated particulates.

Toxic combustion products can have profound effects on the respiratory system, causing acute symptoms, physiologic changes, and chronic diseases. Respiratory irritants such as hydrochloric acid, phosgene, ammonia, oxides of nitrogen, aldehydes, and sulfur dioxide can cause direct damage to the proximal airways, distal airways, and alveolar-capillary membrane. The combustion products of synthetic materials in modern furniture and building

materials may produce smoke that is more toxic than that produced in the past. Clinical manifestations of acute and/or chronic smoke inhalation can range from mild irritant symptoms of the upper and lower airways to life-threatening adult respiratory distress syndrome; irritant-induced asthma, bronchiolitis obliterans, bronchiectasis, chronic bronchitis, airway injuries, and pulmonary fibrosis have also been described.[6] In Fire Department City of New York (FDNY) fire fighters, the incidence and prevalence of Sarcoidosis has also been found to be increased as compared to concurrent and historic control populations.[7] Despite this varied list of smoke inhalation induced respiratory diseases, for FDNY fire fighters, asthma is by far the most common disease and is nearly always the cause of permanent respiratory disability.

The frequency, severity, and duration of smoke exposures appear to be important determinants of clinical outcomes, as well as individual host susceptibility factors.[6,8,9,10] Chemical composition and reactivity, water solubility, particle size, and temperature characteristics of the combustion products also influence the pulmonary effects. Although the complexities of exposure assessment and unpredictable nature of fires have permitted only limited evaluation of acute dose-response relationships and even less refined assessments of the long-term effects of smoke inhalation, many important observations have been made about the acute and chronic effects of smoke inhalation in fire fighters.

Several studies have examined changes in fire fighters lung function in conjunction with measures of airway reactivity. Sheppard and co-workers measured baseline airway reactivity to methacholine in 29 fire fighters, and then followed pre-shift, post-shift, and post-fire spirometry over an eight-week period.[11] Significant declines in the forced expiratory volume at 1-second (FEV_1) and/or the forced vital capacity (FVC) were more frequent following work shifts with fires, and occurred regardless of fire fighters' baseline airway reactivity. Sherman and co-workers performed spirometry and methacholine challenge testing before and after firefighting activities in 18 Seattle fire fighters.[12] Firefighting was associated with acute reductions in FEV_1 (3.4% ± 1.1%) and forced expiratory flow after 25% - 75% of vital capacity had been expelled (FEF_{25-75}), and an acute increase in airway responsiveness to methacholine. Increased airway responsiveness has been identified as a requirement for the diagnosis of reactive airways dysfunction syndrome (RADS; new onset asthma in a non-allergic non-smoker after acute exposure to fumes, gases and possibly other pollutants) and as a risk factor for the development of chronic obstructive pulmonary disease. The finding of increased airway responsiveness in fire fighters suggests that they may be at risk for accelerated loss of ventilatory function.

Chia and co-workers exposed 10 new fire fighter recruits and 10 experienced fire fighters with normal airway reactivity to smoke in a chamber without respiratory protection. Following exposure, the new recruits maintained normal airway reactivity[13]. However, 80% of the experienced fire fighters developed increased airway reactivity. The authors suggested smoke-induced chronic injury or inflammation of the pulmonary epithelium in experienced fire fighters might lead to increased risk of airway reactivity. Evaluating 13 victims of smoke inhalation three days after the fire, Kinsella and co-workers found 12 of 13 (92%) to have airway reactivity, which was strongly correlated

with carboxyhemoglobin levels.[14] Repeat assessment three months later showed most to have improvement in airway reactivity, but not FEV_1 or specific conductance. The authors speculated that airway obstruction following smoke inhalation might be more common and persistent than generally recognized.

Recent studies of fire victims using bronchoalveolar lavage have provided insights into the cellular and biochemical effects of smoke inhalation. Following smoke inhalation, significant numbers of neutrophils are recruited to the airways.[15] Neutrophils are capable of releasing proteolytic enzymes and inflammatory cytokines, which may contribute to injury of the airway epithelium and the development of bronchospasm and airway hyperreactivity. In patients with inhalation injury and cutaneous burns, increased numbers of both alveolar macrophages and neutrophils have been demonstrated in the airways; the alveolar macrophage may further contribute to the inflammatory response by elaborating additional cytokines such as tumor necrosis factor and interleukin-1, interleukin-6, and leukotriene B_4. Although preliminary, these findings suggest potential mechanisms for the decrements in lung function and increases in airway reactivity demonstrated in epidemiologic investigations.

Longitudinal studies of lung function in fire fighters have provided conflicting results. Peters and co-workers reported accelerated loss of FEV_1 and FVC over a one-year follow-up of Boston fire fighters.[16] Rates of decline were more than twice the expected rate (77 ml/year vs. 30 ml/year for FVC), and were significantly related to the frequency of fire exposure. However, in subsequent follow-up studies at three, five and six year intervals, investigators found rates of decline comparable to the general population, which were unrelated to indices of occupational smoke exposure.[17,18,19,20] There was evidence of survival bias in the cohort, as fire fighters with respiratory difficulties were selectively moved to lesser exposed jobs. The authors concluded that selection factors within the fire department and increased use of personal respiratory protective equipment were important in reducing the effects of smoke inhalation; significant attrition in follow-up cohorts may also have influenced the results. A five-year study of fire fighters participating in the Normative Aging Study found fire fighters to have greater rates of decline in FEV_1 and FVC than non-fire fighters (18 ml/year and 12 ml/year, respectively).

It is important to note that the participants in these studies were evaluated before routine use of respiratory protective equipment, and may have sustained very significant smoke exposures. Two more recent studies of fire fighters from the United Kingdom have not shown evidence for longitudinal decline in lung function.[21,22] In FDNY fire fighters, pulmonary function was followed over nearly 5 years (1997 to 2001) prior to the World Trade Center collapse and the mean adjusted decrease in FEV1 was 30 ml/year.[23] Overall, the evidence suggests that fire fighter cohorts using appropriate respiratory protective equipment do not have accelerated loss of ventilatory function, although additional research is needed in this area. It is important to note that wildland fire fighters, who are not provided with or do not typically wear protective respiratory equipment, have been shown to have decrements in lung function and increased airway responsiveness after a season of fighting fires.[24]

The effects of frequent smoke exposure on mortality from chronic respiratory conditions have also been investigated. Studies comparing fire fighters to US population controls have demonstrated reduced chronic respiratory disease mortality rates in fire fighters, despite evidence of acute and chronic pulmonary effects of smoke inhalation. However, these results may be due to the healthy worker effect, where selections of healthy workers results in mortality rates lower than a general reference population. In a study of New Jersey fire fighters, Feuer and Rosenman found an excess of chronic respiratory disease compared to police controls (Proportionate Mortality Ratio = 1.98, <0.05).[25] Rosenstock and co-workers compared a cohort of fire fighters from the northwestern U.S. to police, and found an increased Standard Mortality Rate (SMR) of 141 for chronic respiratory disease, as opposed to a deficit when compared to U.S. rates.[26] However, in a subsequent study of the same cohort with a longer period of follow-up found risks of chronic respiratory disease to be of lower magnitude (incidence density ratio 1.11, 95% CI 0.71–1.73).[27] There is need for additional research on the chronic effects of smoke inhalation using appropriate control groups, especially in the context of changing fire fighter exposures.

Disasters other than fires have also been responsible for significant exposure to aerosolized respirable particles and gases. For example following the Mt. St. Helens eruption in 1980, hospital visits for pediatric asthma were increased in Seattle, Washington.[28]. After the explosion of the Union Carbide Chemical Plant in Bhopal, India, studies documented an increased loss of pulmonary function compared to normal aging and increased presence and severity of obstructive airways disease.[29] In coal miners and construction workers, studies following sub-acute and chronic exposure have also demonstrated increased loss of pulmonary function.[30]

Recently, a great deal of attention has been focused on the respiratory health consequences of World Trade Center (WTC) dust exposure. Over 400 different substances (pulverized building materials and combustion derived pollutants) have been identified in WTC dust. In contrast to volcanic ash, which is highly acidic, WTC dust, or dust following any type of building collapse, is highly alkaline.[30,31,32,33,34,35] Furthermore, during an unexpected urban disaster of this magnitude, effective respiratory protection with the ability to filter small particles, such as an elastomeric P-100 half-face respirator for example, was typically unavailable for the first days to week after a major disaster,[36,37] and adherence with proper use guidelines is usually sub-optimal in the weeks and months that follow.[36,37].

Respiratory health consequences after exposure to a high-concentration particulate during a disaster can be grouped into three major categories: (1) inflammation-related aerodigestive syndromes (i.e., bronchitis, asthma, reactive airways dysfunction syndrome (RADS), rhinitis/sinusitis, reactive upper airways dysfunction syndrome (RUDS), gastroesophageal reflux disease (GERD) and interstitial lung diseases); (2) inhalation lung injury (i.e., pulmonary edema, bronchiolitis obliterans, granulomatous pneumonitis, or interstitial fibrosis); and (3) late emerging diseases (autoimmune disease and malignancy). Following the WTC attack, Gavett and coworkers compared inflammatory and physiologic effects of WTC-derived small particulate matter (<2.5μm) to nontoxic and toxic reference materials in mice (National Institute of Standards and Technology (NIST) 1649a and residual oil fly ash).[38] While

WTC small particulate matter (<2.5μm) caused mild pulmonary inflammation compared to the reference materials, a marked increase in airway reactivity to inhaled methacholine was observed. Corresponding studies in WTC rescue workers have shown rising sputum neutrophil and eosinophil counts and higher cytokine levels as work duration at the WTC site increased when compared to controls[39] and persistent airway hyperreactivity in highly exposed rescue workers.[40,41]

In WTC exposed rescue and recovery workers (FDNY & non-FDNY), the majority of WTC-related respiratory illness can be attributed to aerodigestive tract inhalation injuries, with the greatest severity in those arriving in the first 48 hours.[36,40,42,43,44] High rates of upper & lower respiratory irritant symptoms during the sub-acute post-exposure time period (first year to 2.5 years) have been described in four WTC rescue/recovery worker groups: (1) in previously healthy, exposure-stratified NYC fire fighters, 78% had new upper respiratory symptoms & 73% had new lower respiratory symptoms four weeks post-collapse,[36] (2) in other rescue workers and volunteers who were not FDNY fire fighters, 69% reported respiratory symptoms at WTC with symptoms persisting to the time of examination in 59%. Among the 85% who were asymptomatic before 9/11, 61% developed respiratory symptoms while working at the WTC,[42] (3) 77% of 240 previously healthy NYC police officers, from the Emergency Service Unit, had upper and/or lower respiratory symptoms during the first five months post-collapse,[43] and (4) 77% of 96 ironworkers had upper and/or lower respiratory symptoms six months post-collapse.[44] Respiratory consequences have also been noted in less exposed community residents, children & office workers in lower Manhattan.[45,46,47]

Post-disaster, respiratory symptoms and nonspecific bronchial hyperreactivity following an acute high-level exposure to an inhaled irritant vapor/gas/fume in non-smokers without allergic history has been referred to as reactive airways dysfunction syndrome (RADS) or irritant-induced asthma.[48,49] In an exposure-stratified sample of 179 previously healthy FDNY rescue workers, Banauch and coworkers delineated the emergence of persistent symptomatic bronchial hyperreactivity during serial challenge testing one, three, six and twelve months after the WTC attacks.[41] Bronchial hyperreactivity [methacholine PC20<8mg/ml] during the sub-acute post-exposure period (one to three months) predicted the development of RADS or irritant-induced asthma in 20% and 17% of highly exposed workers and in 8% and 11% of moderately exposed workers at six and twelve months post-collapse, respectively[41]. Similar results were found at two-year follow-up.[50] The presence of such syndrome has been found to correlate with the intensity of exposure to WTC-dust.[40,41,42,50]

Reactive upper airways dysfunction (RUDS) is defined as chronic rhinitis and/or sinusitis triggered by exposure to inhaled irritants[51,52]. In contrast to the objective physiologic evidence of nonspecific hyperreactivity necessary for a diagnosis of RADS, objective testing for diagnosing RUDS is not well defined. High rates of upper airways symptoms have been described in every WTC rescue worker study.[36,40,42,41,44]

Persistent upper gastrointestinal complaints under various diagnostic labels have previously been described in case reports of long-standing RADS[53] and in a case series of persistent gastrointestinal complaints after exposure to chemical irritants.[54] Amongst FDNY rescue workers, who as a group sustained

the most intense exposure to air pollution at the WTC site, multiple studies have now described high rates of gastroesophageal reflux dysfunction (GERD).[36,40] Though no clear mechanism for the development of GERD has been described in this setting, ingestion of airborne or expectorated respirable material are presumed etiologies that may be further exacerbated by disaster-related stress and dietary indiscretions. Questions which remain are: is GERD unique to the WTC exposure or does it represent a previously unrecognized aspect of inhalation injury in general; does it mark more severe total dust exposure as opposed to, or in conjunction with more severe host inflammatory reaction; and will this syndrome persist or resolve. What is clear is that when GERD is present in this setting, treatment should be initiated because of the known causal or exacerbating relationship between GERD and airway diseases such as sinusitis, asthma and chronic cough.[55,56]

Post-disaster, interstitial lung disease is much less common than upper and lower airways disease. An increased incidence of sarcoid-like granulomatous pulmonary disease (SLGPD) has been reported in FDNY fire fighters prior to the WTC,[57] raising the possibility of etiologic agents generated or aerosolized during combustion. Granulomatous pneumonitis has been described in one construction worker working in the recovery effort at the WTC[58] and the incidence of WTC SLGPD was substantially increased in FDNY rescue workers (fire fighters and EMS) in the first five years post-WTC, especially in the first 12 months (Figure 3-1.1).[59] During this time period, most reported no respirator use or "minimal" use of a "dust" or N-95 mask and none reported wearing a P-100 respirator. Other interstitial diseases after WTC exposure have been even rarer with several cases of idiopathic pulmonary fibrosis and two case studies of bronchiolitis obliterans, one with functional improvement after treatment with macrolide antibiotics.[60] One case of eosinophilic pneumonitis requiring mechanical ventilatory support was reported in a NYC fire fighter 6 weeks after the WTC collapse; bronchoalveolar lavage demonstrated particulate material and uncoated asbestos fibers; and there was a prompt resolution after a brief course of systemic corticosteroid treatment.[61] Recently, the U.S. military has reported 18 cases of eosinophilic pneumonitis in personnel deployed in or near Iraq (incidence of 9.1 per 100 000 person-years; 95% confidence interval, 4.3-13.3).[62] All but one reported exposure to fine airborne sand/dust and all were smokers with 78% classified as new smokers. Mechanical ventilation was needed in 67% (median use seven days); two died; the remainder responded to corticosteroids or supportive care; and post-treatment all had normal or near normal spirometry. Taken together, these findings strongly argue for providing improved respiratory protection at future disasters and other significant environmental/occupational exposures.

Following any urban disaster, those exposed will naturally be concerned about their risk for developing malignancies due to their potential exposures to multiple combustion or pyrolysis products, many of which are known carcinogens (e.g., polycyclic aromatic hydrocarbons, such as dioxins and brominated diphenyl ethers, as well as polychlorinated biphenyls, polychlorinated dibenzodioxins, and polychlorinated furans).[31,63] Furthermore, asbestos may become airborne during fires or collapse of older buildings and there are well-described synergistic carcinogenic effects of asbestos with polyaromatic hydrocarbons.[63] As asbestos-related cancers have long latency periods,

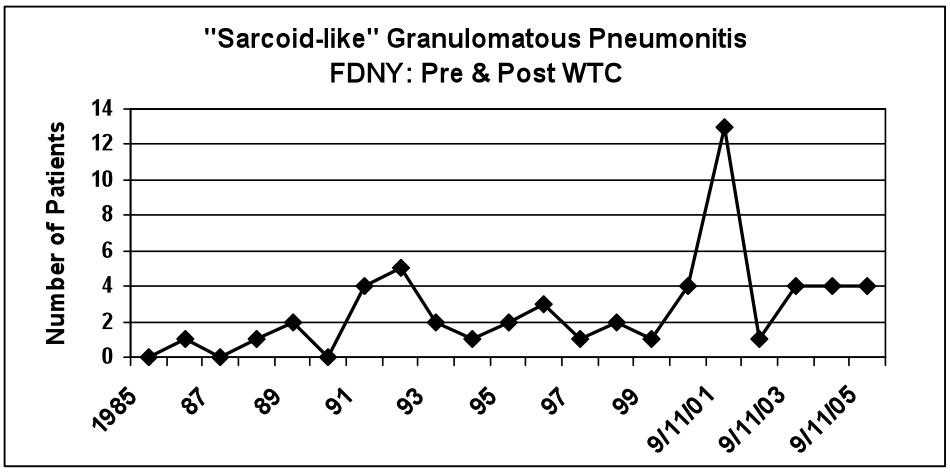

Figure 3-1.1: The number of cases of biopsy proven World Trade Center Sarcoid-like Granulomatous Pulmonary Disease (WTC-SLGPD) since 9/11 as compared to pre-WTC cases of sarcoidosis or SLGPD starting from 1985 in rescue workers from the Fire Department of the City of New York (FDNY). *With permission from: Izbicki G, Chavko R, Banauch GI, Weiden M, Berger K, Kelly KJ, Hall C, Aldrich TK and Prezant DJ. World Trade Center Sarcoid-like Granulomatous Pulmonary Disease in New York City Fire Department Rescue Workers. Chest, 2007;131:1414-1423.*

periodic long-term medical surveillance typically lasting approximately 30 years should be considered for exposed individuals. In contrast, thyroid cancer and leukemia resulting from radiation or certain chemical exposures have short latency periods, especially in children. It is important to consider the biologic plausibility and latency periods in post-disaster exposure counseling and planning.

INHALATION RESPIRATORY ILLNESSES FROM GASES AND VAPORS

The most common chemical asphyxiants are carbon monoxide and hydrogen cyanide. Others include hydrogen sulfide, oxides of nitrogen and acrylonitrile.

Hydrogen Cyanide

Cyanide is a ubiquitous compound that is widely used in industry in its salt form and therefore, can be easily exploited by terrorists. Most information regarding cyanide toxicity comes from accidental disasters such as fires, explosions, industrial accidents, and poisonings (including consumption of apricot pits and cassava roots). Cyanide poisons aerobic metabolism by binding to the ferric ion (Fe^{3+}) of mitochondrial cytochrome oxidase a_3. Cyanide binds reversibly through the action of the enzymes rhodanese, 3-mercaptopyruvate sulfurtransferase, and thiosulfate reductase. These enzymes assist in the formation of the less toxic compound thiocyanate (SCN^-), which ultimately is excreted by the kidneys. Cyanide can readily diffuse through the epithelium and therefore is toxic through inhalation, ingestion, or topical contact.

The clinical presentation of cyanide toxicity results from progressive tissue hypoxia. Initial effects include transient hyperpnea, headache, dyspnea, and excitability of the central nervous system (CNS) (manifested by anxiety and agitation). Late effects include hemodynamic compromise, arrhythmias,

seizures, coma and death[64]. Additional signs and symptoms not specific for cyanide toxicity include diaphoresis, flushing, weakness, and vertigo. The odor of bitter almonds, which is commonly thought to be characteristic, is described by fewer than 60% of persons exposed to cyanide.[64] Lactic acidosis is the primary laboratory abnormality noted. Assay of whole blood, needed to accurately measure cyanide concentrations, correlates with signs and symptoms (lethal dose, >three micrograms/ml) but, is not readily available in most clinical laboratories. Therefore, treatment is often empiric and should be considered from known or suspected exposures when symptoms are severe and not responding to conservative therapy.

The primary goal of treatment is displacement of cyanide from cytochrome oxidase a_3 through the formation of methemoglobin by sodium nitrite. Methemoglobin values should be monitored and maintained at less than 30%[64,65]. Sodium nitrite and sodium thiosulfate must be administered intravenously. Owing to a lack of sulfur donors during acute intoxication, sodium thiosulfate is administered as additional therapy to enhance clearance of cyanide. Sodium thiosulfate combines with sequestered cyanide to form thiocyanate, which is excreted from the body. Recently, the FDA approved hydroxocobalamin as an intravenous treatment for cyanide poisoning. A potential advantage is that methemoglobinemia is not a consequence of hydroxocobalamin therapy.[66]

Carbon Monoxide

Carbon monoxide (CO) is an odorless, colorless, nonirritating gas produced by incomplete combustion of organic materials, especially hydrocarbons. Although automobile exhaust systems, faulty heating systems and fires are the common sources of carbon monoxide intoxication, the improper use of temporary home generators during blackouts is the most common cause in disaster environments.[67] Carbon monoxide binds to hemoglobin forming carboxyhemoglobin (COHb) resulting in decreased hemoglobin oxygen saturation, shift of the oxygen-hemoglobin dissociation curve to the left and inhibition of oxygen delivery to the tissues. The affinity of the hemoglobin for carbon monoxide is over 200 times greater than that for oxygen.[67] Carbon monoxide also binds cytochrome oxidase chain interfering with cellular respiration. All of these properties result in chemical asphyxiation.

Clinical findings of carbon monoxide poisoning are similar to cyanide poisoning, are non-specific and include general malaise, headache, nausea and vomiting, dyspnea and alteration in mental status at high levels of exposure.[67,68,69] Severe exposure may cause coma, seizures, arrhythmias and death. Cyanosis is not found in carbon monoxide poisoning due to the cherry-red color of the carboxyhemoglobin. Carboxyhemoglobin can be measured in blood: levels lower than 6% may cause impairment in vision and time discrimination; levels of 40 - 60% are associated with arrhythmias, coma and death

The most common symptoms following mild CO poisoning (10-20 ppm) are mild headache, fatigue, shortness of breath, and dizziness. Moderate exposures (20 - 30 ppm) commonly present with more severe headaches, fatigue and shortness of breath often accompanied by confusion, blurred vision, nausea and vomiting. Patients presenting with palpitations, dysrhythmias, myocardial ischemia, hypotension, noncardiogenic pulmonary edema, seizures, coma, and respiratory or cardiac arrest have severe toxicity (>30 ppm). The severity

of symptoms is also influenced by their chronicity and by underlying co-morbidity. Two special populations in whom to consider additional affects of CO poisoning are pregnant patients and children. In pregnancy, CO poisoning has been shown (even in the absence of toxic symptoms in the mother) to result in an increased rate of stillbirths or miscarriages, limb malformations, cranial malformations, cognitive disabilities, and even fetal death. These effects are due to the more dramatic effects of CO on fetal hemoglobin and prolonged elimination times from fetal circulation.[67] In children, the effects seen in their adult counterparts (i.e. parents) may be less dramatic than those seen in children. This results from the increased minute ventilation (respiratory rate multiplied by tidal volume). As a result, shorter exposure times are needed in order to achieve clinically significant levels of COHb. For this reason, particularly in very young children and infants in whom the history and neurologic findings may be limited, prehospital treatment should be applied liberally.

The first and most critical treatment for a CO poisoning is the removal of the patient from the environment and the delivery of high-flow oxygen via a non-rebreather mask. High-concentration oxygen facilitates the elimination of CO from the body, in addition to increasing the amount of oxygen dissolved within the blood (but not carried by hemoglobin), thereby promoting tissue oxygenation. In the setting of oxygen provided by a non-rebreather mask, the half-life of CO is reduced from approximately four hours to 40 to 60 minutes. Treatment with oxygen should continue until the COHb level falls below five percent.

Hyperbaric oxygen therapy (HBOT) provides high concentrations of oxygen at elevated atmospheric pressures, thereby increasing the amount of oxygen dissolved in the blood. Such therapy not only ensures adequate oxygen delivery to the body, but also enhances the elimination of CO by reducing the half-life of CO to 20 minutes. One commonly referenced set of criteria for HBOT use includes: neurologic findings (altered mental status, coma, seizures, or focal neurologic deficits), COHb >20% in adults, COHb >15% in pregnancy, loss of consciousness, metabolic acidosis, cardiovascular compromise (ischemia, infarction, or dysrhythmias), or persistent symptoms despite high-flow oxygen therapy. In the only large double blind randomized trial, hyperbaric-oxygen treatment was superior to high-flow oxygen therapy for reducing short-term (six weeks) and long-term (one year) cognitive dysfunction in patients with elevated COHb levels ≧20% or significant metabolic acidosis. A problem with interpreting these studies is that COHb levels measured in the hospital may have already been reduced by use of high flow oxygen therapy by EMS. Thus, appropriate care needs to be considered in outcome analysis and is why the above study is more accurately referred to as an analysis of patients with COHb levels ≥20% rather than ≧25%.[68]

EXPOSURE TO IRRITANT VAPORS AND GASES

Gases, vapors and mists are non-solid suspended toxicants. Examples include chlorine, ammonia, isocyanates, sulfuric acid, nitrogen dioxide, phosgene, benzene and others. The solubility of the toxin affects their absorption and site of injury.[70] In general, the higher the water-solubility of the agent, the more the substance will be absorbed and injure the upper airways. Ammonia, cadmium oxide, hydrogen chloride, hydrogen fluoride and sulfur dioxide are

highly water-soluble and, thus, will mostly be absorbed and injure the upper airways. Chlorine and vanadium pentoxide are moderately water-soluble causing upper and lower airway inflammation. Phosgene, mercury vapor, oxides of nitrogen, and ozone have low solubility and thus, penetrate deeply into the respiratory tract causing small airways inflammation, pneumonitis and pulmonary edema.

Chlorine

Chlorine is a highly reactive green-yellow gas that is 2.5 times denser than air. Exposure occurs in both industrial and non-industrial settings.[70,71] Chlorine is used in the production of chemicals, bleaching and plastics processing, and in a variety of recreational and household settings (swimming pools, cleaning solutions). Given its moderate solubility, most signs and symptoms are related to upper and lower airway inflammation (RUDS, RADS, irritant asthma). Severe and prolonged exposures can result in ulcerative tracheobronchitis, diffuse alveolar damage with hyaline membrane formation and pulmonary edema.

Phosgene

Phosgene is commonly used to manufacture dye and plastics. Exposure to phosgene also may occur during arc welding and in fires involving vinyl chloride. Phosgene and diphosgene are also agents used in chemical warfare.[70,71] Phosgene, which is transported in liquid form, is deadly at a concentration of 2 ppm. It appears as a white cloud and has a characteristic odor of sweet, newly mown hay in lower concentrations. These agents have low water solubility, so have a delayed onset of action (30 minutes to 8 hours). It readily reaches the respiratory bronchioles and alveoli and has direct toxic effects, leading to cellular damage of the alveolar-capillary membrane and subsequent pulmonary edema. Because there is no systemic absorption, other organs are not affected.[70,71] Initial exposure results in a burning sensation of the mucus membranes including eyes, nose, throat and upper respiratory tract. More severe exposures progress to development of cough, wheezing, stridor, dyspnea, hypotension, and non-cardiogenic pulmonary edema. The use of steroids has been advocated but is of unproven benefit.

The clinical presentation depends upon level of exposure. Exposure to low concentrations causes mild cough, dyspnea, and chest discomfort. At high concentrations, airway irritation and alveolar damage occurs. After direct contact of skin to phosgene, there is an immediate burning sensation followed by erythema, blanching and, eventually, necrosis. Systemically, patients may experience dyspnea, chest tightness, cough, substernal discomfort, hypoxia and pulmonary edema within two to six hours of exposure; however, some signs and symptoms may not develop for 24 hours. Pulmonary edema occurring within four hours of exposure indicates a poor prognosis; death occurs if immediate intensive medical support is unavailable.[70,71] Physical exertion within 72 hours of exposure may trigger the development of pulmonary edema. Measurement of oxygen saturation and arterial blood gases is recommended in the initial evaluation of all symptomatic patients. A chest radiograph may show perihilar infiltrates or diffuse pulmonary edema, which may evolve and progress rapidly. Radiographic findings may lag behind clinical findings. Rarely, phosgene causes significant structural damage that may take many

years to recover from completely. In patients who had symptoms following an initial exposure, clinical findings suggestive of bronchiolitis obliterans and chronic bronchitis some time after exposure have been reported.[72] It is prudent to monitor such patients with pulmonary function tests and radiographic imaging, especially those who have persistent symptoms of dyspnea, cough, or chest discomfort.[70,71,72]

DIAGNOSIS AND TREATMENT

In any inhalational lung injury patient (smoke, particulates, gases or chemicals), medical complications range from patients who present with tachypnea due to anxiety to patients with cough from irritant-induced upper and/or lower airway inflammation (i.e., sinusitis, tracheobronchitis, asthma, reactive airways dysfunction syndrome) to those in acute respiratory distress (i.e., neuromuscular failure, status asthmaticus, pulmonary edema). The goal of this section is to concentrate on those aspects that might be unique or specific to an inhalational lung injury.

History and Physical Examination

In addition to a standard medical history and physical examination, a post-inhalational lung injury evaluation should include questions to determine prior and current exposures (environmental and occupational), the intensity and duration of exposure(s), the temporal relationship of symptoms to exposure and whether these symptoms were new in onset or, for those with pre-existing disease, whether they were stable or exacerbations. Strategies for evaluating the intensity of exposure include: completing a timetable recounting exposure, the time of first exposure, the time of last exposure, the number of hours and days exposed, the individual's location during exposure, a description of specific activities during exposure, and for respiratory protection the type and extent of use.[73] Prior pulmonary history is critical in understanding risk for exacerbations. Physical exam should focus on all areas of potential exposure including vital signs, skin, eyes, mucous membranes, upper and lower airways, lung, abdomen and any other exposure specific sites.

An important consideration when obtaining the medical history is accounting for the "healthy-worker effect." Because rescue workers are generally healthy and physically active prior to exposure, their symptoms and findings are expected to be above the average when compared to the general population. Post-exposure, they may remain asymptomatic at rest or even with mild exercise; therefore the history will only be useful if it includes extensive questioning as to provocability, such as the presence of symptoms with work activities, strenuous exercise, and exposures to common irritants in the work or home setting (smoke, diesel exhaust, noxious smells, perfumes and allergens), and extremes or changes in temperature and humidity.[73] Attention should be paid to the emotional impact, not only of the exposure itself, but also of the development of respiratory and physical impairments that may have resulted from the exposure to the mentally and physically stressful environment. Because post-traumatic stress is a common complication, some assessment of prior mental health history, current stress, support system and resilience is important.

Diagnostic Testing

Initial pulmonary function evaluation includes spirometry. As these records may be used for diagnosis, treatment and future legal actions, careful attention to quality control should be maintained. Post-bronchodilator spirometry can be part of this initial evaluation or could be reserved for those patients with (a) symptoms, (b) spirometry that is abnormal (<80% predicted) or even at the lower limits of normal ("healthy worker effect") or (c) show a significant decrease from prior spirometry if available and obtained pre-exposure or pre-symptom development. Abnormalities in pulmonary function should be further investigated as clinically indicated with determination of lung volumes, diffusion, bronchodilator response, nonspecific bronchial reactivity and/or chest CT imaging as resources allow. The "healthy-worker effect," especially in rescue workers, is an important consideration when interpreting pulmonary function tests. Pre-exposure, many may have had above normal pulmonary function when expressed as percent predicted and therefore, use of cut-off points to judge for "normality" in this population should be carefully and individually evaluated.

This fact is highlighted by the FDNY fire fighter WTC study.[40] Spirometry results obtained after WTC-exposure were for most fire fighters above the lower limits of predicted normal for the general population but when compared to their own individual spirometry results obtained pre-exposure, significant losses in pulmonary function were noted and the decrease demonstrated a dose-intensity effect with the greatest decrease observed in those present on 9/11 during the morning of the collapse. Given the unfortunate likelihood that first responders may suffer future exposures, we recommend that all receive annual "baseline" spirometry as part of their general health monitoring.

Other Pulmonary Functions

In symptomatic patients with normal or near-normal spirometry results, and symptoms following the inhalational lung injury consistent with hyper-reactivity or asthma, the methacholine-challenge test should be considered if a formal diagnostic test is required. Methacholine challenge testing has demonstrated persistent hyperreactivity in nearly 25% of FDNY rescue workers who were present at WTC during the morning of the collapse on 9/11.[41] If formal diagnostic proof is not required for legal, disability or research purposes, most physicians reserve this test for symptomatic patients who do not report classic symptoms or who fail to report or demonstrate a response to bronchodilators. Under any circumstance, challenge testing is contraindicated due to safety considerations when spirometry shows anything less than minimal abnormalities.[74] Classically, a $PC_{20} \leq 8$ mg/ml of methacholine is considered a positive response for diagnosing airway hyperreactivity, although a slightly more liberal cut-off point using a $PC_{20} \leq 16$ mg/ml of methacholine may be reasonable in previously healthy individuals who report new asthmatic symptoms.[74] Evaluation of full lung volumes and diffusing capacity has not been routinely reported in most inhalational lung injury studies. In patients who do not report symptoms consistent with hyper-reactivity or asthma or who have significant abnormalities on spirometry or chest imaging, pulmonary function tests including full lung volumes and diffusing capacity are recommended as the next diagnostic test after spirometry and instead of methacholine challenge testing.

Chest Imaging

In asymptomatic individuals, chest radiographs generally find no acute abnormalities. However, there may be widespread interest amongst those exposed to have chest radiographs as new "baselines." In symptomatic patients, chest radiographs and CT scans have been reported to show bronchiectasis, bronchiolitis obliterans, atelectasis, lobar consolidation and interstitial pneumonitis (hypersensitivity, eosinophilic pneumonitis, granulomatous disease and fibrosis). Inspiratory and expiratory CT scanning has been utilized to show air trapping, bronchial wall thickening and mosaic attenuation.[40,75] Because the clinical utility of these findings in a non-research setting remains unclear, we recommend that inspiratory and expiratory CT scan of the chest be reserved for individuals with significant unexplained symptoms after complete pulmonary function tests have already been conducted. Another area of intense research is the use of CT scans of the chest for lung cancer screening.[76] Their future use in high-risk patients (high exposure; tobacco smokers) might be a consideration depending on the results of soon to be completed lung cancer screening studies in tobacco smokers from the general population.

Invasive Diagnostic Methods

Induced sputum, bronchoalveolar lavage and/or biopsy following exposure in asymptomatic and symptomatic rescue workers have been used to demonstrate increased markers of inflammation and particle deposition exposure. While these measures may have value in a research setting, they have limited diagnostic or prognostic value. In a clinical setting, bronchoscopy should be performed on those with significant abnormalities on chest imaging or when there is failure to respond to therapy. Sinus CT scan and direct laryngoscopy are recommended in those unresponsive to medical treatment for at least three months.[77] Gastroesophageal endoscopy is recommended for those unresponsive to medical treatment after two to three months, for those with reoccurrence after successful treatment has been concluded, or for those with risk factors for esophageal cancer.[78]

Treatment

Not many references describing the treatment of inhalational lung injury-related chronic cough or dyspnea have been published.[79] Recently, expert consensus guidelines for the diagnostic evaluation and treatment of WTC related respiratory disease was published by the NYC Department of Health and Mental Hygiene.[80] The recommended approach includes a comprehensive plan of synergistic care treating the upper and lower airway (see Figures 3-1.2 and 3-1.3) with (a) nasal steroids and decongestants, (b) proton pump inhibitors and dietary modification and (c) bronchodilators, corticosteroid inhalers and leukotriene modifiers. Most patients have reported symptoms and required treatment for involvement of at least two of the above organ systems. Consistent with published guidelines, only when the clinical presentation is atypical (for example, interstitial lung disease) or there is failure to respond after approximately three months of treatment do we recommend additional invasive diagnostic testing such as chest CT, bronchoscopy, sinus CT, laryngoscopy, and/or endoscopy.[77-79] Our experience has proven the multi-causality of respiratory

symptoms in an inhalation lung injury population, with contribution of any combination of these aerodigestive processes.

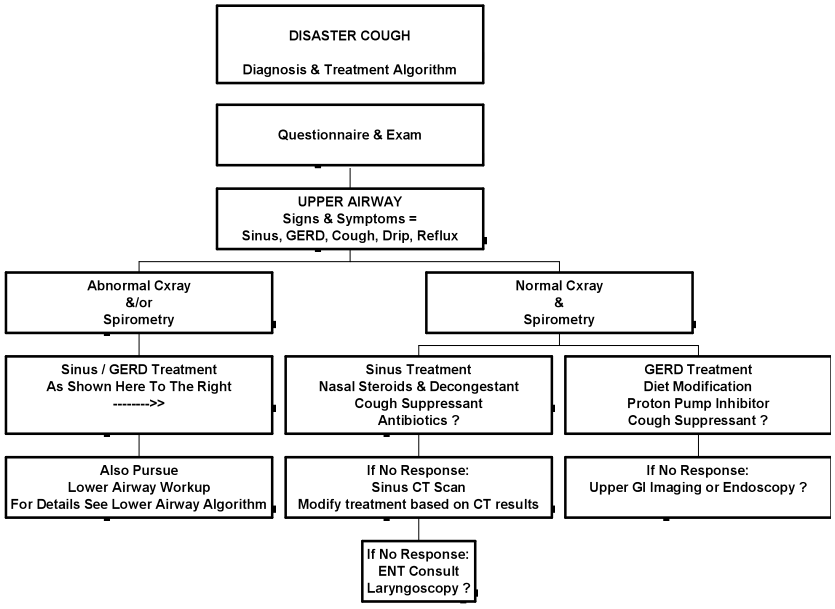

Figure 3-1.2: Disaster Cough Diagnosis & Treatment Algorithm – Upper Airway Predominance

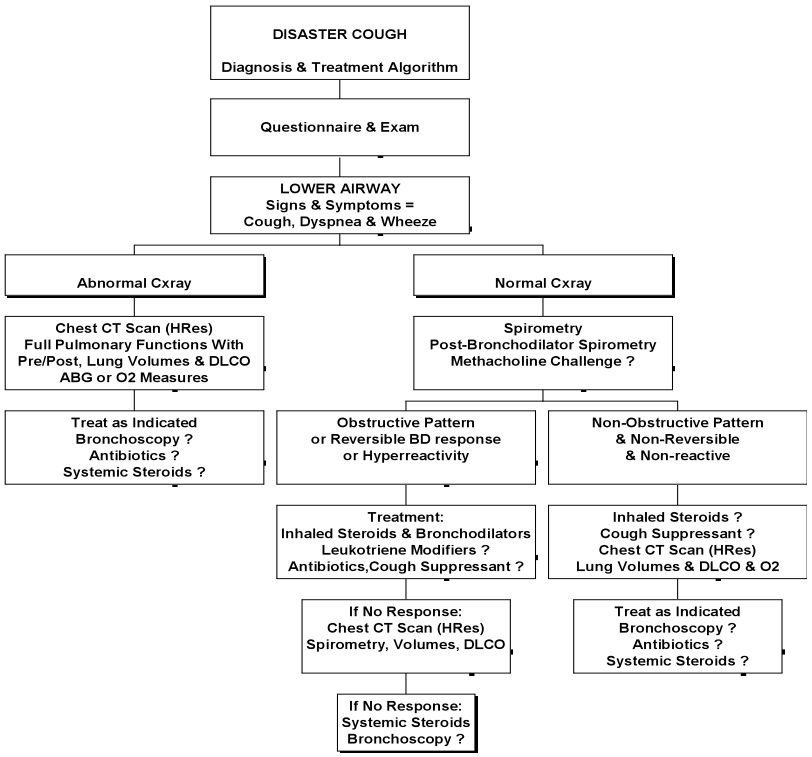

Figure 3-1.3: Disaster Cough Diagnosis & Treatment Algorithm – Lower Airway Predominance

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Chapter 3-2
Inhalation Lung Injury and Radiation Illness

By Dr. Lawrence C. Mohr, MD

Injuries and illness associated with exposure to ionizing radiation can be caused by two types of radiological disasters: dispersion of radioactive particles or by a nuclear explosion. The dispersion of radioactive particles can occur during an accident involving a nuclear facility, such as a nuclear power plant, or by a man-made radiological dispersion device that is detonated for the purpose of harming others. Radiological dispersion devices, or “dirty bombs”, consist of radioactive materials that are placed around a conventional explosive charge. “Dirty bombs” are easy to construct and raw materials are readily available throughout the world. It is important to note that “dirty bombs” are not nuclear weapons and are not weapons of mass destruction. Their adverse health effects depend upon the type and amount of explosive used, the type and amount of radioactive material used and atmospheric conditions at the time of detonation. Most injuries from a “dirty bomb” will come from the blast effects of the conventional explosion. Acute and delayed (i.e., cancer) radiation health effects are unlikely. The risk of developing cancer following a “dirty bomb” attack is low because for most such devices the radiation exposure dose would be minimal. Long-term psychological trauma is likely to occur among some members of a population that have been exposed to radioactive material from a "dirty bomb." Indeed, long-term psychological trauma may be the most significant health effect.

A nuclear explosion results from nuclear fission or from thermonuclear fusion, in which a tremendous amount of energy is suddenly released in the form of heat, blast and radiation. Human injury is caused by exposure to a combination of these three forms of energy following a nuclear detonation. The radiation exposure from a nuclear explosion can be very intense and lead to a life-threatening acute radiation illness, in addition to radiation burns, thermal burns and blast injuries. For survivors, radiation exposure from a nuclear explosion can also result in the development of various long-term health effects such as leukemia, thyroid cancer and other malignancies.

Acute radiation illness is a serious, complex, life-threatening illness that occurs shortly after a high-dose radiation exposure, such as may occur following a nuclear explosion. It requires prompt assessment and management in order to minimize loss of life. In general, the higher the radiation dose, the greater the severity of acute effects, the higher the probability of delayed illnesses and the higher the mortality rate. It is essential that any physician who may be called upon to treat these seriously ill patients following a nuclear explosion be familiar with this unique illness. Acute radiation illness will be the focus of this section.

DECONTAMINATION OF RADIOLOGICAL CASUALTIES

The decontamination of radiation-exposed patients should occur *outside* of the emergency department after the patient is stabilized. Health care workers must be educated to understand that their exposure to this "dirty dust" is of minimal risk as long as they do not inhale or ingest it. Therefore, recommended personal protective equipment for all health care workers is scrubs, gowns, appropriate respirators, gloves and shoe covers during the treatment and decontamination of radiation casualties. The decontamination process is quite simple. All of the patient's clothing must be removed and discarded into a clearly-labeled and secure container, so that it does not further contaminate people and surroundings after removal. The patient is then thoroughly washed with soap and water. This simple soap-and-water process has been shown to be effective in removing more than 95% of residual radioactive material from radiation-exposed patients.

INTERNAL RADIATION CONTAMINATION

In the assessment of patients for acute radiation exposure, it is important to ascertain whether or not they have experienced any internal contamination. Internal radiation contamination can occur by the inhalation, ingestion or transdermal penetration of radioactive material. It can occur via a variety of portals, such as the nose, the mouth, a wound, or, with a large enough dose, by the penetration of gamma rays or neutrons directly through intact skin. Internal organs commonly affected by internal radiation contamination are the thyroid, the lung, the liver and bone. These are the areas where radioactive isotopes tend to accumulate within the human body. Leukemia and various types of cancers can develop in these organs many years after an acute radiation exposure with internal contamination.

The patient history is crucial to determining whether or not they may have experienced internal contamination. Any history which suggests that a patient may have inhaled, ingested, or internalized radioactive material through open wounds should prompt further evaluation for internal contamination. This assessment should attempt to identify both the radiation dose received and, if possible, the specific isotopes that caused the internal contamination. An initial survey of the patient should be performed with a radiac meter, especially around the mouth, nose and wounds, to give some idea of the extent of any possible internal exposure. The analysis of nasal swabs, stool samples and urine samples are the most practical methods of determining the type and extent of internal radiation contamination by hospital-based physicians.

If it is suspected that a person has inhaled a significant amount of radioactive material, bronchoalveolar lavage can be considered for the purposes of identifying inhaled radioactive isotopes as well as for removing residual radioisotopes from the lungs. Chest and whole-body radiation counts can also be helpful in determining the extent of any internal radiation contamination. However, most medical institutions don't have the capability to do either chest or whole-body radiation counts. Patients who have experienced internal radiation contamination should be treated. Specific agents are used to treat internal contamination by specific radioactive isotopes. Such treatment is most effective when given as soon as possible after the radiation exposure. In

deciding whether or not to treat a patient for internal radiation contamination, the physician may need to act on preliminary information and may have to treat potentially-exposed individuals empirically, based upon the information that is available. The treatments for internal contamination by specific radionuclides are summarized in Table 3-2.1.

Specific Treatment for Internal Radiation		
Radionuclide	**Treatment**	**Route**
Cesium-137	Prussian blue	Oral
Iodine-125/131	Potassium iodide	Oral
Strontium-90	Aluminum phosphate	Oral
Americium-241	Ca-DTPA and Zn-DTPA	IV Infusion
Plutonium-239	Ca-DTPA and Zn-DTPA	IV Infusion
Cobalt-60	Ca-DTPA and Zn-DTPA	IV Infusion

Table 3-2.1: Specific Treatment for Internal Radiation.

RADIATION DOSES

Since the severity, prognosis and management of acute radiation illness are all related to the radiation dose received by the patient, it is important for physicians to have a basic understanding of how radiation doses are measured. There are two units of radiation dose that physicians must be familiar with: the Rad and the Gray. It is not essential for physicians to understand the physics that underlie the determination of these doses, but it is important for them to know that these are the units which are used to express the amount of radiation that is absorbed by human tissues. The Rad is the traditional unit of **r**adiation **a**bsorbed **d**ose. One Rad is defined as 100ergs/gram. The Gray (abbreviated Gy) is the newer Standard International unit of radiation exposure. One Gy is equal to 100 Rads, which is defined as 1 Joule/kilogram. One hundred centi-Gray (100cGy) are equal to one Gray.

Radiation doses can be measured by several techniques. The radiac meter is an instrument that directly measures radiation dose using a Geiger-Müller tube or similar device. There are many different types of radiac meters, each of which may be more sensitive to specific types of radiation. Most radiac meters in use today are highly portable and will accurately measure alpha, beta, gamma and neutron radiation. The measurement of serial lymphocyte counts can provide a useful biological estimate of radiation dose, especially in the clinical setting (Table 3-2.2).

Procedure for Determining Approximate Dose Based on Lymphocyte Count					
Determine initial lymphocyte count (L1) and subsequent counts (L2) at 6 or 12 hours. Divide (L1) by (L2) and take natural log of quotient. Divide result by the time change in 24 hours (number of hours between counts divided by 24) to determine "K". Refer below for estimated dose:					
K	**Est. Dose in Gy**	**99% Confidence Limits**	**K**	**Est. Dose in GY**	**99% Confidence Limits**
0.1	1.24	0.98 - 1.5	1.0	6.82	5.95 - 7.69
0.2	2.27	1.87 - 2.68	1.5	8.18	6.9 - 9.46
0.4	3.90	3.36 - 4.43	2.0	9.09	7.43 - 10.74
0.6	5.11	4.5 - 5.73	2.5	9.73	7.76 - 11.71
0.8	6.06	5.33 - 6.79	3.0	10.22	7.98 - 12.45

Figure 3-2.2: Procedure for Determining Approximate Dose. (Adapted from Early Dose Assessment Following Severe Radiation Accidents[1])

Chromosomal aberrations and translocations can provide a useful estimates of both the type of radiation that one has been exposed to as well as the radiation dose. This method requires considerable expertise in fluorescent in situ hybridization techniques as well as expertise in the interpretation of the chromosomal abnormalities. As a result, the analysis of chromosomal aberrations is primarily used as a research tool.

In considering the human dose-response to radiation exposure, a measurement known as the $LD_{50/60}$ (radiation dose that causes a 50% mortality rate in an exposed population within 60 days following exposure) is useful. For whole-body radiation exposure, the $LD_{50/60}$ with no treatment, is three to four Gy. Therefore, 50% of a population that receives a radiation dose of three to four Gy will die within 60 days unless they receive treatment. With treatment following radiation exposure, the $LD_{50/60}$ is five Gy or more.

ACUTE RADIATION ILLNESS

Acute radiation illness is a continuum of dose-related organ system abnormalities that develops after an acute radiation exposure of greater than one Gy. There are three main clinical syndromes that occur in acute radiation illness: the hematopoietic syndrome, the gastrointestinal syndrome and the central nervous system syndrome. Each of these syndromes occurs in a dose-related fashion. The hematopoietic syndrome occurs with radiation exposures greater than one Gy. The gastrointestinal syndrome occurs in addition to the hematopoietic syndrome at radiation exposures greater than six Gy. The central nervous system syndrome occurs in addition to the hematopoietic and gastrointestinal syndromes at radiation exposures greater than 10 Gy.

All cases of acute radiation illness begin with a prodromal phase that lasts for two to six days. This phase is characterized by nausea, vomiting diarrhea and fatigue. The higher the dose, the more rapid the onset and severity of symptoms associated with the prodromal phase. After two to six days of the prodromal phase, the patient enters a latent phase, in which he or she appears to recover and is totally asymptomatic. The latent phase lasts for several days

to one month, with the time period inversely proportional to the radiation exposure dose (i.e., the higher the dose the shorter the latent period). After the asymptomatic latent period, the patient enters the manifest illness phase. This phase of acute radiation illness lasts from several days to several weeks and is characterized by the manifestation of the hematopoietic, gastrointestinal and central nervous system syndromes, according to the exposures dose that the patient received.

The hematopoietic syndrome is characterized by bone marrow suppression resulting from the radiation-induced destruction of hematopoietic stems cells within the bone marrow. Hematopoietic stem cell destruction results in a pancytopenia which is characterized by a progressive decrease in lymphocytes, neutrophils and platelets in the peripheral blood. Both the magnitude and the time course of the pancytopenia are related to the radiation dose. In general, the higher the radiation dose the more profound the pancytopenia and the quicker it occurs. Lymphocytic stem cells are the most sensitive and erythrocytic stem cells the more resistant to radiation. Therefore, the red blood cell count and hemoglobin concentration typically do not decrease to the same extent as lymphocytes, neutrophils and platelets following radiation exposure. Hematological effects that occur in the manifest illness phase of the hematopoietic syndrome following radiation exposures of one Gy and three Gy are depicted in Figure 3-2.1.

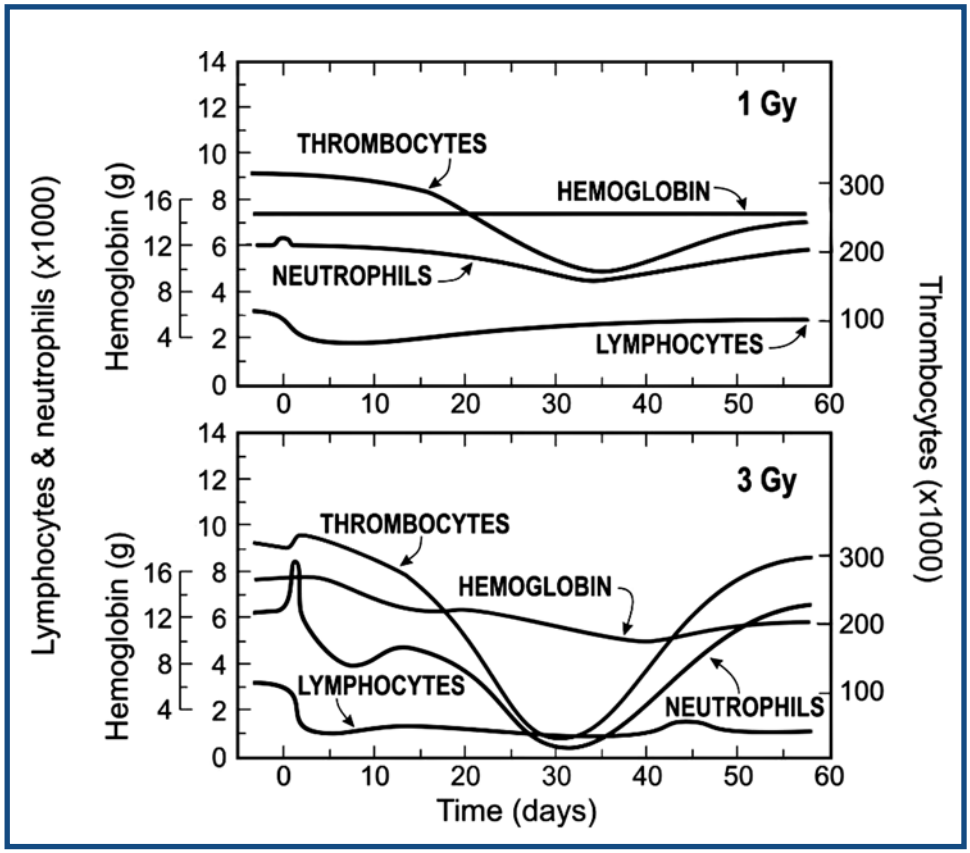

Figure 3-2.1: Hematological Effects of the Hematopoietic Syndrome (manifest illness phase) (Adapted from Acute Radiation Syndrome in Humans[2])

Following a three Gy exposure, lymphocytes decrease very rapidly and remain low for approximately 90 days. Neutrophils, after an initial period of intravascular demargination, will also begin to decline fairly rapidly following a three Gy exposure. Neutrophils do not fall as rapidly as lymphocytes, but between three and five days following exposure such patients will be significantly neutropenic. Platelets also decrease steadily following a three Gy exposure and patients will become significantly thrombocytopenic at two to three weeks. Both platelets and neutrophils will reach a nadir, with values close to zero, at about 30 days following a three Gy exposure. Platelets and neutrophils then recover gradually during the next 30 days. Thus, there is a period of about a month or so following a three Gy exposure, when patients will be significantly lymphopenic, neutropenic and thrombocytopenic. Such patients are susceptible to developing serious infections and serious bleeding problems during that time.

The gastrointestinal syndrome of acute radiation illness typically occurs following a radiation dose of greater than six Gy. It develops as a result of radiation damage to the intestinal mucosa. Following the asymptomatic latent phase, patients enter a manifest illness phase characterized by fever, vomiting and severe diarrhea. Malabsorption and severe electrolyte derangements will follow. Sepsis and opportunistic infections commonly occur as the result of mucosal breakdown. The resulting sepsis can be very severe, and typically involves enteric organisms that migrate into the systemic circulation through the damaged gastrointestinal mucosa. Approximately 10 days after the onset of the manifest illness phase, these patients typically develop fulminate bloody diarrhea that usually results in death.

The central nervous system syndrome is seen with radiation doses greater than or equal to 10 Gy. Following the asymptomatic latent period, such patients develop rapid onset of microvascular leaks in the cerebral circulation and cerebral edema. Elevated intracranial pressure and cerebral anoxia develop rapidly. Mental status changes develop early in the manifest illness phase and the patient eventually becomes comatose. Seizures may occur. Patients typically die within hours after onset of the manifest illness phase of the central nervous system syndrome.

The prognosis of patients with acute radiation illness depends upon the radiation dose to which they were acutely exposed. Patients who are exposed to one to two Gy will probably survive. Survival is possible in patients who are exposed to doses of two to six Gy, but these patients will require intensive medical care in order to survive. Survival is possible, but improbable, in patients who are exposed to doses of seven to nine Gy. Even with the most aggressive treatment, survival is extremely rare following exposure doses of 10 to 15 Gy and impossible following doses greater than 15 Gy.

Treatment

All patients with acute radiation illness should receive basic supportive care. This consists of fluid and electrolyte balance, antiemetic agents to manage vomiting, antidiarrheal agents to manage diarrhea, proton pump inhibitors for gastrointestinal ulcer prophylaxis, pain management, psychological support and pastoral care if death is likely. In patients with acute radiation illness, it is

important not to instrument the gastrointestinal tract, since this could result in perforations that precipitate fulminate bleeding or sepsis.

Cytokine therapy with a colony stimulating factor should be given to patients with a 2 Gy or greater exposure in order to stimulate neutrophil production in the bone marrow [1]. However, in an extreme mass casualty situation, it may be necessary to maximize the use of cytokines by providing only supportive care to the expectant (seven Gy or greater exposure) [1]. Various types of granulocyte colony stimulating can be given to individuals with acute radiation illness: G-CSF (Filgrastim – 5 mg/kg per day subcutaneously, continued until the absolute neutrophil count is greater than 1.0 x 10^9 cells/L); Pegulated G-CSF (Pegfilgrastim – 6 mg as a single subcutaneous dose); or GM-CSF (Sargramostim – 250 mg/m^2 per day subcutaneously, continued until the absolute neutrophil count is greater than 1.0 x 10^9 cells/L).

Antibiotics are also recommended for all with a two Gy exposure or greater, due to expected absolute neutropenia, especially in the setting of burns or other traumatic injuries [1]. Similarly, in an extreme mass casualty situation, it may be necessary to maximize use by providing only supportive care to the expectant (seven Gy or greater exposure) [1]. The specific antibiotic regimen used in the management of acute radiation illness should depend upon the antibiotic susceptibilities of any specific organisms that are able to be isolated. It is generally recommended that a fluoroquinolone with streptococcal coverage be used, along with acyclovir or one of its congeners for viral coverage, and fluconazole for the coverage of fungi and candida. Once again, antibiotic treatment should be given for any specific organisms that can be isolated, such as Pseudomonas aeruginosa. Antibiotics should be continued until the absolute neutrophil count is greater than 0.5 x 10^9 cells/L, until they are no longer effective, or as indicated for specific organisms that have been isolated.

Blood transfusions are indicated for patients with acute radiation syndrome who have severe bone marrow damage or who require concurrent trauma resuscitation. The purpose of blood transfusions in such patients is to provide erythrocytes for the improvement of oxygen-carrying capacity, blood volume to improve hemodynamic parameters and platelets to help prevent bleeding. Cytokines, not blood transfusions, are used to increase absolute neutrophil counts, according to the criteria and doses previously discussed. All cellular products in the blood to be transfused should be leukoreduced and irradiated to 25 Gy in order to prevent a graft versus host reaction. Leukoreduction also helps to protect against platelet alloimmunization and the development of cytomegalovirus (CMV) infections.

Stem cell bone marrow transplantation should be considered for certain patients with acute radiation illness. Allogenic stem cell transplantation is indicated for individuals who have a radiation exposure dose of 7 to 10 Gy. Patients with acute radiation illness who are fortunate enough to have a stored autograft bone marrow specimen or a syngenetic donor, preferably an identical twin, should be consider for stem cell transplantation if they have had a radiation exposure dose of 4 to 10 Gy.

There are several special considerations that need to be taken into account during the management of acute radiation illness. These include concurrent acute radiation dermatitis, combined acute radiation illness and trauma,

decontamination of the patient and appropriate precautions for health care workers.

Acute radiation dermatitis may occur in conjunction with acute radiation illness. The symptoms and signs of acute radiation dermatitis typically appear several days after an acute radiation exposure. Although acute radiation dermatitis is essentially a radiation burn, it is different from the thermal burns that may occur immediately after exposure of the skin to a nuclear explosion. Exposure of the skin to radiation causes loss of the epidermal layer at radiation doses greater than two Gy. This leads to erythema and blisters. Loss of the dermis occurs at radiation exposure doses of greater than 10 Gy; this results in skin ulcers that heal very slowly over many months, if they heal at all. These patients are predisposed to serious infections.

The combination of acute radiation illness and trauma is a unique management challenge. First, there is a significant increase in mortality among patients who have this combination of illness and injury and they typically require very intensive medical care. Their care is complicated by the fact that any surgery that is required should be done within the first 48 hours after radiation exposure or delayed for two to three months, depending upon the radiation dose and the extent of the hematopoietic syndrome. These patients are very susceptible to operative and postoperative infections as a result of decreased neutrophil and lymphocyte counts.

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Chapter 3-3
Inhalation Lung Injury
Vesicants and Nerve Agents

By Dr. James A. Geiling, MD

Chemical weapons are divided into four major classifications based upon their physiologic effects and mechanisms of action. Blood agents such as AC (hydrogen cyanide), (SA) arsine, cyanogen, and hydrogen sulfide were discussed in Chapter 1-2. Pulmonary irritants such as phosgene and chlorine were discussed in chapter 3-1. The remaining two classical categories include the vesicants and nerve agents. These agents can be dispersed from a variety of munitions.

VESICANTS

Vesicants derive their name from the vesicles or blisters that these agents produce. Two agents comprise this group: mustard (HD; bis-2-Chloroethyl sulfide) and Lewisite (L; 2-Chlorovinyl dichloroarsine). They have also been used as a combined mixture. Phosgene oxime (agent CX) is a also vesicant (as well as an urticant).

Clinical Syndrome

Topical exposure to these irritants causes conjunctivitis, corneal opacification, skin erythema and vesicles (blisters). Inhalation injury ranges from mild upper respiratory complaints to marked airway damage including asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, and bronchiolitis obliterans.[1,2,3,4]

The principle difference between these agents is the latency of mustard, with an asymptomatic period of hours. Mustard can also cause gastrointestinal effects and bone marrow suppression. These agents can be detected by a variety of chemical agent or hazardous material (HAZMAT) monitoring devices.

Decontamination

The recommended decontamination solution is hypochlorite in large amounts, though large quantities of soap and water are more practically employed.

Treatment

Early treatment with nonsteroidal anti-inflammatory drugs has been shown to be beneficial against the cutaneous injury caused by mustard.[5] Skin lesions are

treated as per standard burn protocol.[6] Respiratory management is symptom targeted though patients may benefit from bronchoscopy, including bougienage and laser photoresection if findings progress.[7] Lewisite has a specific antidote known as British Anti-Lewisite that may mitigate systemic effects[8,9].

NERVE AGENTS

Nerve agents are highly toxic and include: GA (tabun): Ethyl *N*, *N*-dimethylphosphoramidocyanidate; GB (sarin): Isopropyl methyl phosphonofluoridate; GD (soman): Pinacolyl methyl phosphonofluoridate; GF: O-Cyclohexyl-methylphosphonofluoridate; and VX: O-Ethyl S-(2-(diisopropylaminoethyl) methyl phosphonothiolate.[8,9]

Clinical Syndrome

They act through their inhibition of organophosphorous cholinesterases, specifically plasma butyrylcholinesterase, red blood cell (RBC) acetylcholinesterase, and acetylcholinesterase (AChE) at tissue cholinergic receptor sites.[8,9] Following an acute exposure, the RBC enzyme activity best reflects the tissue AChE activity during recovery. Nerve agents irreversibly bind to AChE and thereby prevent the hydrolysis of the neurotransmitter acetylcholine (ACh); the resultant excess ACh produces the clinical effects of nerve agent toxicity. Because the binding of agent to enzyme is permanent, its activity returns only with new enzyme synthesis or RBC turnover (1%/day). Excess ACh affects both muscarinic and nicotinic sites. Affected muscarinic sites include postganglionic parasympathetic fibers, glands, pulmonary and gastrointestinal smooth muscles, and organs targeted by central nervous system efferent nerves, such as the heart via the vagus nerve. Nicotinic sites include autonomic ganglia and skeletal muscle.

Nerve agents produce a clinical syndrome similar to that of organophosphate insecticide poisoning but, with far greater toxicity. The symptom complex has been previously described by the "SLUDGE" toxidrome: increased salivation, lacrimation, urination, defecation, gastric distress and emesis.[9] The principal effect on the eyes is miosis, which occurs as a consequence of direct contact with vapor. The symptoms appear shortly after exposure, often within seconds. The pupillary constriction is often associated with intense pain (which may consequently induce nausea and vomiting). Miosis results in dim or blurred vision; the conjunctiva often become injected and lacrimation occurs. Exposure results in increased salivary gland secretion as well as other gastrointestinal glandular secretions. Victims may present with significant nausea, vomiting, and diarrhea. Localized sweating may occur at the site of exposure to nerve agent droplets. Generalized sweating appears with high-dose exposure. Skeletal muscles initially develop fasciculations and twitching, but they become weak, fatigued, and eventually flaccid. Respiratory effects include rhinorrhea, bronchorrhea and bronchoconstriction depending upon the severity of exposure. Respiratory compromise develops with diaphragm and other muscle weakness. High dose exposure may result in loss of consciousness, seizure activity and central apnea. Normally, a vagally-mediated bradycardia may be expected with these agents. However, typically these patients have a "fight or flight"-induced tachycardia. Blood pressure remains normal until terminal decline. A variety of dysrhythmias may develop, including QTc

prolongation and Torsade de pointe.[10,11] In survivors, a chronic decline in memory function, post-traumatic stress and depression have been noted after the Tokyo sarin gas release.[12]

While initial effects from nerve agent exposure can be seen within seconds to minutes, the rapidity and severity of symptoms are dose-dependent. High-dose vapor exposure may present as seizures or loss of consciousness in less than one minute, whereas low-dose skin contact may not present as long as 18 hours later when the victim appears with gastrointestinal complaints. Measurement of red cell cholinesterase (ChE) inhibition is more sensitive than measurement of plasma ChE activity in the setting of nerve agent exposure. However, although helpful in confirming exposure, results are not immediately available as few clinical laboratories can perform these tests and levels do not generally correlate with physical findings.

Decontamination

Decontamination is the key element in mitigating the effects of nerve agent poisoning on patients and health care workers. All suspected casualties should be decontaminated prior to entering a medical facility. "Casualties" who remain asymptomatic minutes after an event are unlikely to have sustained a significant vapor exposure. However, if exposed to a liquid agent, even asymptomatic victims should be observed for 18 hours. When triaging multiple casualties, patients recovering from exposure and treatment in the field can normally be placed into a "delayed" category. Ambulatory patients and those with normal vital signs can be categorized as "minimal". "Immediate" patients are those with unstable vital signs or seizure activity. Triaging of patients who are apneic, pulseless, or without a blood pressure will depend on available resources. Airway and breathing management is paramount. Ventilatory support is complicated by increased secretions and airway resistance (50 to 70 cm H_2O).

Treatment

Treatment of nerve agent casualties, like other poisons, requires appropriate administration of antidotes. Atropine is an anti-cholinergic and serves as the primary antidote for nerve agent exposure, with its greatest effect at muscarinic sites. The standard two-milligram dose when administered to non-exposed person will result in mydriasis, decreased secretions and sweating, mild sedation, decreased gastrointestinal motility, and tachycardia. The recommended atropine dose is two-milligrams every three to five minutes, titrated to secretions, dyspnea, retching or vomiting.[13,14] Atropine should not be dosed to miosis, which is treated with topical atropine or homatropine, or more recently tropicamide. Nebulized ipratropium bromide may be of help in managing secretions and bronchospasm. Fasciculations can persist after restoration of consciousness, spontaneous ventilation, and even ambulation. Atropine will normally not be effective in terminating seizures, though other antcholinergics (scopolamine, benactyzine, procyclidine, and aprophen) may be successful if given early.[12,13]

In addition to atropine, pralidoxime chloride (2-PAMCl) is used in an attempt to break nerve agent-enzyme binding. This oxime is effective only at nicotinic sites thereby, improving muscle strength but not secretions. 2-PAMCl is only effective if administered early before binding has become permanent. The

time course for this phenomenon, referred to as "aging", varies according to the nerve agent involved – approximately two minutes for Soman and three to four hours for Sarin. Other oximes, including obidoxime, the H oximes (HI-6, Hlö-7), and methoxime may eventually provide additional options to reactivate the ChE.[15] Atropine and 2-PAMCl are often combined into an injector kit system known as the MARK I kit (Meridian Medical Technologies, Inc; Columbia, MD) or more recently the Duodote Kit (Meridian Medical Technologies, Inc; Columbia, MD) used by the US military and civilian EMS personnel. For seizures, Diazepam is the anticonvulsant of choice, based primarily on its historical use and demonstrated effectiveness, but other benzodiazepams may be substituted. Ketamine has also been used as an anticonvulsant because of its neuroprotective and antiepileptic activities[15]. More aggressive therapy may include the use of hemodiafiltration followed by hemoperfusion, which was successfully employed in the management of one victim of the Tokyo sarin attack.[16] Future therapies may include bacterial detoxification, the use of nerve agent scavengers such as organophosphorous acid anhydride hydrolase, benzodiazepine receptor partial agonists (e.g., bretazenil) in the prophylactic treatment of nerve agent poisoning, or paraoxonases that enzymatically break down nerve agent.[17,18,19,20].

OTHER CHEMICAL AGENTS

Urticants or nettle agents such as phosgene oxime (agent CX, also a vesicant) produce instant and sometimes intolerable pain upon contact with skin and mucous membranes. Vomiting agents such as Adamsite (agent DM) can cause regurgitation, as well as coughing, sneezing, pain in the nose and throat, nasal discharge, and/or tears, as well as dermatitis on exposed skin. Corrosive smoke agents such as titanium tetrachloride (agent FM smoke) and sulfur trioxide-chlorosulfonic acid (agent FS smoke) cause inflammation and general destruction of tissues and can lead to swelling of lung membranes, pulmonary edema, and death following inhalation. Tear agents such as acrolein (no military designation), mace (agent CN), and pepper spray (agent OC) cause tears and intense eye pain and may also irritate the respiratory tract and skin.

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Chapter 3-4
Disaster-Related Infections: Pandemics, Post-Disaster and Bioterrorism

By Dr. Asha Devereaux M.D., Angie Lazarus MBBS, and Dr. David J. Prezant M.D.

There are three broad categories of disaster-related respiratory infections. The first is worldwide pandemic infection, itself the cause of a healthcare disaster. The second is an epidemic that follows a natural or man-made disaster. And the third is bio-attacks such as the inhalational anthrax exposures that occurred in the United States in 2001.

PANDEMIC

Pandemic planning is currently focused on response to the Novel H1N1 influenza A virus. As of June 2010, worldwide more than 214 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,209 deaths. Far greater numbers have been infected as many countries, including the United States and Canada, have not been counting milder cases and only using laboratory testing to confirm more severe cases. The United States and Canada are both reporting rates of influenza-like illness well above seasonal baseline rates. For hospitalized patients with H1N1, the most common symptoms include fever (93%), cough (83%), shortness of breath (54%), fatigue/weakness (40%), chills (37%), body aches (36%), nasal drip/congestion (36%), sore throat (31%), headache (31%), vomiting (29%), wheezing (24%) and diarrhea (24%). Important differences exist between H1N1 influenza and seasonal influenza. Because, most individuals less than 65 do not have natural immunity to H1N1, disease has been more severe in the young than in the elderly. According to the Centers for Disease Control and Prevention (CDC), groups at particular risk include, the young (especially between six months and 24 years old), pregnant women, or persons with chronic diseases (lung disease including asthma, heart disease excluding hypertension, kidney, liver, hematologic including sickle cell disease, diabetes, cancer especially those receiving chemotherapy, immunologic disorders including those caused by medication or HIV, neuromuscular diseases that could compromise respiratory function or increase the risk for pneumonia, and persons younger than 19 years old who are receiving long-term aspirin therapy because of increased risk for Reye Syndrome. These

groups have been identified to be at increased risk because of their high rates of influenza complications leading to hospitalization, intensive care unit stays, mechanical ventilation and death.

For example, in the United States during 2009, 32% of those hospitalized due to H1N1 influenza have had pre-existing asthma. In an effort to reduce their risk, the CDC recommends that these patients at risk receive not only the seasonal influenza vaccine but also the H1N1 vaccine and also, in certain cases, Pneumovax® (vaccination affords protection against common types of pneumococcal pneumonia). In addition, the CDC recommends that these groups at risk receive early treatment with antiviral medications (oseltamivir or zanamivir) if influenza-like illness was to occur. Further, the CDC recommends that all healthcare personnel (including EMS personnel and fire fighters who respond to medical emergencies) receive seasonal influenza and H1N1 vaccinations. The CDC recommends that these vaccinations should not be given to those with severe allergy to chicken eggs, prior severe reaction to influenza vaccination, the rare person who developed Guillan-Bare syndrome within six weeks of getting an influenza vaccine, children less than six months of age, people who currently have moderate-to-severe illness with fever (they should wait until they recover). Those with immunologic disorders or who have household members with immunologic disorders should only receive the flu-shot which contains inactivated vaccine (killed virus) and should not receive the flu-nasal-spray which contains live weakened virus.

H1N1 is not the only novel influenza virus that is of concern. The potential still remains for avian influenza A subtype H5N1 developing the capacity for widespread, efficient, and sustainable human-to-human contagion. The first recognized human outbreak of avian influenza H5N1 occurred between May and December 1997 in Hong Kong[3] infecting 18 persons, mostly children and young adults (half less than 19 years old and only two older than 50 years). [4,5] Between 2003 and January 2007, 265 additional cases, with a 60% mortality rate, were reported to the World Health Organization (WHO) but only a few were suspected to be the result of human-to-human transmission [6]. Fever, cough and dyspnea occur in nearly all patients, and abdominal symptoms, including diarrhea, appear in about half the patients.[4, 5] Pneumonia, lymphopenia and elevated liver enzymes are poor prognostic factors with death occurring on average 10 days after onset of illness, typically from progressive respiratory failure and Acute Respiratory Distress Syndrome (ARDS). [4, 5]

The incidence of pneumonia complicating influenza infection varies widely, from 2 - 38%, and is dependent on viral and host factors.[7,8,9] During an influenza pandemic, pneumonia should be considered in all patients with severe or worsening respiratory symptoms, especially those with pre-existing chronic disease. Influenza-related pneumonia can be viral or a secondary bacterial or mixed infection.[7,8,9,10] Typically, viral pneumonia (bilateral interstitial infiltrates) occurs early in the presentation while secondary bacterial pneumonia (lobar infiltrates) occurs four to five days after onset of initial symptoms. The predominant organisms responsible for secondary bacterial pneumonia vary with Hemophilus influenza, beta-hemolytic streptococci and Streptococcus pneumonia during the 1918 influenza pandemic; Staphyloccus aureus during the 1957 pandemic; and S pneumonia, Staphylococcus aureus (26%) and Hemophilus influenza during the 1968 pandemic.[7, 11] Mixed bacterial and viral

pneumonia can occur concurrently.[12] In these instances, the chest radiograph may demonstrate lobar consolidation superimposed on bilateral diffuse lung infiltrates. The mortality rate in mixed viral – bacterial pneumonia is as high as for primary viral pneumonia (>40%)[7,6,9,10].

The current recommendation during a pandemic flu alert is to treat with an appropriate antiviral medication early on in the presentation of flu-like symptoms and fever (≤ 2 days).[6, 13] Antibiotics should be added if pneumonia is present or considered if risk factors for poor outcome are present such as age over 64 years, nursing home patient, immunosuppression or chronic disease (i.e. respiratory, cardiac, liver, renal or diabetes). Proper respirators and universal droplet precautions are current CDC recommendations.[14] Using CDC computer projections based on the 1918 flu pandemic (35% attack rate, week five of an eight-week pandemic), a city the size of New York today would require approximately 39,000 hospital beds, 19,000 ICU beds, and over 9,000 mechanical ventilators.[15]

EPIDEMICS POST-DISASTER

Epidemics post-disaster are, despite popular misconceptions, actually uncommon and when they do occur are the result of organisms and vectors already endemic to the area or displaced population.[16] The risks of epidemics are increased only when disaster produces large displacements of people to crowded shelters lacking adequate sanitation, climate control, food, vaccines and medications.[17] Dead bodies do not increase infectious disease risk, unless the dead were victims of a communicable disease. Corpses do not need to be buried or burned rapidly and instead victims should be identified and dealt with consistent with legal, cultural and religious beliefs thereby, diminishing psychological stress for the large number of potentially-affected survivors. Disease-related mortality and epidemics[17] can be prevented or reduced if public health infrastructure is maintained or quickly re-established to provide: safety and security of the victims, safe water and food, sanitation services (including human and animal waste removal), shelters with adequate space and ventilation, adequate hygiene, medications, immunization programs, vector control, disease surveillance, and the isolation of patients with communicable diseases. Malnutrition is associated with higher mortality rates from diarrheal illness, measles, malaria, and acute respiratory illness. The interdependency between malnutrition and infectious disease on mortality rates is most evident in vulnerable populations such as children and patients with pre-existing co-morbidity.

During a disaster, the majority of all infectious disease mortality is related to diarrheal disease (not the subject of this review), respiratory infections[18] and measles.[19] In 1992, following the Mount Pinatubo eruption in the Philippines, these three diseases caused nearly all of the infectious disease-related mortality in nearly equal proportion.[20] Knowledge of local endemic diseases and vectors provides a basis for educated surveillance in shelters and refugee camps. Surveillance should be coordinated by a single agency. Clinical field data should be routinely collected, shared, collated, and disseminated at regular meetings among various relief organizations to inform and respond to potential outbreaks. Surveillance case recognition should be based on easily identified clinical scenarios. Cough with fever suggests respiratory infection. Cough with

fever accompanied by mouth sores and rash raises suspicion for measles in an area with poor immunization programs. Immediately after Hurricane Andrew hit Florida in 1992, a surveillance system was initiated utilizing data from over 40 sites. Surveillance focused on five presenting complaints (diarrhea, cough, rash, animal bite and "other infectious symptoms") that were targeted for rapid intervention with the result that morbidity and proportional mortality was not increased for diarrhea or cough.[21]

Respiratory illnesses include all of the viral and bacterial infections common to the area or displaced population. Poor hygiene, overcrowding and malnutrition add to the risk for endemic infections becoming epidemic. Public health measures and early treatment is the mainstay. Tuberculosis[22] can also occur in refugee camps in the developing world but, mortality is typically low.[23] In Bosnia in 1992, tuberculosis cases increased dramatically as the result of medication shortages, overcrowding and malnutrition.[22] In areas with high HIV rates pre-disaster, mortality from co-infection with tuberculosis would be substantially higher.

Measles, prior to mass immunization programs, was the infection most associated with high mortality rates.[19] In the first three months after the Mount Pinatubo eruption, measles accounted for nearly 18,000 cases, 25% of all clinic visits and 22% of all deaths.[24] Measles transmission is by direct contact with respiratory droplets and less commonly by airborne inhalation. The incubation period is 7 to 14 days from exposure to first signs of disease and patients are contagious from approximately one to two days prior to onset of illness until approximately four days after the rash appears. Respiratory complications include pneumonia from measles and bacterial super-infection. Disaster-induced disruption in a region's routine vaccination program may lead not only to measles but to other respiratory diseases such as pneumococcal pneumonia, *Hemophilus influenza* and pertussis, especially in areas where large numbers of displaced persons are crowded together and pre-disaster immunization programs were ineffective. Standard post-disaster immunization recommendations emphasize measles immunization program in areas with low pre-disaster immunization rates. For children older than nine months, vitamin A should be given simultaneously, because it can decrease ophthalmic complications, disease severity and mortality by 30 - 50%. [25]

Post-disaster vector-borne disease epidemics are also uncommon. However, large areas of stagnant water and suspension of pre-existing vector control programs may increase breeding sites, and were the cause of increased malaria rates in Haiti after Hurricane Flora in 1963.[26] *P. falciparum* has the shortest incubation period (weeks to months) and is responsible for significant morbidity and mortality including respiratory complications such as pulmonary edema.[27] Because chemotherapy resistance for malaria is quite variable worldwide, treatment should be based on local chemosensitivity. Other diseases transmitted by mosquito vectors include St. Louis encephalitis, eastern or western equine encephalitis, West Nile encephalitis and Dengue fever.[28] When considering epidemics, dengue is classified by the World Health Organization (WHO) as a major international public health concern. Dengue hemorrhagic shock syndrome is the most serious consequence of this infection and is likely to occur by cross infection with multiple serotypes of the virus. The hallmark of dengue hemorrhagic fever is capillary leakage four to seven days following

the onset of disease, usually at the time of defervescence. A sudden change to hypothermia, altered level of consciousness, and gastrointestinal (GI) symptoms associated with thrombocytopenia herald the onset of capillary leak phenomenon. Emphasis should be on prevention programs for populations that are exposed to mosquitoes, including long-sleeved shirts and pants, insect repellents, bed-nets, and chemoprophylaxis. Infections related to adverse weather conditions can also be caused by other vectors or environmental exposures. For example, the increased incidence of Hantavirus (deer mice in New Mexico following flooding)[29] and coccidioidomycosis (dust clouds in California following the Northridge earthquakes) .[30]

Aspiration pneumonia is not usually thought of as a disaster-related infection. However, following the large earthquake in Indonesia in December 2004, over 100,000 people were swept away by a massive tsunami. Many of the survivors clung to trees and debris as the seawater engulfed them. In this setting, aspiration pneumonia was “common” but, exact numbers were difficult to record.[31, 32] Resultant pulmonary infections from this exposure can be divided into early and late based on the pathogens involved. The initial manifestation of "submersion injury" (early aspiration pneumonia) is aspiration of 3-4 ml/kg of liquid due to reflex laryngospasm. This typically results in an immediate cough and chemical pneumonitis that can progress to Acute Lung Injury or ARDS. Chronic sequelae may include hyperreactive airways dysfunction, bronchiectasis, and recurrent infection. Late tsunami-lung includes necrotizing pneumonia and empyema secondary to aspiration of "tsunami water", mud, and particulate matter. This results in a pneumonic process clinically presenting four to six weeks after the initial aspiration, with radiographic features of cavitation, effusion, empyema, and secondary pneumothorax. Pathogens are polymicrobial and indigenous to the region, including aeromonas, pseudomonas, and streptococcal species. Fungi such as Pseudeallescheria boydii can result in disseminated brain abscesses. Burkholderia pseudomallei, the etiology of meliodosis, require prolonged antibiotic therapy.[32] Wounds contaminated with "tsunami water", soil, and particulate matter included staphylococcus, streptococcus, vibrio, aeromonas, pseudomonas, burkholderia, tetanus and fungi endemic to the area.[32]

Mold exposures may result from water damage during hurricanes and floods, especially in hot climates. Sufficient evidence has been found for an association between damp indoor spaces and mold and upper respiratory symptoms (nasal congestion and throat irritation) and lower respiratory symptoms (cough, wheeze and exacerbation of asthma), and opportunistic fungal infection in immunocompromised patients.[33] Levels of endotoxin, a by-product of bacteria metabolism, and (1-3)-b-D-glucan, a cell-wall component of fungi and other microorganisms, were shown to be elevated after the Katrina disaster in New Orleans.[34] Both these toxins have been associated with respiratory effects.

Molds, the common term for multicellular fungi, and other fungi, may affect human health through three processes: allergy, infection and toxicity.[35, 36] Allergic responses to molds may be IgE or IgG mediated.[35] Exposure to fungal proteins can result in generation of IgE responses in the susceptible host (i.e., atopic individuals), which can lead to the development of allergic rhinitis and asthma.[33, 35, 36] Mold spores and fragments can produce allergic reactions in sensitive individuals, regardless of whether the mold is dead or alive. Penicillium

and Aspergillus species which are usually indoor molds, and the outdoor molds Cladosporium and Alternaria can all induce IgE responses. IgG-mediated responses and cell-mediated immunity against inhaled fungal proteins can result in development of hypersensitivity pneumonitis. This abnormal response may result after short or long-term exposure, but usually requires the inhalation of large quantities of fungal protein.[35] Finally, IgE responses to molds in allergic patients may result in allergic bronchopulmonary mycosis (also known as allergic bronchopulmonary aspergillosis when it is induced by Aspergillus sp.), or allergic fungal sinusitis.

A very limited number of pathogenic fungi may cause pulmonary and systemic infection in non-immune compromised subjects. Blastomyces, Coccidioides, Cryptococcus, Hystoplasma and Paracoccidioides have all been reported as systemic pathogens in both, immune compromised and non-immune compromised subjects. Other fungi, such as Aspergillus and Candida have been associated with systemic infection in immune-compromised individuals. Different species of molds have been associated with superficial skin and mucosal infections that are extremely common.

Irritant and toxic effects due to exposure to molds and mold products affecting the eyes, skin, nose, throat and lungs, have been described. Volatile compounds produced by molds and released directly into the air, known as microbial volatile organic compounds, and particulates from the cell walls of molds, including glucans and mannans in spores and hyphae fragments, have been reported as capable of inducing transient inflammatory reactions. Mycotoxins, low-molecular-weight chemicals produced by molds as secondary metabolites that are not required for the growth and reproduction of these organisms, have been associated with systemic toxicity especially via the ingestion of large amounts of moldy foods, especially in the veterinary setting.[37] Ingestion of aflatoxins, mycotoxins produced by Aspergillus flavus and A. parasiticus, has been demonstrated as an important risk factor for hepatocellular carcinoma in humans. Organic dust toxic syndrome, a noninfectious, febrile illness associated with chills, malaise, myalgia, dry cough, dyspnea, headache and nausea in the presence of normal chest films, no hypoxemia and no sensitization, has been reported upon exposure to high concentration of fungi, bacteria and organic debris in settings such as agricultural works, silage and exposures to soiled grain.[38]

BIOLOGICAL TERRORISM AGENTS

Biological terrorism agents have been classified by the Centers for Disease Control and Prevention (CDC) into three groups based on their potential for adverse health impact, mass casualties and death (Table 3-4.1).[39] As they have the greatest potential for mass casualties and death, category A agents (smallpox, anthrax, tularemia, plague and botulism) are the subject of this review and are described based on their pathogenesis and clinical presentation, laboratory diagnosis, treatment and infection control.

Bioterrorism Agents and Threat Categories		
Category A	Category B	Category C
Bacillus anthracis (Anthrax) Yersinia pestis (Plague) Variola Major (Smallpox) Clostridium Botulinum (Botulism) Francisella tularensis (Tularemia) Viral Hemorrhagic Fevers	Coxiella Burnetti (Q Fever) Brucella species (brucellosis) Burkholderia mallei (Glanders) Ricin Clostridium perfringens Epsilon toxin Staphylococcus enterotoxin B	Nipah virus Hantavirus Tickborne hemorrhagic fever viruses Tickborne encephalitis viruses Yellow fever Multi-drug resistant tuberculosis

Table 3-4.1: Bioterrorism Agents and Threat Categories. (Adapted from Public Health Assessment of Potential Biological Terrorism Agents [39])

Smallpox

Smallpox last occurred in Somalia in 1977, but in recent years there has been renewed concern about its' potential for use as a biological weapon.[40] The causative agent of smallpox, the variola virus, is a member of the *Poxviridae* family, sub-family *Chordopoxvirinae*, and genus *Orthopoxvirus*. This genus also includes vaccinia (used in the smallpox vaccine), monkeypox virus, camelpox, and cowpox. The variola virus is stable and maintains infectivity for long periods of time outside the human host.[41] Person-to-person transmission occurs by respiratory droplet nuclei dispersion. Although infrequent, infection has also been known to occur from contact with infected clothing, bedding, or other contaminated fomites.[42]

Pathogenesis and Clinical Presentation

Following inhalation, the variola virus seeds the mucus membranes of the upper and lower respiratory tract and migrates to regional lymph nodes, where replication occurs, leading to viremia and end-organ dissemination. During the incubation phase (7 to 17 days) infected individuals are most likely asymptomatic, but may have low-grade temperature elevation or a mild, erythematous rash. Smallpox is not contagious during the incubation phase, but may be so during the prodrome phase which lasts two to four days and is characterized by the abrupt onset of high fever (greater than 104°F/40°C), headache, nausea, vomiting and backache. These symptoms are sometimes accompanied by abdominal pain and delirium.[42,43] The eruption phase occurs two to four days later, beginning as small, red maculopapular lesions approximately two to three millimeters in diameter on the face, hands and forearms. Lower extremity lesions appear shortly thereafter. During the next two days, the skin lesions become distinctly papular and spread centrally to the trunk. Lesions on the mucous membranes of the oropharynx and oropharyngeal sections are highly infectious. Over the next two weeks, skin lesions progress synchronously from papules to vesicles to crusts. Desquamation then begins, virus particles are found in the fallen-off crusts, and patients remain infectious until all crusts fall off, a process that may take several more weeks.

The mortality rate from smallpox is three percent in vaccinated individuals and 30% in the unvaccinated.[44, 45] Death from smallpox is presumed to be secondary to a systemic inflammatory response syndrome, caused by overwhelming quantities of immune complexes and soluble variola antigen, which may result in severe hypotension during the second week of illness. Respiratory complications, including pneumonia and bronchitis are common.[44, 45] Severe intravascular volume and electrolyte imbalance may occur that may lead to

renal failure. Encephalitis and bacteremia may contribute to mortality. Two atypical manifestations of smallpox have higher mortality rates.[45] Hemorrhagic smallpox occurs in less than three percent of infected individuals, and is characterized by a short incubation period and an erythematous skin eruption that later becomes petechial and hemorrhagic, similar to the lesions seen in meningococcemia. The malignant form, or "flat smallpox," also occurring in about 3% of infected individuals, is characterized by a fine-grained, reddish, non-pustular and confluent rash, occasionally with hemorrhage. Patients with hemorrhagic or malignant forms of smallpox have severe systemic illness and die within several days. Pulmonary edema occurs frequently in both hemorrhagic and malignant smallpox and contributes to the high mortality rates.[45]

The differential diagnosis of papulovesicular lesions that can be confused with smallpox includes: chickenpox (varicella), shingles (varicella zoster), disseminated herpes simplex, monkeypox, drug eruptions, generalized vaccinia, eczema vaccinatum, impetigo, bullous pemphigoid, erythema multiforme, molluscum contagiosum and secondary syphilis. Chickenpox (varicella) is the most common eruption that can be confused with smallpox. In contrast to the synchronous and centrifugal nature of the smallpox skin lesions, chicken pox (varicella) skin lesions are greatest on the trunk, spare the hands and soles, and are at multiple stages at any given time, with papules, vesicles, and crusts all present simultaneously (Table 3-4.2).[43,44]

Clinical Features in Smallpox and Chickenpox		
	Smallpox	**Chickpox**
Prodrome:	2-4 days of high fever, headache, backache, vomitting, and abdominal pain	Absent-mild, 1day
Rash:	Starts in oral mucosa, spreads to face and expands centrifugally	Starts on trunk and expands centripetally
Palms/Soles:	Common	Rare
Timing:	Lesions appear and progress at same time	Lesions occur in crops and at varied stages of maturation
Pain:	May be painful	Often pruritic
Depth	Pitting and deep scars	Superficial, doesn't scar

Table 3-4.2: Distinguishing Clinical Features in Smallpox and Chickenpox

Laboratory Diagnosis

Confirmation of smallpox can be performed by the analysis of skin scrapings, vesicular fluid, and oropharyngeal swabs. Serologic testing is not useful in differentiating the variola virus from other orthopoxviruses. Laboratory specimens should only be manipulated and processed at laboratories with biosafety level 4 (BSL4) facilities. Local public health departments can assist in getting specimens to an appropriate laboratory.

Treatment

There is no FDA-approved drug for the treatment of smallpox. Patients should be vaccinated if the disease is in its early stage as vaccination may decrease symptom severity.[45] At the present time, treatment is supportive and includes appropriate antibacterial therapy for secondary skin infections, daily eye irrigation for severe cases, adequate nutrition and hydration. Topical treatment with idoxuridine can be considered for corneal lesions. Recent studies in animals suggest that cidofovir has activity against orthopoxviruses, including variola. Cidofovir®, given at the time of, or immediately following exposure, has the potential to prevent cowpox, vaccinia, and monkeypox in animal studies.[46] There is no evidence that the use of vaccinia immune globulin offers any survival or therapeutic benefit in patients infected with smallpox.

Infection Control

If an outbreak were to occur, it is anticipated that the rate of transmission may be as high as 10 new cases for every infected person. All individuals who have direct contact with the index case should be quarantined for 17 days. Home quarantine will be necessary in mass casualty situations. Healthcare workers caring for infected individuals should be vaccinated and use strict airborne and contact isolation procedures.[47,48,49] Infected patients should be placed in respiratory isolation and managed in a negative-pressure isolation room, if possible. Patients should remain isolated until all crusted lesions have fallen off.

Inhalational Anthrax

Inhalational anthrax occurred in 2001 after envelopes containing anthrax spores were sent through the United States Postal System and resulted in five out of 22 fatalities.[50, 51] *Bacillus anthracis* is a large, gram-positive, aerobic, spore-forming, non-motile bacillus.

Pathogenesis and Clinical Presentation

Virulence is determined by two plasmids that produce exotoxins.[52] One of these exotoxins, known as lethal factor, stimulates the over-production of cytokines, primarily tumor necrosis factor-alpha and interleukin-1-beta that cause macrophage lysis. The sudden release of inflammatory mediators appears to be responsible for the marked clinical toxicity of the bacteremic form of anthrax.

The three forms of anthrax infection are determined by the route of entry – *Cutaneous anthrax,*[53] *Gastrointestinalpharyngeal anthrax,*[44, 45] and *Inhalational anthrax*.[54] The latter two forms can be fatal.[55] Anthrax spores are 1 to 1.5 micrometers in size and easily deposit in the alveoli following inhalation. There, the endospores are phagocytosed by the pulmonary macrophages and transported via lymphatics to the mediastinal lymph nodes where they may remain dormant as "vegetative cells" for 10 to 60 days, or longer. Once germination in the lymph nodes is complete, replication occurs, releasing edema and lethal toxins that produce a hemorrhagic mediastinitis. In some patients, the initial symptoms are relatively mild and non-specific, resembling an upper respiratory tract infection. Fever, chills, fatigue, non-productive cough, nausea, dyspnea, chest pain and myalgias are common presenting complaints.[52, 55] These symptoms typically last for two to three days and then

progress to severe, fulminant illness with dyspnea and shock. Some patients present with fulminant illness without prodromal symptoms. The number of spores inhaled, age of the patient and the underlying immune status most likely effect the clinical course of the disease.[56] Chest radiographs show mediastinal widening and pleural effusions.[57, 58] *B. anthracis* bacilli, bacillary fragments and anthrax antigens can be identified by immunohistochemistry (IHC).[57, 58] Almost 50% of patients with inhalational anthrax develop hemorrhagic meningitis as a result of the hematogenous spread of *B. anthracis*. According to the Defense Intelligence Agency, the Lethal Dose to kill 50% of persons exposed (LD_{50}) to weapons-grade anthrax is 2500 - 55,000 spores but, as few as one to three spores may be sufficient to cause infection.[45,52]

A high index of suspicion is necessary to make the diagnosis of anthrax when patients present with a severe flu-like illness. One hundred percent of the patients with inhalational anthrax in 2001 had an abnormal chest radiograph with mediastinal widening, pleural effusions, consolidation and infiltrates. In this setting, the presence of mediastinal widening should be considered diagnostic of anthrax until proven otherwise.[57, 58] Hemorrhagic necrotizing lymphadenitis and mediastinitis are pathologic findings.[44, 45]

Laboratory Diagnosis

B. anthracis is easily cultured from blood and other body fluids with standard microbiology techniques. The laboratory should be notified when the diagnosis of anthrax is being considered, as many hospital laboratories will not further characterize *Bacillus* species unless requested. Bio-safety level two conditions apply for workers handling specimens because most clinical specimens have spores in the vegetative state that are not easily transmitted.[52] The presence of large gram-positive rods in short chains that is positive on India ink staining is considered presumptive of *B. anthracis*, until culture results and other confirmatory tests are obtained. Nasal swabs are not recommended due to false negatives in patients with fatal inhalational anthrax. In June 2004, the FDA approved the Anthrax Quick Enzyme-linked Immunosorbent Assay (ELISA) test that detects antibodies to the PA (protective antigen) of *B. anthracis* exotoxin. The test can be completed in less than one hour and is available at hospital and commercial laboratories.[59]

Treatment

Treatment improves survival if instituted promptly.[52] Ciprofloxacin® (400 mg) or doxycycline (100 mg) given intravenously, every 12 hours, with one to two other antibiotics is currently recommended.[52] Additional effective antibiotics include rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, and clarithromycin. Two survivors of inhalation anthrax during the United States outbreak received parenteral ciprofloxacin, clindamycin and rifampin. The addition of clindamycin may attenuate toxin production.[52] Ciprofloxacin® and Rifampin®, due to their excellent central nervous system penetration, should be used when meningitis is suspected. Although ciprofloxacin and doxycycline are relatively contraindicated for pregnant women and children, one of these agents should be given for the treatment of inhalational anthrax because of its high mortality rate. Therapy should continue for 60 days. Patients can be switched to oral therapy with

ciprofloxacin (500mg twice daily) or doxycycline (100 mg twice daily) after fulminant symptoms have resolved. The use of systemic corticosteroids has been suggested for meningitis, severe edema, and airway compromise.

Infection control

All those exposed to anthrax should receive prophylaxis with oral ciprofloxacin (500mg twice daily), levofloxacin (500mg daily) or doxycycline (100mg twice daily) for 60 days, regardless of laboratory test results.[52] Nasal swabs can confirm exposure to anthrax, but cannot exclude it. High-dose penicillin or ampicillin may be an acceptable alternative for 60 days in patients who are allergic or intolerant to the recommended antibiotics.[52] More than 5,000 people received post-exposure prophylaxis following the 2001 United States outbreak, but only about half completed the 60-day course.[52] The main reasons for discontinuing therapy were gastrointestinal or neurologic side effects (75%) or a low-perceived risk (25%). The anthrax vaccine is not available to the general public.

Tularemia

Tularemia is a zoonosis found in a wide range of small mammals and is caused by *Francisella tularensis*, an intracellular, non-spore forming, aerobic gram-negative coccobacillus. It can survive in moist soil, water, and animal carcasses for many weeks. Transmission of *F. tularensis* to humans occurs predominantly through tick and flea bites, handling of infected animals, ingestion of contaminated food and water, and inhalation of the aerosolized organism. There is no human-to-human transmission of *F. tularensis*. In the United States, most cases are reported in spring and summer. As a biologic weapon, the organism would most likely be dispersed as an aerosol and cause mass casualties from an acute febrile illness that may progress to severe pneumonia.[60, 61] Hunters and trappers exposed to animal reservoirs are at high risk for exposure.[62] The WHO estimated that 50 kg of aerosolized *F. tularensis* dispersed over a metropolitan area of five million people could cause 19,000 deaths and 250,000 incapacitating illnesses.[60, 61]

Pathogenesis and Clinical Presentation

The clinical manifestations of tularemia depend on the site of entry, exposure dose, virulence of the organism, and host immune factors. Tularemia can have various clinical presentations that have been classified as primary pneumonic, typhoidal, ulceroglandular, oculoglandular, oropharyngeal, and septic. The *ulceroglandular form* is the most common naturally occurring form of tularemia. After an incubation period of three to six days (range 1 to 25 days) following a vector bite or animal contact, patients present with symptoms of high fevers (85%), chills(52%), headache (45%), cough (38%) and myalgias (31%). They may also have malaise, chest pain, abdominal pain, nausea, vomiting, and diarrhea. Pulse-temperature dissociation is often seen. At the site of inoculation, a tender papule develops that later becomes a pustule and ulcerates. Lymph nodes draining the inoculation site become enlarged and painful (85%). Infected lymph nodes may become suppurative, ulcerate and remain enlarged for a long period of time. Exudative pharyngitis and tonsillitis may develop following ingestion of contaminated food or inhalation of the aerosolized organism. Pharyngeal ulceration and regional lymphadenopathy

may be present. A systemic disease caused by *F. tularensis* without lymph node enlargement and presenting with fever, diarrhea, dehydration, hypotension, and meningismus is referred to as the *typhoidal form*.

The *pneumonic form* of tularemia may occur as a primary pleuropneumonia following the inhalation of aerosolized organisms or as a result of hematogenous spread from other sites of infection or following pharyngeal tularemia.[63] After an inhalational exposure, constitutional symptoms, such as fever and chills, typically precede the onset of respiratory symptoms. The respiratory symptoms include a dry or minimally-productive cough, pleuritic chest pain, shortness of breath and hemoptysis. Pleural effusions, either unilateral or bilateral, can occur. Pneumonic tularemia can rapidly progress to respiratory failure with acute respiratory distress syndrome (ARDS), multi-organ failure, disseminated intravascular coagulation, rhabdomyolysis, renal failure, and hepatitis.[63,64] Rarely, peritonitis, pericarditis, appendicitis, osteomyelitis, erythema nodosum, and meningitis may occur. The mortality rate for untreated tularemic pneumonia is 60%, but with proper antibiotic therapy is decreased to less than three percent.[61] Chest radiographic findings in 50 patients with tularemia[65] showed the following abnormalities: patchy airspace opacities (74%- unilateral in 54%); hilar adenopathy (32%- unilateral in 22%); pleural effusion (30%-unilateral in 20%); unilateral lobar or segmental opacities (18%); cavitation (16%); oval opacities (8%); and cardiomegaly with a pulmonary edema pattern (6%). Rare findings such as apical infiltrates, empyema with bronchopleural fistula, miliary pattern, residual cyst, and residual calcification occurring in less than five percent of patients were also reported.[65]

Laboratory Diagnosis

F. tularensis is difficult to culture. Culture media must contain cysteine or sulphydryl compounds for *F. tularensis* to grow. Notification of laboratory personnel that tularemia is suspected is essential. Routine diagnostic procedures can be performed in Biosafety Level Two conditions. Manipulation of cultures and other procedures that might produce aerosols or droplets should be conducted under Biosafety Level Three conditions.[61,62] Examination of secretions and biopsy specimens with direct fluorescent antibody or immunochemical stains may help to identify the organism. The diagnosis is often made through serologic testing using enzyme-linked immunosorbent assay (ELISA). Serological titers may not be elevated early in the course of disease. A four-fold rise is typically seen during the course of illness. A single tularemia antibody titer of 1:160 or greater is supportive of the diagnosis.[61, 64] The combined use of ELISA and confirmatory Western blot analysis was found to be the most suitable approach to the serological diagnosis of tularemia.[66] Other diagnostic methods include antigen detection assays and polymerase chain reaction (PCR).[66]

Treatment

Treatment for tularemia is streptomycin, one gram given intramuscularly (IM) twice daily. Gentamicin®, 5 mg/kg, given IM or intravenously (IV) once daily, can be used instead of streptomycin.[60,61,62,67] For children, the preferred antibiotics are streptomycin, 15 mg/kg, given IM twice daily (not to exceed 2 g/day) or gentamicin, 2.5 mg/kg, given IM or IV three times daily. Alternate choices are doxycycline, chloramphenicol, or ciprofloxacin. Gentamcin® is preferred over

streptomycin for treatment during pregnancy. Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days. Treatment with doxycycline or chloramphenicol should be continued for 14 to 21 days. In a mass casualty setting caused by tularemia, the preferred antibiotics for adults and pregnant women are doxycycline, 100 mg, taken orally twice daily, or ciprofloxacin 500 mg, taken orally twice daily. For children, the preferred choices are doxycycline, 100 mg, taken orally twice daily if the child weighs 45 kg or more, doxycycline, 2.2 mg/kg, taken orally twice daily if the child weighs less than 45 kg, or ciprofloxacin, 15 mg/kg, taken orally twice daily and not to exceed one gram/day. In immunosuppressed patients, either streptomycin or Gentamicin® is the preferred antibiotic in mass casualty situations.[61]

Infection Control

Individuals exposed to *F. tularensis* may be protected against systemic infection if they receive prophylactic antibiotics during the incubation period. For postexposure prophylaxis, either doxycycline, 100 mg, taken orally twice daily, or ciprofloxacin, 500 mg, taken orally twice daily for 14 days, is recommended. Both doxycycline and ciprofloxacin can be taken by pregnant women for postexposure prophylaxis, but ciprofloxacin is preferred. Postexposure prophylaxis for children is the same as treatment during mass casualty situations.[61] The current vaccine does not offer total protection against inhalational exposure and is not recommended for post-exposure prophylaxis.[60,61,62]

Plague

Plague is a zoonotic infection, primarily seen in rodents and rabbits.[68] Plague is caused by *Yersinia pestis*, a gram negative, non-motile coccobacillus of the family Enterobacteriaceae. Plague is naturally transmitted by the bite of a plague-infected flea. Rodents, particularly rats and squirrels, are the natural reservoirs that transmit *Y. pestis* to fleas. Transmission to humans also occurs by direct contact with infected live or dead animals, inhalation of respiratory droplets from patients with pneumonic plague, or from direct contact with infected body fluids or tissue.[69,70,71] Over 90% of plague cases reported in the United States come from Arizona, New Mexico, California and Colorado. The majority of cases occur in spring and summer, when people come in contact with rodents and fleas. Aerosolized droplets of *Y. pestis* could be used as a biowarfare agent, resulting in the highly fatal pneumonic form of plague.[69] Pneumonic plague is contagious from person to person and can result in a greater number of casualties than those initially exposed and infected. The WHO estimates that 50 kg of *Y. pestis* aerosolized over a population of five million people may result in 150,000 infections and 36,000 deaths. Intentional dispersion of *Y. pestis* as an aerosol will lead to pneumonic plague, while the release of infected fleas will usually result in bubonic or septicemic plague.[69]

Pathogenesis and Clinical Presentation

The lipopolysaccharide endotoxin is responsible for the systemic inflammatory response, acute respiratory distress syndrome, and multiorgan failure.[69-71] The incubation period and clinical manifestations of plague vary according to mode of transmission. Of the plague cases seen in the United States, 85% are bubonic plague, 10 - 15% are primary septicemic plague and less than

one percent are primary pneumonic plague. Bubonic plague may progress to septicemic or pneumonic plague in 23% and 9% of cases respectively.[68,69,70,71] Inhalation of infected droplets of *Y. pestis* results in primary pneumonic plague. The primary pneumonic form is rapid in onset with an incubation period of one to six days (mean: two to four days). Presenting features are fevers, chills, cough, and blood-tinged sputum. Following inhalation into the lungs, *Y. pestis* organisms are engulfed by macrophages, transported to the lymphatic system and regional lymph nodes, followed by bacteremia that may seed other organs such as the lung, spleen, liver, skin, and mucous membranes. Secondary pneumonic plague can occur as sequelae of bubonic or primary septicemic plague. Primary septicemic plague occurs when there is direct entry of *Y. pestis* bacilli into the bloodstream. Other rare forms of plague are plague meningitis and plague pharyngitis.[70]

Bubonic plague involves lymphadenitis, buboes and severe pain (Figure 3-4.1). Based on site of inoculation, palpable, regional buboes appear in the groin, axillae or cervical regions, with erythema of the overlying skin. A minority of patients exposed to *Y. pestis* develop septicemic plague, either as a primary form (without buboes) or secondary to the hematogenous spread of bubonic plague.

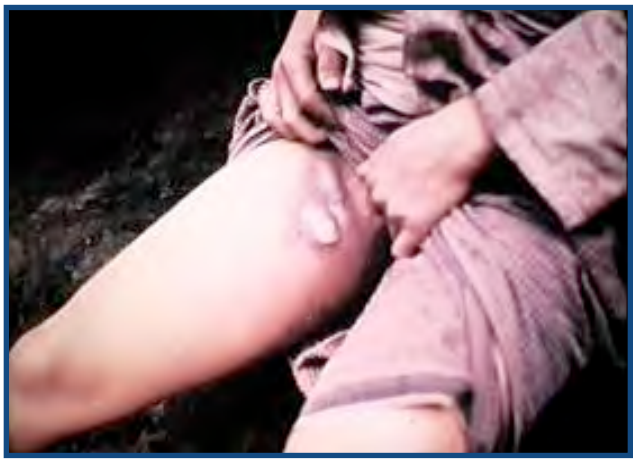

Figure 3-4.1: Bubonic plague with the characteristic bubo. From CDC website: http://www.cdc.gov/ncidod/dvbid/plague/diagnosis

The clinical features are similar to those of gram-negative sepsis, with fever, chills, nausea, vomiting, hypotension, renal failure and ARDS. Untreated, the mortality rate of septicemic plague is 100%.[68-71] Primary pneumonic plague is characterized by a severe, rapidly progressive pneumonia with septicemic features that is rapidly fatal if not treated within 24 hours. Following an incubation period of one to six days, there is a rapid onset of fever, dyspnea, chest pain, and cough that may be productive of bloody, watery, or purulent sputum. Tachycardia, cyanosis, nausea, vomiting, diarrhea, and abdominal pain may occur. Buboes are generally absent, but may develop in the cervical area. Acute respiratory failure requiring mechanical ventilation may occur. Strict respiratory isolation should be observed, as pneumonic plague is highly contagious.[68] Chest radiographs show bilateral alveolar opacities (89%) and pleural effusions (55%). Cavitations may occur.[72,73] Alveolar opacities in secondary pneumonic plague may have a nodular appearance. Mediastinal adenopathy is very rare in primary pneumonic plague. This can help to distinguish primary

pneumonic plague from anthrax if bioterrorism is suspected and a causative agent has not yet been identified[72, 73]. Without prompt treatment, the mortality rate of primary pneumonic plague is 100%.[70, 71] Secondary pneumonic plague, from hematogenous spread, occurs in approximately 12% of individuals with bubonic plague or primary septicemic plague. It typically presents as a severe bronchopneumonia (Figure 3-4.2). Common symptoms include cough, dyspnea, chest pain and hemoptysis. Chest radiographs typically show bilateral, patchy alveolar infiltrates that may progress to consolidation. In contrast to primary pneumonic plague, mediastinal, cervical and hilar adenopathy may occur.[72, 73]

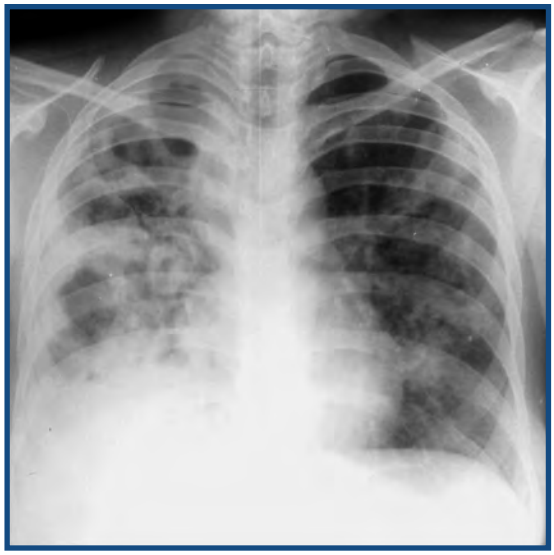

Figure 3-4.2: A 38-year old male from Himachal Pradesh admitted with complaints of fever, cough, hemoptysis and dyspnea. There is endemicity of pneumonic plague where the patient came from due to the prevalent custom of hunting wild rats and rodents. Sputum examination showed Yersinia pestis. Patient was successfully treated with antibiotics. (Chest radiograph is courtesy of Dr Sanjay Jain, Additional Professor, Dept of Internal Medicine and Dr. Surinder K. Jindal, Professor of Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India)

Laboratory Diagnosis

The presence of gram-negative rods in bloody sputum of an immunocompetent host should suggest pneumonic plague. Cultures may be positive for *Y. pestis* within 24 to 48 hours.[69] Misidentification of *Y. pestis* may occur with automated bacterial identification devices. Direct fluorescent antibody staining for *Y. pestis* and dipstick antigen detection tests are highly specific.[69]

Treatment

Recommendations of the Working Group on Civilian Biodefense for treatment of adult patients with plague in a small, contained casualty setting is streptomycin one gram IM, given twice daily; gentamicin, five mg/kg IM or IV, once daily; or a 2 mg/kg loading dose of gentamicin followed by 1.7 mg/kg IM or IV three times daily.[68-71] For children, the preferred antibiotics are streptomycin, 15 mg/kg IM, given twice daily (maximum dose of two grams/day), or Gentamicin®, 2.5 mg/kg IM or IV, given three times daily. Alternate choices include doxycycline, ciprofloxacin or chloramphenicol. The duration of treatment is 10 days. In pregnant or breast-feeding mothers, the treatment of choice is Gentamicin®. For breast-feeding mothers and infants, treatment with

gentamicin is recommended. In a mass casualty situation from the intentional release of plague, the Working Group on Civilian Biodefense recommends the use of doxycycline, 100 mg, taken orally twice daily, or ciprofloxacin, 500 mg, taken orally twice daily for adults and pregnant women, both for treatment and post-exposure prophylaxis. For children, the preferred choices are the adult dose of doxycycline if the child is over 45 kg weight and 2.2 mg/kg orally twice daily for child under 45 kg weight. Children may also be given ciprofloxacin, 20mg/kg, taken orally twice daily. For breast-feeding mothers and infants, treatment with doxycycline is recommended. The duration of treatment is 10 days.

Infection Control

All individuals who come within two meters of a pneumonic plague patient should receive postexposure prophylaxis.[74] The vaccination against pneumonic plague does not provide adequate protection and therefore is not recommended biowarfare setting.[74] Patients suspected of plague should be isolated and antibiotic therapy should be instituted promptly.[75] Universal exposure precautions, respiratory isolation using droplet precautions and special handling of blood and discharge from buboes must be followed. In cases of pneumonic plague, strictly enforced respiratory isolation in addition to the use of masks, gloves, gowns and eye protection must be continued for the first few days of antibiotic therapy. Following two to four days of therapy with appropriate antibiotics, patients may be removed from isolation.[75] Laboratory workers must be warned of potential plague infection.

Botulinum

Botulinum is an extremely-potent toxin produced by *Clostridium botulinum,* an anaerobic, spore-forming bacterium that is present in the soil. Botulinum toxin has been designated as a Category A bioterrorism threat by the CDC.[1] It has been estimated that one gram of botulinum toxin added to milk that is commercially-distributed and consumed by 568,000 individuals can result in 100,000 cases of botulism. One gram of botulinum toxin has the capacity to kill over one million persons if aerosolized.[76] Botulinum is not a respiratory infection; if aerosolized the route of transmission would be through lungs, but the effects would still be neurologic.

Pathogenesis and Clinical Manifestations

There are three forms of naturally-occurring botulism: *foodborne botulism, wound botulism,* and *intestinal (infant and adult) botulism*.[76,77] All forms of botulism can produce a serious paralytic illness leading to respiratory failure and death.

Treatment

Treatment of botulism includes supportive care, mechanical support for inadequate ventilation and the administration of botulinum antitoxin.[76, 77] Prompt administration of botulinum antitoxin can reduce nerve damage and disease severity. However, any muscle paralysis existing prior to antitoxin

administration will not be reversed. The goal of antitoxin therapy is to prevent further paralysis by neutralizing unbound botulinum toxin in the circulation. If the type of botulinum toxin is known, a type-specific antitoxin can be given. If the toxin type is not known, the trivalent antitoxin containing neutralizing antibodies against botulinum toxin types A, B and E should be given. Botulinum antitoxin is available from the CDC through state and local health departments. If another type of toxin is intentionally dispersed during a bioterrorism attack, consideration may be given for the use of an investigational heptavalent antitoxin (A B C D E F G), maintained by the United States Department of Defense. Patients should be carefully assessed for refractory problems, such as rapidly-progressing paralysis, severe airway obstruction or overwhelming respiratory tract secretions.

Infection Control

Person-to-person transmission does not occur. In the United States, a pentavalent botulinum toxoid is available from the CDC for the immunization of laboratory workers who may be exposed to botulinum toxin and for the protection of military personnel in the event of a biowarfare attack.[78] Mass immunization of the public with botulinum toxoid is not recommended or available. It takes several months to attain acquired immunity following the administration of botulinum toxoid and, therefore, it is not effective for post-exposure prophylaxis.

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Chapter 3-5
World Trade Center Respiratory Diseases

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INTRODUCTION

After the attack on and the collapse of the World Trade Center (WTC) towers, fire fighters, other rescue/recovery workers, volunteers and community members were exposed to high concentrations of aerosolized particulate matter and to incomplete products of combustion that were produced during the fires that continued from the first day on September 11, 2001 (9/11) to the middle of December 2001. Fire fighters from the Fire Department City of New York (FDNY) operated continuously during the days, weeks and months that followed, suffering some of the greatest exposures. Because environmental monitoring was not available immediately, we may never know the full extent of the chemical gaseous exposure but the dust has been well-characterized and shown to be highly-alkaline and inflammatory in nature. Approximately 70% of the buildings' structural components were pulverized[1] and the collapse produced a plume of dust and ash that spread throughout lower Manhattan and beyond. Hydrocarbons, PCBs (polychlorinated biphenyls), dioxins, volatile organic compounds, asbestos, silicates, heavy metals and other potentially-carcinogenic compounds were found in WTC dust.[1,2] Environmental controls and effective respiratory protection (e.g., fit-tested P-100 respirators) are often unavailable during the initial rescue effort and adherence with proper use guidelines is typically difficult to achieve during prolonged rescue/recovery efforts and the WTC response was no exception.[3]

The subject of this chapter is to review what we currently know about the respiratory health consequences of WTC dust exposure. Much of this work has been previously published in various forums.[4,5,6,7] Because there has been little scientific study on the respiratory consequences of acute and/or sub-acute exposures to respirable particulates and chemical vapors/gases/fumes after other disasters, much of what we learn about the WTC is groundbreaking science. Important for all fire fighters and first responders, this knowledge will help not only those who were exposed to WTC dust but, should also be transferable to help those who may be exposed at future disasters.

What we do know from prior disasters is that after smoke inhalation, asthma (bronchial hyperreactivity or reversible airways obstruction that increases with irritant exposures and reverses with bronchodilators) and bronchitis (productive cough) may occur within hours[8,9,10] and one study showed persistent airway hyperreactivity in 11 of 13 subjects at three-months post-exposure.[10] Following

the Mt. St. Helens eruption in 1980, hospital visits for pediatric asthma were increased in Seattle Washington, presumably related to exposures to aerosolized volcanic dust.[11] During building collapses, aerosolized exposure to construction materials (ex. gypsum-containing wallboard, cement, glass, and man-made vitreous fibers, heavy metals) have been implicated in inflammatory syndromes involving the respiratory mucosa and lung parenchyma.[12,13] Acute exposures to chemical gases, vapors and fumes may result in airway hyperreactivity and when this occurs in non-smokers without a prior history of asthma or allergies, it is often referred to as the reactive airways disorders syndrome (RADS), a variant of irritant-induced asthma.[14] After the Union Carbide Chemical Plant explosion in Bhopal, India, studies documented an increased loss of pulmonary function and an increase in the prevalence of obstructive airways diseases such as asthma and chronic bronchitis.[15,16,17] Although the most common respiratory disease pattern after disaster-related exposures to dusts, gases, vapors and fumes is obstructive airways diseases, lung inflammation and fibrosis can occur. For example, pneumonitis (a life-threatening disease that results in fibrosis thereby blocking oxygen absorption) has been reported in US military personnel deployed in or near Iraq after exposure to fine airborne sand/dust[18] and has been reported in chronic occupational exposures to coal, silica, asbestos, heavy metals and other dusts.[19,20,21,22,23,24]

After the WTC, there is abundant evidence that the upper and lower respiratory symptoms were the result of aerosolized WTC dust, coated with numerous chemicals, that was inhaled and ingested. A clear exposure-response gradient, with the highest symptom prevalence found in those directly exposed to the dust cloud, arriving during the morning of 9/11 was first demonstrated in FDNY fire fighters[25] and confirmed in other exposed groups.[26] Ninety-five percent of the respirable WTC dust was composed of large particulate (≥10 microns in diameter) matter.[1] Particles of this size have conventionally been thought to be filtered by the upper respiratory tract, rarely entering the lower respiratory structures.[27] However, there are a number of reasons to expect lower airways also to be at risk from the dust cloud. First, it has been shown that alkaline dust impairs nasal clearance mechanisms,[27] and most WTC dust samples had a pH greater than 10[1]. Second, the nasal filtration system is optimally functional during restful breathing. WTC rescue/recovery workers, as a consequence of their work activities (moderate to high level physical exertion), were breathing at high minute ventilations where mouth breathing predominates. Third, although only five percent of the WTC dust was smaller than 10 microns in diameter, the extraordinary volume of dust in the air meant that the respirable fraction (particles less than 10 microns) still represented a significant amount of the dust. Similarly, although only a small percentage of particles larger than 10 microns tend to impact in lower airways, the huge magnitude of the WTC dust cloud meant that a small percentage of the larger particles that penetrated deep into the lung may have added up to a significant amount. In fact, in a study of 39 FDNY fire fighters 10 months after exposure,[28] it was demonstrated the WTC dust did make it down into the lower airways, as particulate matter (>10 microns) consistent with WTC dust, with associated increases in inflammatory cells and cytokines in induced sputum. Finally, compared to dust, inhalation of vapors, fumes, and gases during the first days at Ground Zero had equal if not greater potential for inducing airway or lung injuries.

Respiratory health consequences after aerosolized exposures to high-concentrations of particulates and chemicals during any disaster are thought to occur from chronic inflammation and can be grouped into four major categories:

1. *Upper respiratory disease* including chronic rhinosinusitis sometimes referred to in this setting as reactive upper airways dysfunction syndrome (RUDS).
2. *Lower respiratory disease* including asthma sometimes referred to in this setting as reactive (lower) airways dysfunction syndrome (RADS), bronchitis and chronic obstructive airways diseases.
3. *Parenchymal or interstitial lung diseases* including pneumonitis, sarcoidosis, pulmonary fibrosis, bronchiolitis obliterans (fixed airways obstruction) and incidental pulmonary nodules.
4. *Cancers of the lung and pleura*. Cancers are late emerging diseases, but the first three categories (upper, lower and parenchymal respiratory diseases) have already been well documented in WTC exposed rescue/recovery workers, presenting early on as the "WTC Cough Syndrome."

The WTC Cough Syndrome was first reported by the FDNY Bureau of Health Services after 9/11, in a 2002 article published in the New England Journal of Medicine[25] and is a chronic cough syndrome, thought to be a consequence of persistent bronchitis (usually asthmatic), rhinosinusitis, gastroesophageal disorder (GERD), or any combination of the three after exposure to WTC dust. During the first six months following the WTC attack, FDNY described a syndrome of clinical, physiologic and radiographic abnormalities associated with airway inflammation in an initial cohort of 332 FDNY rescue workers. Because so many were affected, the case definition specified a persistent cough severe enough to require at least four weeks of continuous leave (medical, light duty or retirement) with onset during the six months following the WTC collapse, but future studies have not had medical leave as a requirement.

In 2007, FDNY reported that between 9/11 and 6/30/07, 1,847 (~13%) FDNY members had met this strict case definition and 728 have qualified for permanent respiratory disability benefits based on persistent abnormal pulmonary function tests including, when indicated, methacholine challenge testing. [29] By 2009, over 1,000 have qualified for permanent respiratory disability benefits. Clinical symptoms were consistent with aero-digestive mucosal inflammation, with a high rate of GERD complaints (87%).[25] Physiologic evidence of asthmatic airway inflammation in those with the syndrome included response to bronchodilators (63% of those diagnosed) and nonspecific bronchial hyperreactivity determined by methacholine challenge testing (24% of those diagnosed), indicating that these FDNY members had a high rate of asthmatic physiology.[25] Radiological confirmation of airway inflammation in these fire fighters included CT scan evidence of air-trapping (abnormal retention of air in the lungs after expiration in 51%, and bronchial wall thickening in 24%).[25] Both air-trapping and bronchial wall thickening are typically due to airways obstructions such as asthma, chronic bronchitis or emphysema. The incidence of WTC Cough Syndrome increased as WTC dust exposure intensity (estimated by initial arrival time at the WTC site) increased. Nearly all FDNY fire fighters and EMTs who developed WTC cough syndrome had been exposed during the first 48 hours post-collapse and most had been exposed during the morning of 9/11.[25,30]

UPPER RESPIRATORY DISEASE

Reactive Upper Airways Dysfunction Syndrome (RUDS) & Chronic Rhinosinusitis

RUDS is defined as chronic rhinosinusitis (nasal and/or sinus inflammation) initiated by high level exposure to inhaled irritants, with recurrence of symptoms after re-exposure to irritants. Diagnosis depends largely on symptoms (nasal congestion, drip, sinus tenderness, sore throat and/or headaches), and there is no simple way to quantify the severity of the condition. Upper airways symptoms have been described in various occupational groups involved in rescue, recovery and cleanup at the WTC site, with higher prevalence of symptoms in those workers that were more highly exposed. In 10,378 previously-healthy FDNY rescue workers, stratified for severity of exposure by arrival time at the WTC site, self-reported chronic sinus congestion and/or drip was reported by less than five percent pre-WTC and was present in 80% on day one (9/11), 48% during the first year post-collapse and remained at 45% during the next two to four years[29,30] (Figure 3-5.1). In this same group, sore or hoarse throat was reported in 63% during the first year post-collapse and 36% during the next two to four years[29,30] (Figure 3-5.1). As with the WTC Cough Syndrome, an exposure intensity gradient was evident. In the NY/NJ Consortium of non-FDNY rescue workers/volunteers, 66% of those directly exposed to the dust cloud reported upper respiratory symptoms such as congestion, runny nose, headache, sinus pain, sore throat, ear pain or blockage, hoarse voice, etc.[31] They found that rescue workers arriving in the afternoon of 9/11 were similarly affected with 62% reported experiencing upper respiratory symptoms.[31] In 96 ironworkers, who were on the pile from the afternoon of 9/11, usually on long shifts, without respiratory protection, 52% had persistent sinus complaints, with corresponding physical signs such as nasal mucosinusitis and swollen turbinates in at least 30% of the cohort.[35] In 240 New York City Police Department's Emergency Services Unit (ESU)officers, between one to five months after the collapse, 41% had persistent nasal and/or throat symptoms.[34] The main diagnoses associated with these symptoms are chronic rhinosinusitis but as discussed later on there is considerable overlap with asthmatic and gastroesophageal reflux (GERD) symptoms. Furthermore, the literature pre- and post-WTC shows that without successful sinus treatment, it is difficult to successfully treat those patients who also have asthma.[42,43,44]

LOWER RESPIRATORY DISEASE

During the first five years post-9/11, high rates of respiratory irritant symptoms have been described in at least seven WTC rescue/recovery worker groups:

1. In 10,378 previously-healthy, exposure-stratified FDNY rescue workers, self-reported daily cough was present in 99% on day one (9/11), 54% during the first year post-collapse and 16% during the next two to four years[29,30] (Figure 3-5.1).
2. In the NY/NJ WTC consortium that follows the non-FDNY cohort of WTC rescue workers and volunteers (police, sanitation, transportation, construction, and others), 69% of the first 9,442 responders reported new or worsened upper (62.5% of 9,442) or lower (46.5% of 9,442) respiratory

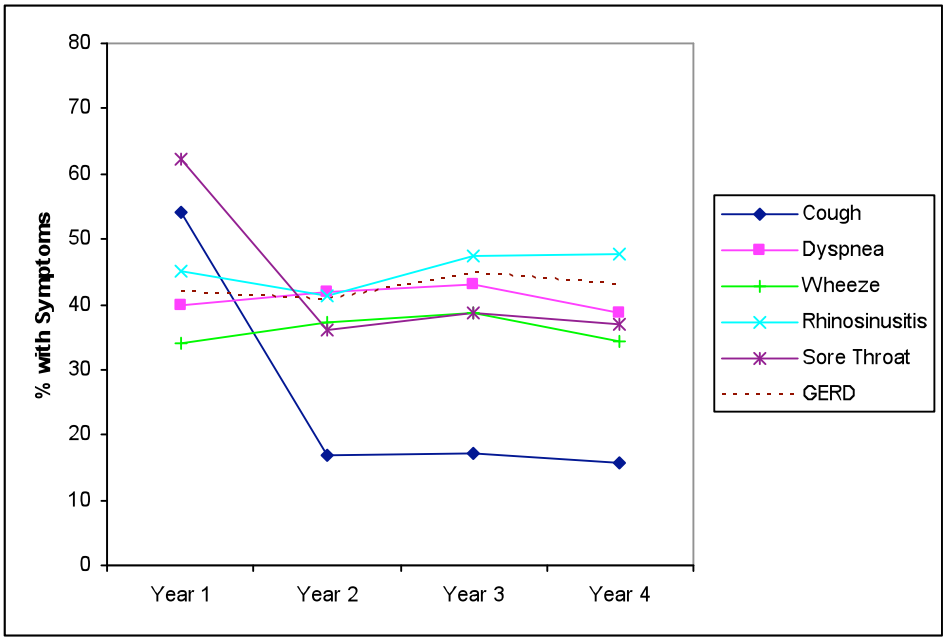

Figure 3-5.1: Trends in Symptoms in 10,378 Fire Fighters from 2001 through 2005.

symptoms during their WTC-related efforts, with symptoms persisting to the time of examination in 59% (on average eight months after they stopped their rescue/recovery/clean-up activities)[31]; and in another study, they found that in the previously asymptomatic group, 44% developed lower respiratory symptoms during their work at the WTC site. Analysis again demonstrated that the incidence of lower respiratory symptoms was directly related to arrival time.[32]

3. 77% of 240 previously-healthy ESU police officers had upper and/or lower respiratory symptoms during the first five months post-collapse.[33]
4. In 471 NYC police officers (426 with no pre-9/11 chronic respiratory disease), 44% reported having a cough at both one and 19 months post-collapse but over this same time interval reported increasing prevalence of shortness of breath (18.9% to 43.6%) and wheeze (13.1% to 25.9%).[34]
5. 77% of 96 ironworkers had upper and/or lower respiratory symptoms six months post-collapse.[35]
6. In a study of 269 transit workers, those caught in the dust cloud had significantly higher risk of persistent lower respiratory and mucous membrane symptoms.[36]
7. In 183 clean-up workers, the prevalence of upper and lower respiratory symptoms increased as the cumulative number of days spent at WTC increased.[37]

Respiratory consequences have also been noted in WTC studies on community residents, children and office workers in lower Manhattan.[38,39,40] The WTC Health Registry study confirmed that out of 8,418 adults who were caught in the collapse on 9/11, 57% experienced new or worsening respiratory symptoms after the attacks.[41]

Pulmonary function declines or abnormalities were significantly related to WTC exposure intensity (based on arrival time) in FDNY and non-FDNY workers and this remained true even after accounting for pre-existent disease and/or cigarette smoking.[25, 31,45,46,47,48,49] For 12,079 FDNY rescue workers in the first year post-WTC, a significantly greater average annual decline in forced expiratory volume in one-second (FEV_1, a measure of airflow speed that decreases with increased resistance or obstruction) of 372 ml was noted in the first year post-9/11 when compared to the normal annual decline of 31 ml found in the five years of pre-WTC testing – a substantial accelerated decline in pulmonary function.[49] Similar findings were found for the forced vital capacity (FVC, a measure of lung capacity), leading to a normal FEV_1/FVC ratio. Preservation of the FEV_1/FVC ratio is unusual in airways obstruction but, can be found when air-trapping is present. In the NY/NJ consortium report on 8,384 non-FDNY workers/volunteers, 28% had abnormal pulmonary function test results[31] during exam one performed between July 2002 and April 2004. They also found that a low FVC was five times more likely among the non-smoking portion of their cohort than expected in the general U.S. population (which includes smokers and non-smokers).[31] Overall, WTC dust exposure intensity was related to lower FVC and a higher rate of pulmonary function test abnormalities[31], demonstrating that WTC exposure had a substantial impact on lung function.

In a follow up FDNY study[50], pulmonary function (FEV_1) in 12,781 FDNY rescue workers was followed for seven years post-WTC (Figure 3-5.2). The average follow up was over six years for fire fighters and EMS workers and included those who had retired. Over the first post-9/11 year, FEV_1 decreased substantially, more for nonsmoking fire fighters (439 ml) than for nonsmoking EMS (267 ml). Over the next six years, these declines in FEV_1 were persistent and without meaningful recovery in lung function. By the end of the study (9/10/2008), the proportion of nonsmokers left with abnormal lung function was 13% for fire fighters and 22% for EMS. Smoking, although a significant factor in predicting post-WTC lung function decline, was dwarfed by the impact of WTC dust exposure.

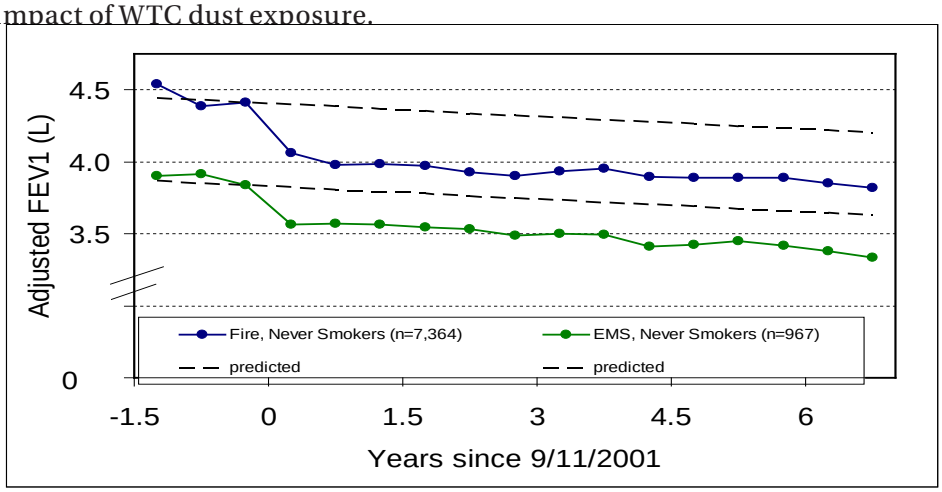

Figure 3-5.2: Lung function (FEV-1) decline in non-smoking FDNY fire fighters and EMS rescue workers pre- and 7 years post-WTC exposure. A substantial decline in lung function was noted within 12 months after 9/11 and then this decline persisted without meaningful recovery over the next six years.

In a follow up study, from the NY/NJ consortium, 3,160 non-FDNY workers/volunteers who returned for a second pulmonary function test at exam two (performed anytime between September 2004 and December 2007, with a minimum of 18 months between exam one and two) were compared to their original pulmonary function test at exam one (between July 2002 and April 2004). More than one-third had abnormal spirometry at exam two. The most common abnormality was a low FVC – with 16% having a lower than normal predicted FVC at exam two as compared to 20% at exam one.[51] Most importantly, the average decline in lung function (FVC or FEV_1) between these two exams was not greater than expected after adjusting for normal aging and for the majority of workers, further accelerated declines in lung function were not occurring during this time period. However, for those who did have greater than expected declines, bronchodilator responsiveness (asthma) and weight gain were significant predictors.[51]

Reactive (Lower) Airways Dysfunction Syndrome (RADS) and Asthma

Occupational RADS is defined as persistent respiratory symptoms and nonspecific airway hyperreactivity in patients with a history of acute exposure to an inhaled agent (gas or aerosol) and no prior history of allergies, smoking or asthma.[52] Strictly speaking, RADS can only be diagnosed by demonstrating abnormally brisk or intense lower airways obstruction (measured by spirometry) in response to standard provocations (ex. methacholine, histamine, mannitol, cold air, exercise challenge). However, for practical purposes, RADS can be assumed to be present when there are new episodic respiratory symptoms (chest tightness and cough) with spirometric evidence of lower airways obstruction, especially when the obstruction can be reversed by administration of bronchodilating drugs. Asthma or RADS may progress to irreversible lower airways obstructive disease due to chronic inflammation and airway remodeling.

Although RADS was initially reserved for acute exposures to chemical gases and fumes[52], it's use has been extended by some to include acute and even chronic exposures to respirable particulates. Others prefer to use the term irritant-induced or occupational asthma for such exposures. WTC studies have allowed us to describe the incidence of bronchial hyperreactivity and RADS (or irritant-induced asthma) after a major disaster and to evaluate its persistence longitudinally in a large cohort.

In a sample of FDNY rescue workers whose bronchial hyperreactivity was measured six months after 9/11, those who arrived at the WTC site on 9/11 were 7.8 times more likely to experience bronchial hyper-reactivity than were those fire fighters who arrived to the site at a later date and/or had lower exposure levels.[45] In this FDNY study, RADS emerged in 20% of highly exposed (present during the morning of collapse) and 8% of moderately-exposed rescue workers (present after the morning of 9/11 but within the first 48 hours).[26,45] Consistent with human observational studies, mice acutely-exposed to high levels of WTC particulate matter developed pulmonary inflammation and airway hyperreactivity.[53] Findings in FDNY rescue workers demonstating RADS with documented continuing bronchial hyperreactivity [47,49] or obstructive airways disease [54] are consistent with non-WTC scientific literature indicating persistance even after exposure had ceased and even with appropriate therapy.[47,48]

Currently, for asthma in general and for WTC-exposed subjects specifically, not enough is understood about the mechanism of disease to know if there are important distinctions (mechanism of occurrence, degree of severity, response to treatment, prognosis, etc.) between RADS, irritant-induced asthma and occupational asthma. Currently, treatment regimens remain identical, regardless of the term used to describe the airways disease. All we know is that these conditions are lower airway inflammatory diseases that present with provocability (reaction to airborne irritants, cold air and exercise) and at least partially reversible airways obstruction. In the first year of the NY/NJ Consortium Program for non-FDNY workers/volunteers, it was found that 45% reported symptoms consistent with lower airway disorders, including asthma and asthma variants.[32] The WTC Registry has published its findings on self-reported "newly diagnosed asthma (post-9/11) by a doctor or other health professional" in WTC rescue and recovery workers.[55] Of the 25,748 WTC workers without a prior history of asthma, newly-diagnosed asthma was reported by 926 workers, for a three-year incidence rate of 3.6%, or 12 times higher than the expected rate of 0.3% in the general adult population.[56] Increased incidence of newly-diagnosed asthma was associated with the following:

- Being caught in the dust cloud on 9/11,
- Earlier arrival time relative to the collapse,
- Work on the pile,
- Cumulative exposure (especially greater than 90 days).

When all of the above factors were adjusted for in a multivariate analysis, occupation and work tasks were not significant predictors of risk.[55] Similarly, increases in airway hyperreactivity or asthma severity have been reported in exposed residents living near the WTC[38,39,40]

Gastroesophageal Reflux Disease (GERD)

In the general population, GERD is increased in middle-aged males and has been described as a causal or exacerbating factor for upper and lower airway diseases such as sinusitis, laryngitis, asthma and chronic cough syndrome.[42,43,44] It is unclear if GERD is a cause, effect or complication of these illnesses but, it is clear that concurrent treatment is important if therapeutic success is to be optimized; and for these reasons some investigators prefer to describe this group of upper and lower respiratory diseases as aerodigestive diseases. Because disaster-related GERD is a new finding after the WTC, we could find no reports after other major disasters. Among FDNY rescue workers, several studies have now described high rates of reflux disease. In 10,378 previously healthy FDNY rescue workers, stratified for severity of exposure by arrival time at the WTC site, self-reported GERD symptoms were reported by five percent pre-WTC, 42% during the first year post-collapse and remained between 40 and 45% during the next two to four years[29,30] (Figure 3-5.1). However, the prevalence of GERD symptoms was far higher (87%) in those FDNY rescue workers requiring treatment for WTC Cough Syndrome.[25]

Reports of GERD have not been limited to FDNY rescue workers, as the NY/NJ consortium of non-FDNY worker/volunteers has also reported that in their first year of operation, 54% of their patients had GERD.[31] The WTC Health Registry reported that out of a cohort of 8,418 adult survivors caught in the collapse, 23.9%

reported heartburn or acid reflux, not dissimilar from the general population.[41] The authors' personal experience shows that many responders have persistent symptoms that have required prolonged or even chronic use of medications to control acid production. Though no clear mechanism for the development of GERD has been described in this setting, ingestion of airborne particulate WTC material or particulates cleared from the airways, along with stress, dietary triggers, alcohol, weight gain and medication use (GERD is increased with antibiotics, theophylline and oral steroids, medications used for WTC-related conditions) are the presumed causes, often acting in combination. Whether GERD is unique to the WTC exposure or represents a previously unrecognized aspect of inhalational injury in general; whether it marks more severe total dust exposure in conjunction with more severe host inflammatory reaction or exacerbation of prior disease; what the mechanism is by which highly alkaline dust can cause GERD; and whether this GI syndrome will persist or resolve, are all unresolved questions. Regardless of the mechanism, consensus treatment guidelines show that without successful GERD treatment there can be only minimally effective treatment for upper/lower respiratory conditions such as sinusitis, laryngitis, asthma and chronic cough.[42,43,44]

PARENCHYMAL LUNG DISEASES

Reports have shown a higher than expected rate of sarcoidosis or sarcoid-like granulomatous lung disease in FDNY WTC rescue workers.[57] Sarcoidosis is a disorder of the immune system in which groups of white blood cells congregate together to cause lymph node enlargement and the formation of small inflammatory nodules called granulomas. Most cases have unknown cause, but environmental causes of sarcoidosis or sarcoid-like granulomatous disease are well established, especially after industrial exposure to beryllium.[58,59,60] Any organ can be affected, but the most common is the lung and its intra-thoracic lymph nodes. In the first five years post-WTC (9/11 to 9/10/06), pathologic evidence consistent with new-onset sarcoidosis was found in 26 FDNY rescue workers (Figure 3-5.3); all with intra-thoracic adenopathy (enlarged lymph nodes) and six (23%) with additional disease outside the chest.[57]

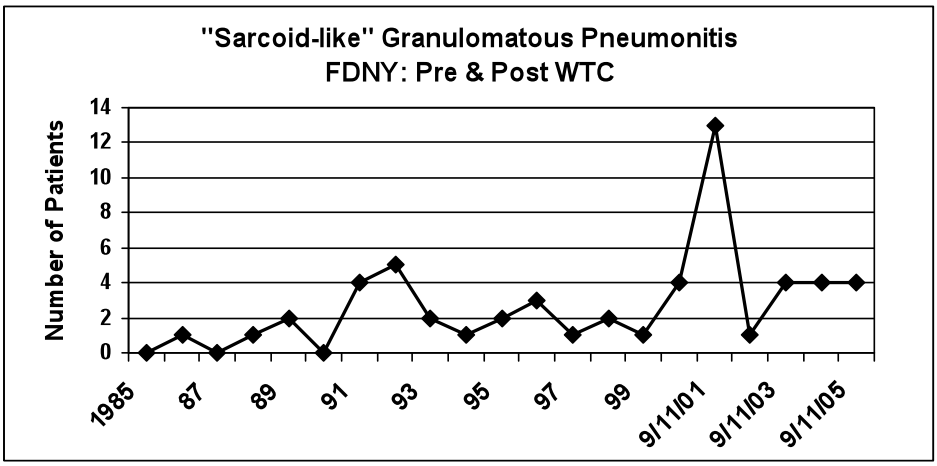

Figure 3.5.3: The number of cases of biopsy-proven WTC Sarcoidosis or Sarcoid-like Granulomatous Pulmonary Disease in the five years since 9/11 as compared to pre-WTC cases of sarcoidosis starting from 1985 in FDNY rescue workers.

Thirteen were identified during the first year post-WTC (yielding an incidence rate of 86/100,000) and 13 during the next four years (yielding an average annual incidence rate of 22/100,000; as compared to 15/100,000 for the FDNY personnel during the 15 years pre-WTC and 5-7/100,000 for a male Caucasian population).[57,61] Early arrival time was not a predictor of disease, and cumulative exposure time was not reported, but the number of patients with disease was too small to reliably demonstrate an effect. This abnormally-high incidence raises the possibility that unknown causative environmental agents were generated or aerosolized during the WTC collapse/combustion.[57] Thus far, studies of WTC patients with sarcoidosis have not identified definitively which environmental agent(s) may be responsible for this disease, and the role of individual immunologic susceptibility to such exposures remains to be studied. Urine beryllium levels were not increased in WTC FDNY rescue workers with or without sarcoidosis but specialized t-cell studies for beryllium exposure remain to be performed.[57]

To date, with the exception of sarcoidosis, interstitial lung diseases have not been reported in any population study of WTC workers, but single-case reports of eosinophilic pneumonia[62], bronchiolitis obliterans,[63] and granulomatous pneumonitis[64] have been described and the lay press has reported at least four case fatalities in non-FDNY WTC-exposed subjects due to interstitial pulmonary disease.[65] In addition, the FDNY WTC Medical Monitoring and Treatment Program has identified two cases of eosinophilic pneumonitis[62] (both resolved on systemic corticosteroids without reoccurrence) and two cases of severe pulmonary fibrosis requiring lung transplantation (personal communication D. Prezant).

PULMONARY MALIGNANCIES

Because of the various carcinogenic compounds (ex. dioxins, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons) that were found either in the WTC dust or as combustion products from WTC fires[1,2], there remains the potential for late emerging malignancies. In the only bio-monitoring study, a sample of 321 exposed FDNY fire fighters tested four weeks after the collapse had measurements of over 100 analytes, with elevations in only a few (urinary PAH metabolite, antimony, and two dioxin congeners) reaching statistically significant differences from background, all falling far short of levels associated with clinical illness.[66] In addition, over 10,000 FDNY rescue workers were tested for urine beryllium, urine mercury, serum lead and serum total PCB. Only one individual showed significant mercury elevation (thought to be unrelated to WTC), and fewer than 50 had elevated PCB levels, none of which was clinically significant.[29] Samples of sedimented WTC dust from surfaces have shown the presence of asbestos fibers at varying amounts and PAHs adherent to particulates.[1] As yet, there has not been any correlation shown between WTC exposure and increased cancer rates. Since cancers are latent diseases that can develop long after carcinogen exposure, it is crucial that long-term monitoring be implemented for those who were exposed to the WTC contaminants if we are to ever determine if cancer rates are altered by WTC exposures.

The Impact of Exposure Time on Respiratory Disease

In prior environmental and occupational disasters, much has been made of linking disease to long-term cumulative rather than short-term acute exposures, because diseases such as cancers typically correlate best with cumulative unprotected chronic exposure (e.g., mesothelioma and asbestos exposure). However, increased rates of disease have been reported following short-term, high intensity asbestos exposures.[67] The critical role of long-term exposure, does not apply to asthma and sinus conditions, where disease can result from either a single acute exposure in previously healthy non-allergic non-smokers (RADS) or from recurrent, relatively short-term exposures (occupational asthma, irritant asthma or sensitization). Similar findings have also been reported for acute and chronic rhinosinusitis (RUDS). And, of course, exacerbations of previously well-controlled asthma and sinusitis are common after exposures to allergens, irritants and stress. WTC studies have documented increased respiratory symptoms, severe persistent cough ("WTC Cough"), persistent airways hyperreactivity, RADS or asthma, and declines in pulmonary function among surviving first responders and rescue/recovery workers.[25,29,31,32,33,34,35,36,45,46,47,48,49,50,51,68] In these studies, there was a significant exposure-response gradient, with declines in respiratory health correlating with earlier time of arrival relative to the collapse of the towers.[25,29,31,32,33,34,35,36,45,46,47,48,49] Likewise, for surviving occupants, being caught in the dust cloud on 9/11 was significantly associated with increased respiratory symptoms.[41]

For upper and lower respiratory illnesses, given the high volume of aerosolized, respirable dust on 9/11, and the lack of appropriate respiratory protection early on, it is not surprising that arrival time provides the best practical measure for a WTC exposure-response index. For nearly all of the FDNY rescue workers, WTC aerodigestive disease has occurred primarily in those arriving during the first 48 hours after the collapse, with the greatest incidence in those arriving during the morning of the collapse.[25,29,31,45,46,47,48,49] This is not to say that there is no one in the FDNY WTC cohort with WTC aerodigestive disease whose first exposure occurred more than 48 hours post-collapse. And, in fact, a recent WTC registry study on newly-diagnosed (post-9/11) asthma in rescue and recovery workers showed an effect of cumulative exposure (especially greater than 90 hours) even after controlling for initial dust cloud exposure and early arrival time.[53] Aerosolized dust was re-suspended during the rescue-recovery operations and during clean-up of surrounding interior spaces, and fires continued to burn until mid-December 2001. Although relatively far less common, occurrences of WTC aerodigestive disease in rescue workers/volunteers whose first exposure was more than 48 hours post-collapse could be explained either by "high-level" exposures generated by activities that disturbed dust in place, while entering enclosed, poorly-ventilated areas, or by the accumulation of repeated "low-level" exposures over time. Of note, in none of these studies has smoking status been found to be a significant confounder.[25,29,31,32,33,34,35,36,45,46,47,48,49]

TREATMENT OF WTC UPPER AND LOWER AIRWAYS DISEASE

Consensus treatment guidelines have been published and recently updated as a joint collaborative effort between the three WTC Centers of Excellence

(FDNY, NY/NJ consortium coordinated by Mt. Sinai Medical Center and the Environmental Health Center at Bellevue Hospital) and the WTC Registry.[42]

The recommended approach includes a comprehensive plan of synergistic care treating the upper and lower airway including:

- Nasal/sinuses with nasal steroids and decongestants (Figure 3-5.4).
- Gastroesophageal reflux with proton pump inhibitors and dietary modification (also Figure 3-5.4).
- The lower airway with bronchodilators, corticosteroid inhalers and leukotriene modifiers (Figure 3-5.5).

For the minority that uses tobacco products, a multi-modality tobacco cessation program similar to that initiated by FDNY after WTC[69] should be used to reduce the incidence of late-emerging diseases such as lung, heart, cancer and cerebral vascular (stroke) disease. Most patients have reported symptoms and required treatment for involvement of at least two of the above organ systems. Our experience has proven the multi-causality of respiratory symptoms in a disaster-exposed population, with contribution of any combination of upper and lower respiratory processes. When the clinical presentation is atypical (for example, interstitial lung disease) or there is failure to respond after approximately three months of treatment, we recommend additional invasive diagnostic testing such as chest CT, bronchoscopy, sinus CT, laryngoscopy, and/or endoscopy.[42,43,44,70,71]

"World Trade Center (WTC) Cough"
Diagnosis & Treatment Algorithm – Upper Airway Predominance

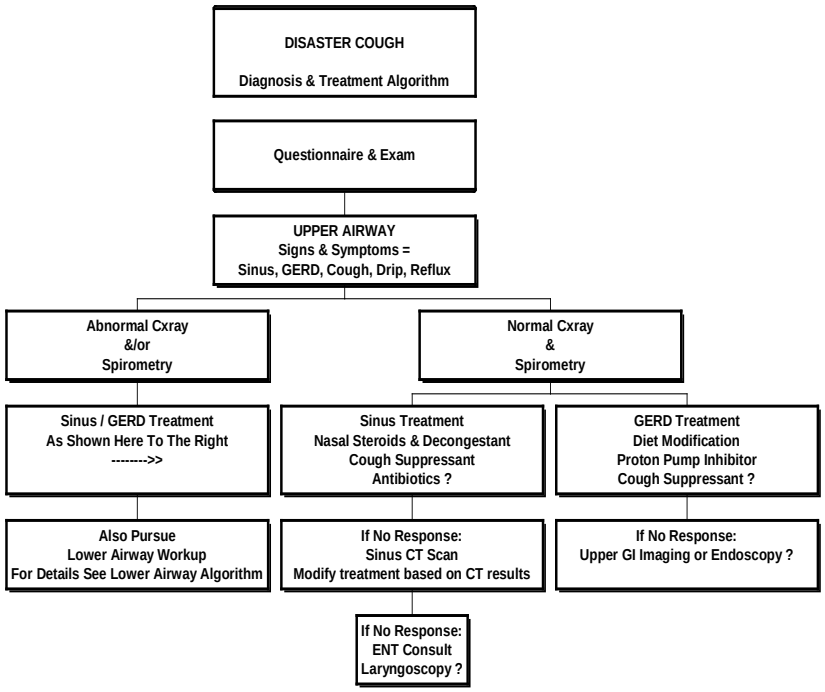

Figure 3-5.4: Treatment algorithm for "WTC Cough" when presentation suggests that the primary causes are upper airway related – chronic rhinosinusitis and/or gastroesophageal reflux disorder.

"World Trade Center (WTC) Cough"
Diagnosis & Treatment Algorithm – Lower Airway Predominance

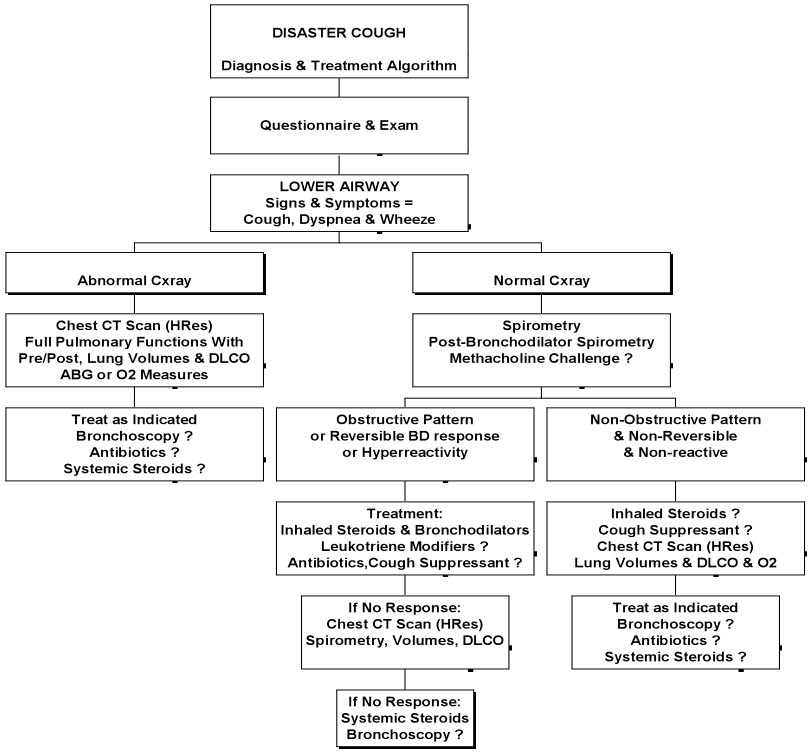

Figure 3-5.5: Treatment algorithm for "WTC Cough" when presentation suggests that the primary causes are lower airway related – obstructive airways (ex. asthma, bronchitis) or restrictive (parenchymal diseases).

CONCLUSION

A growing body of literature has developed that describes the respiratory health consequences of disaster-related exposures to victims, rescue workers, volunteers and nearby residents. Compared to most occupational exposures, disaster-related exposures are far more acute, are often to a wider range of contaminants and are more difficult to prepare for. Yet, the consequences are similar to many occupational and environmental respiratory diseases.

For both occupational and disaster-related exposures the primary emphasis should be instituting preventive measures through the use of environmental controls and respiratory protection. However, the disaster environment is difficult to control given the unexpected nature and often overwhelming magnitude of the incident, the immediate imperative to rescue survivors, the lack of or difficulty accessing stockpiled respiratory protective equipment, and the widespread use of volunteers. Even after fit-tested respirators have been provided, there are far greater challenges to their effective use in a disaster than in a controlled occupational environment. Valid issues affecting adherence with respirator use include:

- Comfort, especially during prolonged use and temperature extremes
- Inability to communicate in a potentially-dangerous environment
- Training
- On-site supervision

For example at the WTC site, FDNY has reported that respirators were not available early on and were not used "most of the time" even when available.[3,46] The WTC registry recently reported that for rescue/recovery workers who arrived on 9/11 and worked in all subsequent time periods, use of masks or respirators did not eliminate the risk for newly diagnosed asthma; but that delays in the initial use of a mask or respirator were associated with an increased incidence of newly diagnosed asthma.[55]

To better prepare for the next disaster a multi-pronged effort is needed that begins with an understanding that the immediacy of the event will lead to acute exposures, but that this time period should be limited by a dedicated, system-wide approach to provide (as rapidly as possible) and to wear (as frequently as possible) respiratory protection. A thorough understanding of user difficulties in wearing respirators should prompt a re-design of respirators for this environment and if this is not possible then work protocols, especially during the recovery phase should be adjusted to minimize unprotected exposures. Workers and volunteers, untrained for this environment should not be allowed on-site but instead should used off-site as support personnel.

Exposures can be reduced but can never be prevented and therefore a robust health program for pre-screening, monitoring, disease surveillance and early treatment should be planned for in advance and then rapidly instituted beginning with on-site registration of all workers and volunteers.

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Chapter 4-1
Pulmonary Function Tests for Diagnostic and Disability Evaluations

By Dr. Andrew Berman, MD and Dr. Naricha Chirakalwasan, MD

INTRODUCTION

Pulmonary function tests (PFTs) are a group of studies designed to evaluate how the lung functions in health and in disease. They are usually performed in a lab or in a doctor's office and can be used to diagnose, assess severity and progression, and guide treatment of pulmonary diseases. PFTs can uncover clinically undetected dysfunction.

Most pulmonary function measurements are routinely expressed as a percent predicted of normal so that the patient can see how they are doing compared to the population. Since pulmonary function measurements are known to be lower in shorter, older or female subjects, the percent predicted normal value automatically adjusts for age, height and gender. While obesity also has a direct effect in lowering pulmonary function measurements by placing a greater stress on the lungs, heart and skeletal muscles, the impact of obesity is not adjusted for automatically in the percent predicted equations. Therefore, if your values are low and you have central obesity (chest and/or abdomen) your values would likely be higher if you lost weight.

For PFTs to be accurate and to provide the correct diagnosis it is important that the patient, physician and technician performing the test remember the following points:

- Most PFTs are effort dependent and the patient must be coached to breathe in as deep as possible and to blow out as hard as possible.
- Reproducibility is required and multiple efforts may be needed. As with the Olympics, the best effort counts and not the number of efforts required to produce that best effort.
- Tobacco smoke should be avoided as it can negatively influence both your health and these measurements.

Unless otherwise advised by your physician, bronchodilator medications (ex. albuterol, ventolin, proventil, ipratropium bromide or Atrovent, Combivent, Seravent, Foradil, Advair, Symbicort and Spiriva) and caffeine should not be taken the morning of the test. However, if you have a history of taking these medications you should bring them with you, tell the technician administering the test about them and be prepared to use them, if necessary, after the test.

This chapter will review some of the many ways lung function can be evaluated.

PEAK FLOW/SPIROMETRY/BRONCHODILATOR RESPONSIVENESS

Peak Flow Meter

A peak flow meter is a portable handheld device that measures air flow. It is easy to use, inexpensive, and patients can do this in their own home. Simply, the patient blows as hard and fast as they can into a tube that measures the highest (or "peak") flow rate. The peak flow measurement occurs very early in expiration, when the flow rates are effort dependent. It is important to take a full breath in and blow out as hard as you can but after the first few seconds you don't have to blow out any further. Because of that, some patients find this easier to do. Peak flow measurements are helpful in monitoring the status of chronic asthma, assessing the severity of acute exacerbations, evaluating therapy, and evaluating temporal (time-related or seasonal-related) relationships to triggers (ex. humidity, heat, irritants, smells) that my cause asthma attacks. Patients can manage their own asthma by knowing their best peak flow and referring to a written action plan with recommendations from their physician regarding what to do when the peak flow is reduced to different levels (Figure 4-1.1).

Figure 4-1.1: A typical Peak Flow meter with colored zones that can be set to a percentage of the individual's best score. An asthma action plan can be written with instructions of what to do if the peak flow falls into these zones.

Of note, falls in peak flow can occur even before symptoms worsen, making this a tool which potentially can lessen the severity of an exacerbation if the results are acted upon early on. Disadvantages of this test are that the results are not always reproducible and are effort dependent. A peak flow measurement does not obviate the need for spirometry to make the diagnosis of asthma.

Spirometry

Spirometry measures how much and how fast air moves in and out of the lungs. After placing a clip over the patient's nose to direct all respiration to the mouth, the patient is coached to breathe in deeply and then blow out for at least six seconds, as fast and as hard as possible, and then to breathe in again, all through a tube which is connected to a device called a spirometer. The spirometer records the forced flow of air throughout the respiratory cycle, as

opposed to the peak flow which only provides one measure early in exhalation. It is important when doing spirometry, that you breathe all the way in, and then blow all the way out until you have reached the end of your expiration (typically, this takes about six seconds of expiration, however healthy, young fire fighters may empty their lungs sooner than six seconds).

Spirometry, therefore, provides more data than a peak flow measurement and allows for a more accurate and reproducible measurement of asthma control. In addition, by plotting inhaled and exhaled flow against the amount of air (i.e., the volume) inhaled and exhaled, a graphic figure can be drawn called a flow-volume loop, which may reveal characteristic patterns associated with certain pulmonary diseases, as described in the next section. A typical study involves repeating the maneuver at least three times and the best of the three trials is accepted. Just like in the Olympics, it is your best recording that counts. Because spirometry tells us about disease and about breathing capacity, it is used in fire fighter candidate evaluations and duty determinations (NFPA 1582) and is the best measure of how you are doing (IAFF/IAFC Wellness-Fitness Initiative). Every fire fighter and HAZMAT worker should have a baseline measurement and then a repeat measurement annually. The following is a list of measurements obtained during spirometry:

- **FVC** (forced vital capacity) is the maximum volume of air which can be forcefully exhaled after full inspiration. FVC is similar to a slow vital capacity in normal lungs, but lower when airflow obstruction is present.
- **FEV_1** (forced expired volume in one second) is the volume of air expired in the first second of forced expiration after a full inspiration; it is a measure of how quickly full lungs can be emptied.
- **FEV_1/FVC** is the FEV_1 expressed as a percentage of the FVC. A reduced ratio is how we define airflow obstruction.
- **$FEF_{25-75\%}$** (Forced expiratory flow at 25% point to the 75% point of FVC) is the average expired flow over the middle half of the FVC maneuver and is felt to be a measure of small airway obstruction. This result may be a more sensitive indicator of mild airway obstruction than the FEV_1/FVC ratio, though is less reproducible and non-specific and frequently does not correlate with challenge tests (see below). Therefore, the clinical significance of this measurement remains controversial and it is not used for candidate evaluations of duty determinations (NFPA 1582).

Individual results are compared to normal values (predicted values) which are defined by a healthy population, adjusted for age, height and gender, and are expressed as a percentage of the predicted value. In healthy adults, spirometry results are normally distributed, meaning that 95% of test results in healthy adults will be between 80% - 120% of a predicted value. An abnormal result then is one that falls outside of this range: an FEV_1 or FVC of less than 80% of the predicted value, since it is uncommon (less than 5%) for a normal patient to have measurements in this range. Perhaps more useful, however, is whether there is a rise or fall in these values in an individual patient over time. Because there are day-to-day variations in breathing capacity, a decline that is 15% or greater from your typical past recordings should be further evaluated by a physician.

Spirometry results can usually differentiate obstructive lung disease from restrictive lung disease. In obstructive lung diseases (such as asthma, emphysema and chronic bronchitis), the total amount of air that gets exhaled is normal or close to normal, but it takes more time for it to come out due to air flow limitation. The FEV_1, therefore, is reduced, while the FVC is close to normal, making the ratio (FEV_1/FVC) reduced. Airway obstruction is often defined by a reduced FEV_1/FVC to less than or equal to 0.70, though some question this cut-off value and require further confirmatory tests (see below). In restrictive lung diseases (such as pulmonary fibrosis, asbestosis, moderate to severe sarcoidosis, kyphoscoliosis, obesity or neuromuscular disease), the lung cannot fill completely and so the amount of air exhaled initially is reduced as is the total amount exhaled. The FEV_1/FVC ratio in this case is normal or elevated since both the FEV_1 and FVC are low. A combination of restrictive and obstructive disease (mixed pattern) can also be seen and is suggested by a reduced FEV_1, a reduced FVC and a reduced to normal FEV_1/FVC ratio. Table 4-1.1 reviews the finding of spirometry results and lung diseases.

Lung Diseases and Spirometry Results			
Interpretation	**FVC**	**FEV_1**	**FEV_1/FVC**
Normal Spirometry	Normal	Normal	Normal
Airway Obstruction	Low or Normal	Low	Low
Lung Restriction	Low	Low	Normal
Combination of Obstruction & Restriction	Low	Low	Low

Table 4-1.1. Lung Disease and Spirometry Results

As opposed to a reduced FEV_1/ FVC ratio which defines obstruction, a normal FEV_1/ FVC ratio does not define restriction. A reduced FEV_1 and FVC (and therefore a normal ratio) can also be seen during testing of some patients with severe airway obstruction who may not be able to exhale fully because their air tubes close as they try to force air out. These patients may stop testing before the lungs are fully emptied (i.e., the air is trapped), which leads to a falsely reduced FVC. For this reason, bronchodilator tests and full lung volumes (discussed later in this chapter) are necessary to distinguish obstructive from a restrictive abnormality.

Flow Volume Loop

The flow volume loop is a graph plotting forced expiratory and inspiratory flow against volume, and may reveal characteristic patterns associated with certain pulmonary diseases. The contour of expiratory portion of the flow volume loop can be used to differentiate obstructive lung disease from restrictive lung

disease, while the inspiratory contour may suggest upper airway pathology. The latter might be due to vocal cord abnormalities or obstruction in the upper trachea or larynx (voice box).

Patterns in normal and disease states are shown in Figure 4-1.2. In those without lung disease, there is a straight contour in the expiratory loop and a rounded appearance in the inspiratory loop (see Figure 4-1.2a). In patients with obstructive lung disease, the expiratory curve is curvilinear or scooped in appearance, due to a reduction in flow as the volume of the lung decreases, which occurs as the patient exhales. As the obstruction becomes worse, the expiratory curve becomes more scooped (see Figures 4-1.2b and 4-1.2c). In restrictive diseases, the curve is tall and narrow (see Figure 4-1.2d). A saw-tooth pattern is sometimes seen in patients with obstructive sleep apnea. Upper airway lesions alter inspiratory flow and will show as a flattening of the inspiratory loop. When there is limited flow during both inspiration and expiration, there is a fixed obstruction and this appears as a box pattern (see Figure 4-1.2e). This can occur in patients with tracheal stenosis (scar in the wind pipe), which may occur after severe upper airway burns, prolonged intubation and mechanical ventilation.

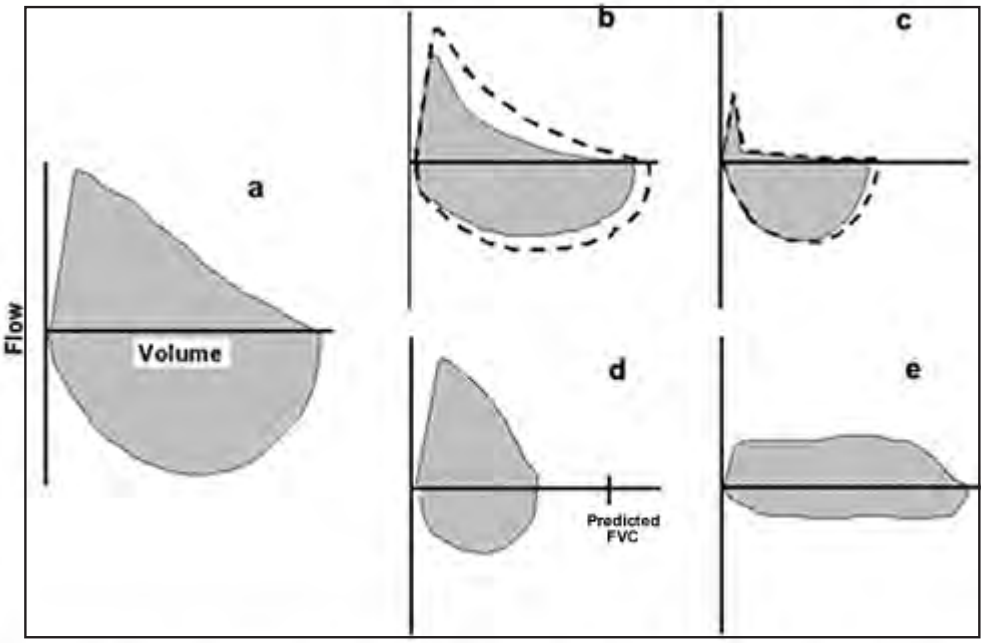

Figure 4-1.2 a-e: Flow-volume curves showing different patterns. a: Normal. b: Airway obstruction. c: Severe airway obstruction. d: Restriction. e: Fixed airway obstruction. (Adapted from Johns D, Pierce R. Pocket Guide to Spirometry. 2003. McGraw-Hill. Australia)

Bronchodilator Responsiveness or Reversibility

As discussed in Chapter 1, there is smooth muscle in parts of the bronchial tree. When the smooth muscle contracts, the diameter of the airways is reduced, resulting in a decrease in airflow. Certain inflammatory lung conditions, such as asthma or reactive airway disease (both discussed in later chapters), are characterized by hyperreactive (irritable/twitchy/spasmodic) airways, whereby certain triggers (ex. humidity, temperature change, exercise, irritants, noxious fumes) may lead to smooth muscle contraction and the development of symptoms such as cough, shortness of breath and/or wheezing. A characteristic

of these conditions on spirometry is a decrease in the FEV_1 and the FEV_1 / FVC ratio (an obstructive pattern) that is at least partially reversible after the patient receives a medication that causes the bronchi to dilate (i.e., a bronchodilator such as albuterol). This relieves the airflow obstruction and can be demonstrated by repeating the spirometry after the bronchodilator is administered and waiting 10 minutes. The American Thoracic Society (ATS) recommends that vital capacity (slow or forced) and the FEV_1, be the primary spirometric indices used to determine bronchodilator response. A 12% increase above the pre-bronchodilator value and a 200-ml increase in either FVC or FEV_1 indicate a significant response in adults. $FEF_{25-75\%}$ should be considered only secondarily in evaluating reversibility.

TEST OF LUNG VOLUME AND DIFFUSION CAPACITY

Lung Volume Measurements

Lung volume is the amount of air in the lungs, and measurement often requires further testing in addition to spirometry. Recall, spirometry only measures the amount of air entering or leaving the lungs and even after fully breathing out we always have some air left in our lungs. Therefore, in order to know the total amount of air in the lungs, one needs to know how much air is left in the lung after a complete exhale, or the residual volume. This amount can vary in disease states and by gender. Listed below and shown in Figure 4-1.3 are the volumes and capacities (defined as two or more primary volumes) of the lung.

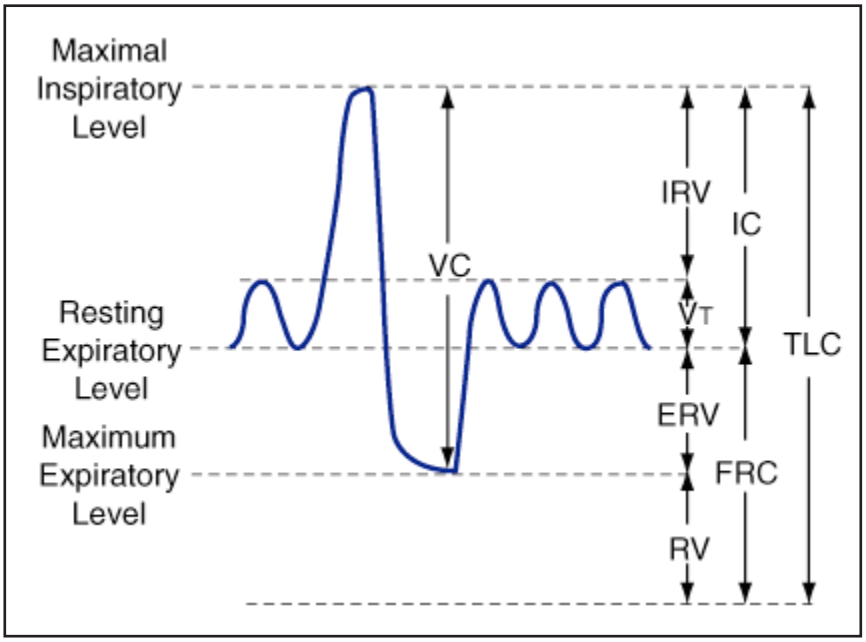

Figure 4-1.3: Lung Volumes.

The primary volumes are as follows:

- V_T = Tidal Volume: volume of air normally inhaled or exhaled during each respiratory cycle. This value can be obtained during spirometry.
- IRV = Inspiratory Reserve Volume: the additional volume of air inhaled after a normal inspiration, achieved by taking a full deep breath in; it is the maximal volume of air inspired from end-inspiration.

- ERV = Expiratory Reserve Volume: the additional volume of air exhaled after a normal exhalation, achieved by forcing out a full deep breath until no more air can be expired; it is the maximal volume of air exhaled from end-expiration.
- RV = Residual Volume: the volume of air that remains in the lungs following a maximal exhalation; this volume may be increased in patients with severe airway obstruction. Residual volume can only be measured indirectly by gas dilution methods or body plethysmography.

The capacities are as follows:

- VC = Vital Capacity: maximal volume of air that can be forced out of the lungs following a maximal inspiratory effort, regardless of the amount of time it takes. This is the same as the FVC measured during spirometry if air does not get trapped due to collapsing airways, as can occur in obstructive lung disease. When airway obstruction is present, a slow vital capacity measurement may be more reflective of the true value. The VC equals IRV + V_T + ERV or alternatively, the TLC – RV.
- TLC = Total Lung Capacity: the total amount of air in the lungs. The TLC includes the maximal volume of air that can be exhaled (VC) plus whatever air remains in the lung afterwards (the RV).
- FRC = Functional Residual Capacity: the amount of air in the lungs after one breathes out normally. This equals ERV + RV.
- IC = Inspiratory Capacity: the maximal volume of air that can be inspired at the end of a resting exhale. This equals IRV + V_T .

There are three methods to determine lung volumes: spirometry, the gas dilution technique and body plethysmography (also known as a body box). Spirometry has been discussed earlier and is limited by the inability to measure residual volume and therefore total lung capacity and functional residual capacity, because both contain the residual volume as part of their capacity.

The other two techniques allow for the measurement or calculation of all lung volumes. Usually, after FRC is measured, other lung volumes are measured including ERV. RV is calculated by subtracting ERV from FRC. By adding the residual volume to the vital capacity, total lung capacity can then be calculated. Since restrictive lung disease is defined by a reduced TLC, gas dilution or body plethysmography must be performed to make this diagnosis.

Typically, labs using the gas dilution technique utilize either the closed circuit helium (He) method or an open circuit nitrogen (N2) method. The helium dilution method (as depicted in Figure 4-1.4) starts with the patient breathing a gas mixture containing helium via a closed circuit. The starting volume of gas containing the helium is known and the amount of helium in the lungs at the start is zero. Since helium is inert, it does not diffuse across the alveolar-capillary membrane, and the gas equilibrates throughout the entire system. The total amount of helium does not change during the test. After the patient breathes normally for up to 10 minutes, equilibration usually occurs, and the amount of helium in the system is again measured. The equilibrated volume is subtracted from the starting volume enabling calculation of the volume of the lung at the end of a normal breath which is FRC. One limitation of this method is that the volume of gas measured is only that which communicates with the

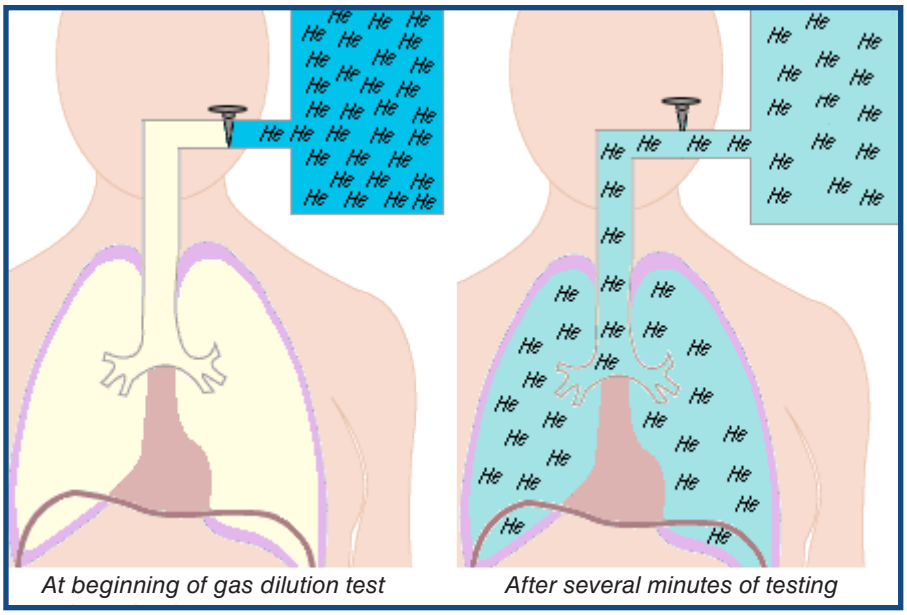

Figure 4-1.4: Helium dilution technique of lung volume measurement.

airways, which does not include lung bullae which can occur in patients with emphysema. In obstructive airway diseases, especially emphysema, TLC may be underestimated. Body plethysmography would be a better method of measuring TLC in these patients.

The open circuit nitrogen method is based on a similar principle of the helium technique, except here the expired concentration of nitrogen normally present in the lungs is now measured. In this technique, the patient is given 100% oxygen to breath in order to wash out the air (mostly made up of nitrogen) from the lungs. The concentration of nitrogen is continuously monitored in the expired gas, and when the exhaled concentration of nitrogen is essentially zero, the test ends. The volume of nitrogen-containing gas present in the lungs can be measured. The difference in nitrogen volume at the initial concentration and at the final exhaled concentration allows a calculation of intrathoracic volume, usually FRC. This measurement is subject to the same limitations as the helium technique.

Body Plethysmography

Body plethysmography is another technique used to measure lung volumes. This method incorporates the physiologic principle of Boyle's law which states that the product of the pressure times the volume of a gas is constant if the temperature is unchanged, or P1V1=P2V2. In plethysmography, the patient sits inside an airtight box that resembles a telephone booth (thereby accounting for the alternative test name of body box, see Figure 4-1.5). The initial box volume and pressure are known (P1V1). The patient then breathes in and out through a mouthpiece. At the end of a normal exhale (FRC), the mouthpiece gets occluded and the patient is instructed to gently pant in and out against the closed shutter. This causes the chest volume to expand which in turn causes a decrease in the box volume and a corresponding increase in box pressure. The pressure change in the box is recorded and thereby allows for a calculation of the change in box volume, which is equal to the change in lung volume. This

Figure 4-1.5: Body plethysmography, or body box.

volume is referred to as thoracic gas volume (TGV) and represents the lung volume measured when the shutter was closed, typically at FRC.

Lung volumes measured by body plethysmography, may be higher than volumes measured by using gas dilution method. This is primarily due to the measurement of both communicating and non-communicating compartments of the lungs with plethysmography, as opposed to just measuring the communicating compartments alone using the gas dilution techniques. It is therefore a more accurate test in patients with severe airway obstruction (where there is trapped air from airways that collapse at low lung volumes) as well as those with bullous lung disease or emphysema. Disadvantages are that the values may be off if the shutter is closed at a volume which is not FRC, as well as the need for a patient to sit in a small enclosed space.

Diffusing Capacity

Diffusing capacity is a measurement of the ability of gases like oxygen to transfer from the alveoli into the pulmonary capillary blood. A low diffusing capacity is rarely a cause for hypoxia (low oxygen levels) at rest but can be a cause during physical exertion.

Diffusing capacity is a non-invasive test which involves the inhalation of a gas mixture containing a small amount of carbon monoxide because this gas is normally not present in the lungs or blood, and is very soluble in blood. This small amount will not be harmful to the patient and does not last long in the body so it will not be present later that day if a fire fighter has carbon monoxide level taken at a fire or in an emergency room. During the diffusing capacity test, a known amount of carbon monoxide is breathed in and then whatever is not subsequently breathed out should represent the amount that diffused through the lung and into the pulmonary capillary system. The most widely used and best standardized method of measuring diffusing capacity is known as the "single-breath diffusing capacity using carbon monoxide," or the DL_{CO}. In this technique, the patient exhales completely, and then inhales a gas mixture deeply, that contains 0.3% carbon monoxide and a low concentration of inert gas (usually 10% helium). The patient then holds their breath for 10 seconds, during which time the carbon monoxide leaves the air spaces and enters the blood. The exhaled helium concentration is used to

calculate a single-breath estimate of total lung capacity. DL_{CO} is calculated from the total volume of the lung, breath-hold time, and the initial and final alveolar concentrations of carbon monoxide.

The amount of gas diffused from the lung into the pulmonary capillary system is related to the surface area of the lung, the capillary blood volume, and the thickness of the alveolar-capillary membrane. Any condition which alters any one of these factors can cause a reduction in diffusion. In emphysema, the walls between the alveoli break down, creating fewer alveoli, and this loss of surface area is associated with reduced diffusion. Pulmonary embolism (blood clots) or pulmonary hypertension results in the obliteration and/or obstruction of pulmonary arteries. In these patients, the measurement of gas transfer for carbon monoxide is usually reduced. Interstitial lung diseases affect the meshwork of lung tissue (alveolar septa) other than the air spaces (alveoli), and can result in thickening of the alveolar-capillary membrane making it harder for gas to diffuse. Examples of interstitial lung disease include Idiopathic Pulmonary Fibrosis (IPF), moderate to severe sarcoidosis, lung diseases caused by certain dusts (e.g., asbestosis) and certain drug reactions. Pulmonary diseases that essentially just affect the airways, such as asthma or chronic bronchitis, do not demonstrate a reduced diffusion capacity. Increased diffusion capacity is rarely important but may occur if the patient is bleeding into their lung.

Diffusion capacity is a valuable tool in the diagnosis and monitoring of pulmonary diseases. While a reduced TLC signifies restrictive disease, the DL_{CO} may suggest the etiology. For example, a reduced DL_{CO} with a reduced TLC suggests interstitial disease (e.g., pulmonary fibrosis), while a normal DL_{CO} with reduced TLC suggests the lung parenchyma is not damaged and the restriction is extrapulmonary (as in obesity, chest wall or neuromuscular diseases). A decreased DL_{CO} with an obstructive pattern on spirometry can be seen in patients with emphysema, while those with chronic bronchitis often have obstruction with a normal diffusion capacity. Pulmonary vascular disease and anemia may present with normal spirometry and lung volumes and a decreased DL_{CO}. It should be noted however that there are some patients with interstitial lung disease who are found to have diffusion abnormalities before lung volume abnormalities are present. Typically, these patients also have evidence for interstitial lung disease on high-resolution chest CT scans.

Diffusing capacity can also be low in the absence of lung disease. It is low in some patients with obesity due to compression of the lung and its circulation. It can be low, normal or high in cardiac disease. Low hemoglobin concentration (as in anemia) also leads to a reduced diffusion capacity as there is less blood to diffuse onto; a correction for anemic patients is sometimes used. Likewise, diffusing capacity can be elevated in a condition called polycythemia (increased number of red blood cells). It can also be low in patients with carbon monoxide intoxication (acute or chronic exposures even from tobacco smoke).

PROVOCATIVE CHALLENGE TESTING (METHACHOLINE, COLD AIR AND EXERCISE)

In patients with a history suggestive of asthma, but with a normal physical exam and spirometry, further testing is sometimes required to document bronchial hyperreactivity. Provocative challenge testing incorporates the delivery of

a medication to provoke constriction of the airways (bronchoconstriction) leading to asthma symptoms and a fall in lung function. People with asthma will respond to bronchoprovocation with a greater degree of airway obstruction than will normal subjects. Methacholine is a commonly used provocative agent that is a nonspecific stimulus of bronchoconstriction, though cold air and exercise testing are also sometimes used. In methacholine challenge testing, a baseline FEV_1 is recorded following the inhalation of saline. Methacholine is then delivered in increasing concentrations with a repeated FEV_1 measurement following each dose. In contrast to normal subjects, asthmatics will report typical asthma symptoms, such as coughing, wheezing and shortness of breath, and their FEV_1 will fall as the dose increases. The test is terminated following any dose that lowers the FEV_1 by 20%. This is termed the PD_{20}, or the provocative dose that produces a 20% fall in FEV.

Following testing, a bronchodilator is administered and lung function returns to normal and symptoms resolve. Hyperresponsiveness is deemed present when the PD_{20} is less than or equal to 8 micromol or mg/ml of methacholine. Some physicians believe that a more liberal definition (higher PD_{20} such as 16 mg/ml) should be used in workers where the risk for irritant exposure is high (e.g. fire fighters and other HAZMAT workers). The lower the dose that is required, the more hyperreactive the individual's airways are. Cough variant asthma, in which the patient has asthma though only coughs as the main presentation, can also be diagnosed by this method. It also has been used to follow subjects with exertional asthma, occupational asthma, document the severity of asthma and to assess the response to treatment. Presence of increased airway responsiveness is a significant predictor of subsequent accelerated decline in pulmonary function.

It is important to understand that provocative testing is only of use in patients with normal lung function when the diagnosis of asthma is in question. It should never be performed in patients with moderate to severe reductions in lung function at rest (FEV1 <65% predicted). Medications may influence this test and therefore should be carefully discussed with the physician before provocative challenge testing is ordered. Corticosteroids, leukotriene antagonists (such as Singulair) and antihistamines may interfere with the accuracy of provocative testing. As with all pulmonary function testing, bronchodilator medications (ex. albuterol, ventolin, proventil, ipratropium bromide or Atrovent, Combivent, Seravent, Foradil, Advair, Symbicort and Spiriva) and caffeine should not be taken the morning of the test. However, if you have a history of using these medications you should bring them with you, tell the person administering the test about them and be prepared to use them on your way home if necessary.

EXERCISE TESTING

Cardiopulmonary Exercise Testing

Observations and testing made during the resting state may not be able to explain why some patients complain of shortness of breath on exertion. Exercise testing allows for the correlation of exercise-induced symptoms with objective data. Exercise tests can quantitate the degree of functional impairment and help determine whether the limiting factor is pulmonary, cardiac, pulmonary vascular, or due to decreased conditioning. For this reason, exercise testing

is often referred to as cardiopulmonary exercise testing (CPET). CPET can also be utilized to evaluate disability, prescribe exercise rehabilitation, and to determine risk from major surgery.

Before beginning a CPET, it is important to evaluate patients for any contraindications to exercise testing. This would include any individual who has severe physical or emotional impairments where testing is deemed unsafe. Examples include patients with severe arthritis or neuromuscular disorders who may not be able to perform the required maneuvers. Patients with severe cardiac disease such as unstable angina or aortic stenosis should not be tested. In addition, patients with uncontrolled asthma should not be tested until their asthma is under better control.

Standard exercise testing is performed on a treadmill or stationary bicycle. Prior to initiating the exercise, a blood pressure cuff, EKG leads, and a pulse oximetry probe are applied. A mask that allows for expired air to be monitored and a nose clip are placed on the patient. An indwelling arterial canula for blood gas sampling is sometimes inserted. The patient then performs progressive step-wise exercise at multiple work loads. Figure 4-1.6 shows a standard clinical exercise protocol using cycle ergometry.

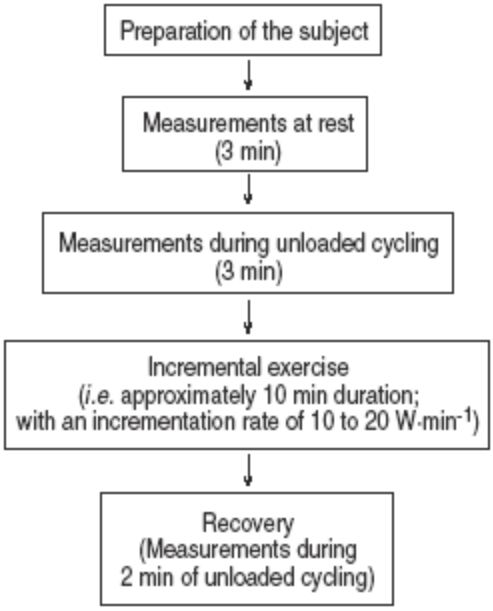

Figure 4-1.6: Recommended incremental exercise protocol using cycle ergometer

The test continues until the target heart rate is reached. After exercise testing, the subject "recovers" for about two to three minutes by pedaling at a low work rate to prevent hypotension caused by pooling of blood in dilated vessels. Exercise testing can also be terminated if the patient develops exhaustion, severe shortness of breath, chest pain, dizziness, or pallor. In addition, the test is stopped if there are significant EKG changes, serious arrhythmias, a dramatic rise or fall in blood pressure, abnormal rapid respiration or significant drop in oxygen saturation (<80%).

A number of physiological indices are measured and calculated during cardiopulmonary exercise testing, and are beyond the scope of this chapter. The maximal oxygen uptake, or VO_2max, however, is the primary

determinant of whether there is normal or reduced exercise capacity. A reduced VO_2max can be seen in several diseases and conditions such as cardiovascular disease, lung disease, or anemia. An integrative approach using clinical data and patterns of physiologic responses based on measured indices is used to determine the cause; no one single index is considered diagnostic of a cause for exercise limitation.

Six-Minute Walk Test

The six-minute walk test (6MWT) is a test that measures the maximal distance that a patient can walk on a flat hard surface in a period of six minutes. Patients walk at their own pace and are allowed to rest when necessary. It is felt that since most activities of daily living are performed at this level, the 6MWT may better reflect the functional capacity of the individual for daily physical activities than complete cardiopulmonary exercise testing. This would not be true for fire fighters and EMS rescue workers who must be able to perform at a much higher level of physical exertion. The primary advantage is that the test is simple and practical; no exercise equipment is necessary. The disadvantage is that the test does not provide specific information on the role of the different organ systems that can contribute to exercise limitation. This test is used for preoperative and postoperative evaluations, and to monitor patients with cardiac and pulmonary vascular disease as well as to measure the response to therapeutic interventions. Lastly, it can used to measure the response to pulmonary rehabilitation, as patients may increase either or both their maximum capacity and endurance for physical activity, even though lung function does not change.

DISABILITY EVALUATION

Dyspnea, a sensation of uncomfortable awareness of breathing, is the most common complaint in a disability evaluation. Disability evaluations incorporate objective quantitative measures, such as the pulmonary function tests described earlier, with other factors such as age, gender, education, and job requirements. Two individuals with the same degree of physiologic impairment may therefore have different levels of disability. For example, asthma would be a disability for fire fighters who work in an irritant environment but would not be a disability (unless severe) for most EMS workers.

Respiratory impairment is often determined using certain spirometric measures, such as the FEV_1 and FVC. The diffusion capacity for carbon monoxide is also used (Table 4-1.2). Many clinicians, however, feel that a percent predicted cut-off value used in isolation to determine whether an individual can perform their job or not may be inaccurate. Interpretation in the context of other diagnostic tests and patient history is more informative. The U.S. Social Security Administration, for example, considers asthma disabling if severe attacks occur at least once every two months or an average of at least six times a year.

Classification of Respiratory Impairment			
Class 1, 0%–9%: No Impairment of the Whole Person	**Class 2, 10%–25%: Mild Impairment of the Whole Person**	**Class 3, 26%–50%: Moderate Impairment of the Whole Person**	**Class 4, 51%–100%: Severe Impairment of the Whole Person**
FVC ≥ lower limit of normal* and FEV1 ≥ lower limit of normal* and DLCO ≥ lower limit of normal*	FVC between 60% and lower limit of normal or FEV_1 between 60% and lower limit of normal or DLCO between 60% and lower limit of normal	FVC between 51% and 59% of predicted, or FEV_1 between 41% and 59% of predicted, or DLCO between 41% and 59% of predicted	FVC ≤ 50% of predicted, or FEV_1 ≤ 40% of predicted, or DLCO ≤ 40% of predicted
or	*or*	*or*	*or*
VO_2 max > 25 mL/kg/min	VO_2 max between 20 and 25 mL/kg/min	VO_2 max between 15 and 20 mL/kg/min	VO_2 max < 15 mL/kg/min
DLCO is diffusing capacity for carbon monoxide; FVC is forced vital capacity; FEV_1 is forced expiratory volume in one second; VO_2 max is maximal oxygen uptake.			

Table 4-1.2: American Medical Association Classification of Respiratory Impairment

Exercise testing and the measurement of VO_2max has been advocated as the gold standard for assessing a patient's capacity to perform work, though is not part of the routine evaluation of pulmonary impairment. CPET, however, may be helpful when dyspnea is greater than either spirometry or the diffusing capacity would indicate, or the results of these tests are inconclusive. In patients suspected of malingering, review of prior test results may show evidence of consistent lack of effort over time. In such cases, exercise testing will demonstrate the relationship of heart rate and ventilatory rate at workloads actually achieved. In general, individuals with VO_2max value under 15 ml/kg/min can be declared unfit or incapacitated for work. However, they may be able to perform work if their maximal oxygen uptake is in the range of 15-24 ml/kg/min, depending on the physical activity required. Individuals with VO_2max greater than 25 ml/kg/min are expected to be able to perform vigorous work (see Table 4-1.2) and it has been advocated that fire fighters should be able to reach a level of 37 ml/kg/min. Unfortunately, CPETs are expensive and require a highly trained staff to perform and interpret testing, and may, therefore, not be readily available.

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Chapter 4-2
Imaging Modalities in Respiratory Diseases

By Dr. Subha Ghosh, MD and Dr. Linda B. Haramati, MD

COMMONLY USED MODALITIES

Chest X-Ray (CXR)

X-rays are the oldest and most commonly-used form of medical imaging. Chest x-ray (CXR) is the most commonly-performed x-ray examination. A CXR is a picture of the chest that shows the heart, lungs, airways, blood vessels and bones of the spine and chest wall. It is a painless medical test that involves exposing the chest to a small dose of ionizing radiation to produce images of the chest contents. It may help physicians diagnose and treat respiratory diseases.

Science Behind X-Rays

X-rays, like radio waves, are a form of electromagnetic radiation that can pass through most objects including the human body. After careful positioning, the x-ray tube emits x-rays aimed at a specific body part (like the chest). While passing through the human body, these rays are absorbed by different body parts in varying degrees. Dense bone absorbs more radiation while soft tissues (for example, skin, muscle, body fat or glands) of the body absorb less and air-filled lungs allow most of the x-rays to pass through. The x-rays that pass through record an image of the body part on the special photographic plate. As a result, bones appear white, air in the lungs appears black and soft tissues appear different shades of gray. These images can either be stored as film (hard copy) or electronically (digital image). A technologist who is trained to perform radiology examinations performs the entire procedure. Studies are read by radiologists, who are physicians specially trained to interpret radiology examinations. The reports and films are then communicated to the patient's physicians.

Equipment and Procedure

Equipment consists of a source of x-rays (x-ray tube) and a special recording plate (image plate). The patient is positioned with the plate in contact with the patient's chest and the x-ray tube positioned six feet away. The test requires no prior preparation except for removal of jewelry, eyeglasses, metallic objects or clothing that may obscure underlying body parts. Patients are asked to remove their clothing and wear a gown. Women should inform the technologist if they are pregnant or if there is any chance of pregnancy.

Patients who are able to stand are positioned such that they are against an image recording plate. Typically, two views are obtained. The PA (front) view is

taken with the plate pressed against the chest of the patient with the patient's hands on the hips. The x-ray tube is located six feet behind the patient's back (thus, the patient faces away from the x-ray source). The patient is then asked to stop breathing and not move for a few seconds while the x-ray tube is fired and an image is obtained. In the lateral (side) view, the patient is turned to face the x-ray tube sideways with the arms elevated and the image plate pressed at the patient's side. Patients may be positioned lying down on a table if they are unable to stand. Several other views of the chest are also possible. One of the most common is the anteroposterior (AP) view performed with portable x-ray machines on patients who are sick and bed bound in the intensive care unit. The patient typically faces the x-ray source and the x-ray plate is placed behind the patient's back. Additional views include decubitus views (for example, a left lateral decubitus film would mean a film taken with the left side down , which are useful for diagnosing pleural effusions (fluid); lordotic views (an apical lordotic film is taken with the x-ray film cassette behind the patient's back while the patient tries to bend backwards), to better visualize the lung apices for hidden tumors or tuberculosis; Expiratory views to diagnose pneumothorax, air-trapping; and Oblique views to delineate rib fractures.

Common Uses

A CXR is usually the first imaging test to be performed on patients complaining of persistent cough, fever, difficulty breathing and trauma to the chest leading to chest pain.

Commonly-diagnosed conditions on a CXR include pneumonia, tuberculosis, pleural effusion (fluid around the lung), heart failure and other heart problems, chronic obstructive lung disease (emphysema), scarring or inflammation within the lungs (pulmonary fibrosis, sarcoidosis), cancer within the lungs (primary lung cancer and metastatic cancer), rib fractures and collapsed lung from air leak (pneumothorax).

Benefits of Procedure

This procedure is painless, relatively inexpensive and widely available with equipment which can be operated easily and gives relatively quick results; making the test ideally suitable for use in both office settings as well as in emergency rooms.

Risks of Procedure

There is risk of radiation exposure. The typical dose of radiation received by an adult during a CXR is small. It is similar to the dose received by an average person from the earth's background radiation in 10 days (calculated as 0.06 to 0.1 mSv or 6 to 10 mRem). However, there is always a small chance of developing cancer from the exposed radiation. This risk is negligible and estimated to be less than 1 in 1,000,000. Benefits of obtaining a diagnosis by getting the x-ray often easily outweigh this risk. Another risk with x-rays involves their use in pregnancy. Ionizing radiation, such as that used in x-rays, has been implicated in several harmful effects on the embryo or fetus within the womb. Women should always inform the staff that they are pregnant or may be pregnant. It may be advisable in certain cases to do a urine screen for pregnancy before obtaining any x-ray examination. Several steps are taken to minimize the

radiation exposure in a CXR. Certain radiation safety organizations monitor standards and update techniques used by radiology personnel. Modern x-ray machines have devices built-in to reduce scatter or stray radiation. This, as well as protective x-ray proof shields, are often employed to ensure that body parts not being imaged receive only minimal radiation exposure.

Limitations

In proper settings, a CXR is a very useful examination. However, some parts of the chest remain hidden on standard views. Some chest conditions like asthma, COPD, smoke inhalation or blood clot(s) within the lungs (pulmonary embolism) cannot be detected on a CXR examination. Any abnormal finding on a CXR would typically prompt additional imaging (e.g., Chest CT scan) which may confirm or rule out the initial CXR findings.

Abnormal Patterns on CXR

- **Nodules**: Nodule is a term given to a rounded lesion seen on a CXR (Figure 4-2.1a). It may be due to pneumonia, scar, inflammation, tuberculosis, or cancer (lung cancer or metastases). If the nodule is old (unchanged for last two years) and/or calcified it is unlikely to be or become a cancer.

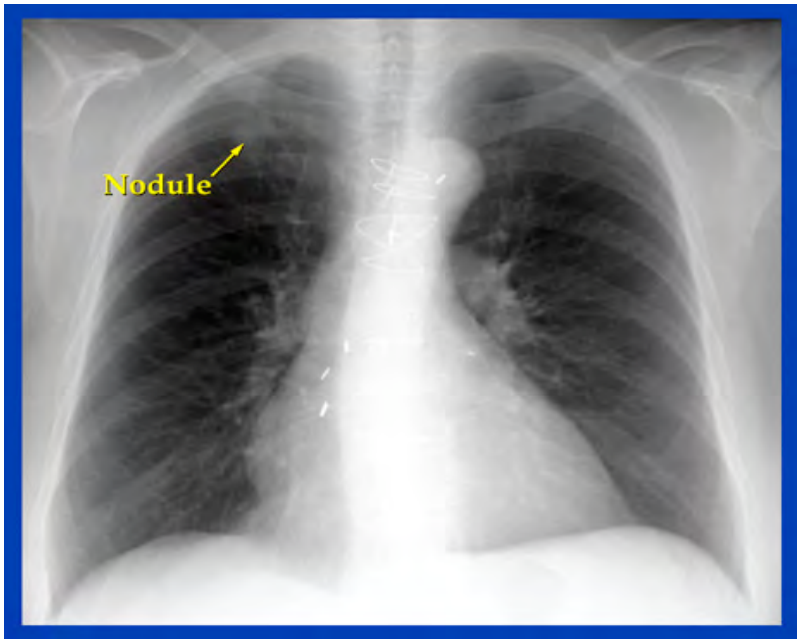


Figure 4.2.1a: Chest x-ray showing a nodule (less than 3 cm in diameter) without spread to adjacent structures.

- **Rate of Growth**: Since most tumors start as rounded nodules, a 28% increase in their size on an x-ray would mean doubling of the tumor volume (e.g., a two millimeter increase in size for a nodule that was seven millimeters in size). Rarely, some highly-aggressive tumors, like small cell lung cancers, can double their volume in 30 days while other slow-growing tumors may take as long as 18 months to double their size. In contrast, most benign lesions take less than one month or more than 18 months to double their size.

- **Granulomas**: Small nodules, often calcified, that are related to old insults such as tuberculosis, fungal disease or sarcoidosis. These too are unlikely to be or become cancer.
- **Calcifications:** Usually indicate benign (non-cancerous) scar, granuloma or hamartoma (non-cancerous congenital tissue).
- **Margins:** Typically, smooth in benign nodules and spiculated (irregular, serrated) in cancers but exceptions to the rule exist.
- **Cavities**: "Holes" in the lung; may be due to congenital causes, infection, lung disease or cancer.

Pleural Abnormalities

The pleura is a double-layered skin between the lung and chest wall. A CXR is able to detect collections of fluid within the pleural space (which is a potential space between the lining or membranes covering or surrounding the lungs). At least 200 ml, 75 ml and 5 ml of fluid are necessary for detection on the PA view, lateral view and decubitus views, respectively). Pleural nodules may be due to cancer. Pleural plaques, especially when calcified and on both sides, may be due to asbestos-related pleural disease (Figure 4-2.2). Pleural plaques when on only one side are more likely due to healed infection or trauma. Pleural fluid may be due to infection, heart failure, rheumatologic diseases, cancer, to name just a few.

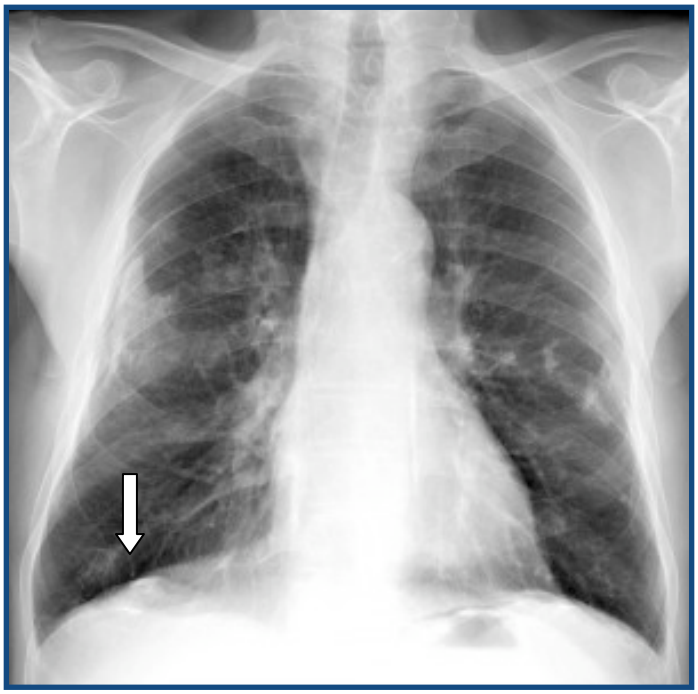


Figure 4-2.2: Chest x-ray showing asbestos plaques and pleural calcifications (arrow).

Shadows And Other Markings

The list of different conditions that can be associated with theses patterns are long. Correlation with clinical symptoms is necessary to help determine if the abnormality is related to infection, inflammation or an exposure. CT scanning and lung biopsy may be necessary.

Examples are as follows:

- Reticular pattern (crisscrossing lines) may be due to interstitial lung disease, sarcoidosis, or heart failure.
- Nodular pattern (small rounded lesions in large numbers) may be due to interstitial lung disease, sarcoidosis, metastatic cancer (spread from other organs to lung) and infections like tuberculosis or fungal infections.
- Cysts (ring like) may be due to bronchiectasis (dilated airways from old infection or inflammation).
- Honeycombing are small cysts within reticular lines seen in fibrosis.
- Ground glass (hazy areas) is a sign of acute or chronic inflammation. When acute it is typically due to infection or inhalation injury. When chronic it is typically interstitial lung disease or rarely heart failure.
- Consolidations (dense, opaque, with "air-bronchograms") are typically due to infectious pneumonias and less commonly due to alveolar hemorrhage, lung cancers and even rarer conditions like eosinophilic pneumonia.

Computerized Tomography (CT) Scan

CT scanning is a medical imaging test that uses special x-ray equipment to produce multiple pictures of the inside of the human body. These pictures are then integrated with the help of a computer to produce a cross-sectional image of a particular body part. The test in itself is painless and generates images of internal organs which are of much higher clarity (resolution) than conventional x-ray images.

Equipment and Procedure

CT scanners typically comprise of a CT table, which moves in and out of a small tunnel. The patient is positioned to lie down on the CT table. The tunnel consists of a ring of x-ray tubes and x-ray detectors, which are opposite one another in a machine called the gantry. The gantry rotates around the patient while the CT table slides in and out of the tunnel. A separate computer workstation located in a different room processes the data generated by the CT scanner to produce crisp images of "slices" of the human body (cross-sectional images). In many ways, CT scanners follow the same principle of image formation making use of x-rays which pass through the body and are absorbed to different extents by different body tissues leading to differences in their contrast on the resultant image. Thus, bone (which absorbs most of the x-rays) appears white, air (which allows most x-rays to pass through) appears black and most soft tissues and fluid appear different shades of gray.

The x-ray beam in a CT scanner traces a spiral path. This is because the gantry which hosts multiple arrays of x-ray tubes and detectors rotate around the patient who is on the CT table which slides in and out of the tunnel containing the gantry. This data is processed to generate cross-sectional images (resembles "slices" of the human body). Newer CT scanners have the ability to acquire multiple image slices in a single rotation. Thus, thinner slices with greater

clarity can be obtained in a shorter time, making these scanners particularly useful in scanning unstable, sick patients and children.

All necessary precautions that are followed before obtaining a CXR should also be followed for a CT scan, including awareness of patient's coexistent medical problems, medications and possible pregnancy. Patients are often asked to fast overnight (8 to 12 hours) before scanning, particularly if intravenous or oral contrast material needs to be given. These are iodinated dyes, which are used to opacify blood vessels and intestines to allow better contrast from adjacent un-opacified structures. All jewelry and metallic objects are removed from the patient who is positioned to lie down either on his back or on his stomach on the CT table. Loose fitting gowns and straps, which secure the patient to the CT table, may be used. If contrast is necessary, it is administered shortly before starting the scan and the patient is instructed on breath holding for a few seconds while the scan is taken (actual scan time is less than 30 seconds, while the entire process may take less than a half-hour).

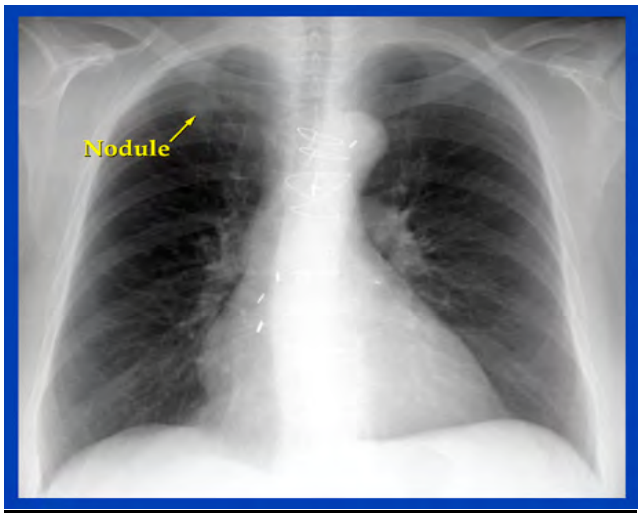
Some common side effects of injected dye include a feeling of warmth while the injection is in process. Minor itching and hives are not uncommon and can be treated with medications. More serious side effects from injected dye are discussed below. Ingested contrast may not taste palatable and rectal contrast may cause minor abdominal discomfort. After an uncomplicated study is completed, the patient can return to normal baseline activities and usually no special instructions are necessary.

Common Uses

- Primary comprehensive diagnostic imaging test for evaluation of several respiratory symptoms and disease states.
- Problem-solving tool for further evaluation of potentially-abnormal findings on a CXR.
- Diagnosis and staging of cancer: both for primary lung tumors as well as for tumor that has spread to the lungs from elsewhere within the body.
- Planning radiation therapy and assessing treatment response.
- Detection of disease of the blood vessels and circulation.

Role of Chest CT in the Diagnosis of Respiratory Diseases

The chest CT is a powerful tool to evaluate for diseases in the lung. It can be used to determine if there is spread of a malignant tumor to the lungs from elsewhere in the body (like breast cancer, abdominal cancers, or female genital tract cancers). Cancerous growths within the lungs often start off as small nodules (Figure 4-2.1b), which can only be detected with a CT, and not be visible on a CXR. In addition, a CT may detect presence of enlarged lymph nodes, which may harbor tumor cells. A CT may help in staging of tumor and evaluate for tumor progression or recurrence after surgery, chemotherapy or radiation treatment. A CT scan is commonly-used to detect non-cancerous lung diseases as well, such as pulmonary fibrosis (Figure 4-2.3).



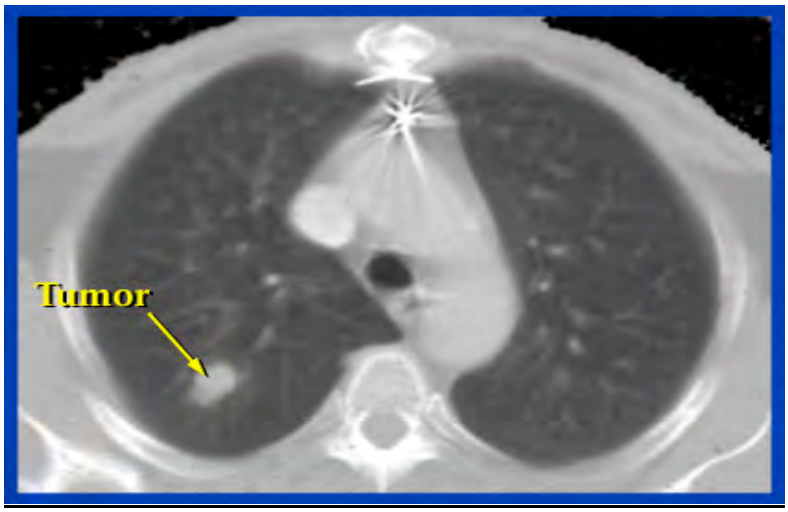


Figure 4-2.1b: Chest x-ray and CT scan showing a nodule (less than three centimeters in diameter) without spread to adjacent structures.

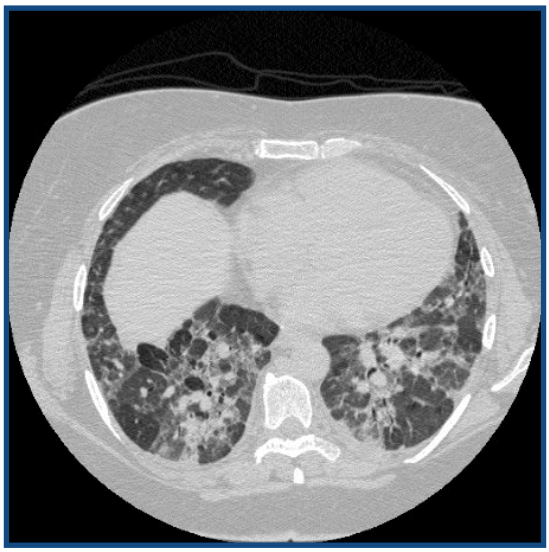


Figure 4-2.3: CT showing pulmonary fibrosis with reticular linear shadows, honeycombing and traction bronchiectasis.

CT findings may be non-specific and require further testing. Additional imaging tests such as PET scanning (see below) or obtaining a biopsy (tissue sample) from the abnormal area within the lungs for microscopic analysis can be performed. A CT can be used in either instance to improve diagnostic yield. CT images can be electronically combined with PET images to generate "fusion" images. Such PET-CT scans help to provide anatomical and functional information at the same time (as an example, CT may localize a rounded lung nodule and the PET scan may show the nodule to have no metabolic activity, thus both in combination would help characterize the lesion as potentially-benign, non-cancerous in nature). CT scanning can be used to help guide biopsy needles with precision to abnormal areas within lungs, thereby allowing sampling of tissue for microscopic analysis.

A Chest CT can also demonstrate diseases such as bacterial pneumonia (Figure 4-2.4) and tuberculosis. It can be used to detect complications of infections such as pleural effusion (fluid around the lung), lung abscess (pus forming cavity within the lungs), bronchiectasis (abnormal dilatation of airways) and chronic scarring.

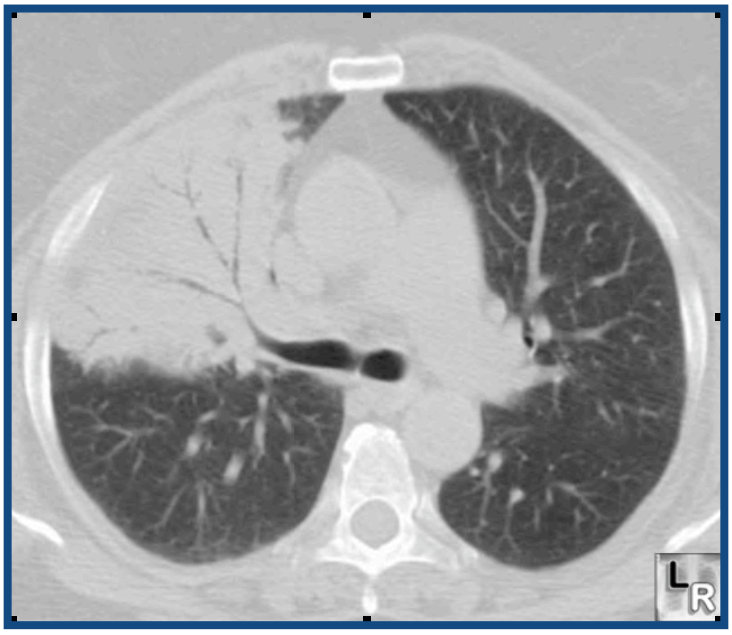


Figure 4-2.4: Chest CT showing infiltrate with air bronchogram consistent with pneumonia.

An important role of a CT scan in the lungs is the diagnosis of air-trapping and diffuse lung disease (Figure 4-2.5). Air trapping is a non-specific sign of small airway disease and can be seen in asthma, bronchitis, emphysema, or bronchiolitis obliterans. This is manifest on a CT scan (particularly on scanning done at the end of expiration) as areas of relative lucency, which do not show a decrease in volume with expiration. Air trapping was the most common radiological sign of "WTC Cough" (a disease term coined after several fire fighters were affected with the disease while engaging in rescue and recovery operations after the September 11, 2001 attacks on the World Trade Center), which correlated with other markers of airway hyperreactivity (pulmonary function tests and chemical challenge tests). Other findings include a mosaic pattern of lung attenuation and non-specific bronchial wall thickening.

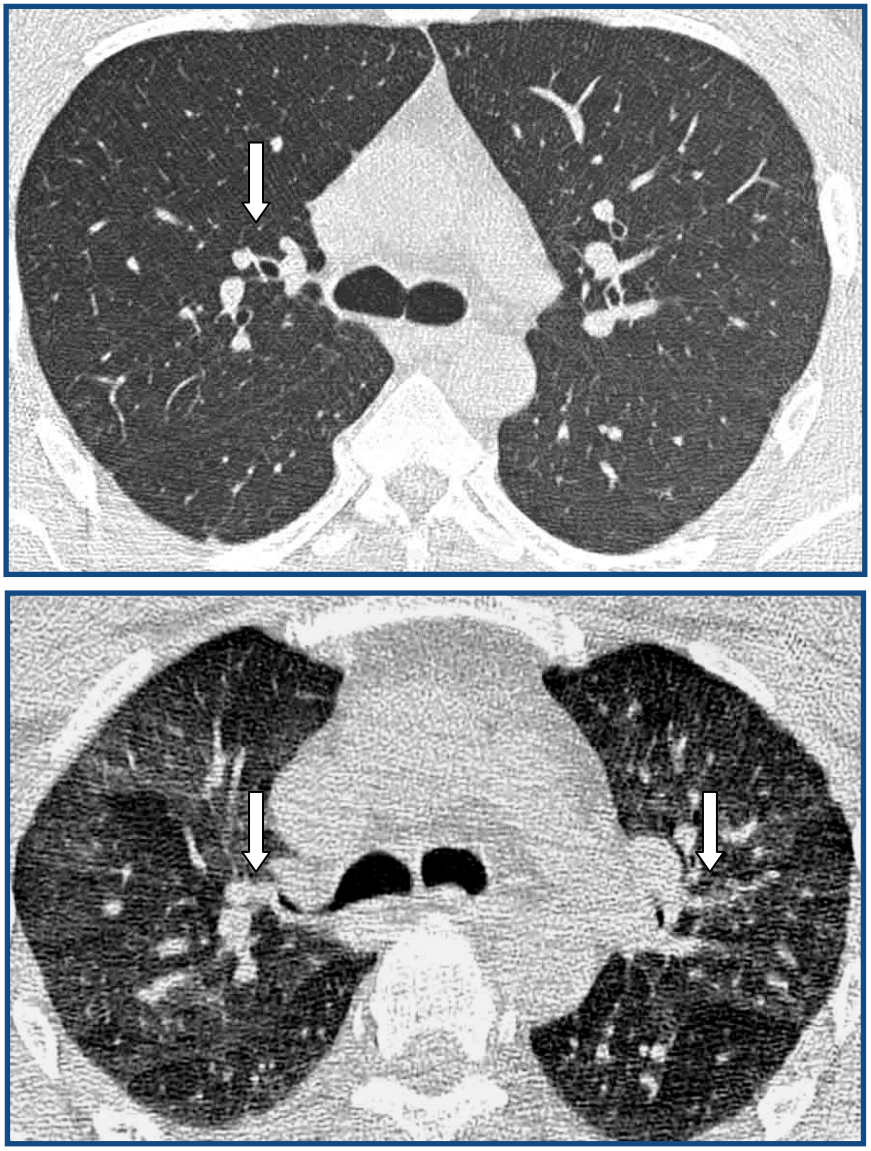


Figure 4-2.5: Upper panel shows CT scan taken during inspiration with bronchial thickening (white arrow). Bottom Panel shows CT scan taken during expiration with air-trapping (white arrow).

Presence of discrete small nodules along small airways in a "budding tree" pattern may suggest acute or active inflammatory bronchitis. Treatment with antibiotics can often lead to resolution. Bronchiolitis obliterans can go unrecognized (in the absence of chest CT or lung biopsy) or can be mislabeled as asthma. In the absence of appropriate therapy, bronchiolitis obliterans can progress and lead to disability or death.

Diffuse lung diseases include several forms of interstitial lung disease which cause fibrosis or inflammation of the lungs leading to progressive shortness of breath and impaired oxygen-carrying capacity. Disease progression may lead to chronic respiratory failure (end stage lungs). Some forms of the disease may not be amenable to any form of treatment except for lung transplantation. While it is not feasible to describe the chest CT findings of all forms of interstitial lung disease, some are particularly relevant to fire fighters and are highlighted below.

Sarcoidosis is a common chronic granulomatous disease, which is of uncertain cause. It affects lungs and other organ systems. Sarcoidosis and/or Sarcoid-Like-Granulomatous-Pulmonary Disease (SLGPD) have been detected with a higher incidence in fire fighters who were exposed to the dust and debris that were released into the surrounding environment after the collapse of the WTC towers. On imaging, the disease within the lungs has four characteristic stages. Patients may present at any stage and the stage may not correlate with symptoms or pulmonary function tests. Stage I is symmetric enlargement of lymph nodes within the both sides of the chest. Stage II shows both involvement of lymph nodes and lung tissue (Figure 4-2.6). The latter is present as reticular and nodular opacities, hazy ground glass opacities and ring-like cystic opacities which are predominantly seen along the airways and vessels (peribronchovascular bundles). Stage III no longer shows lymph node enlargement on imaging but continues to show lung tissue involvement. With shrinking of the lymph nodes, they can occasionally show a characteristic pattern of calcification. Stage IV can show lung cavities and fibrosis. Most patients do not progress and many resolve spontaneously without treatment. For those with progression or significant functional impairment, corticosteroids and/or other anti-inflammatory medications are very useful (see separate chapter on Sarcoidosis for further details).

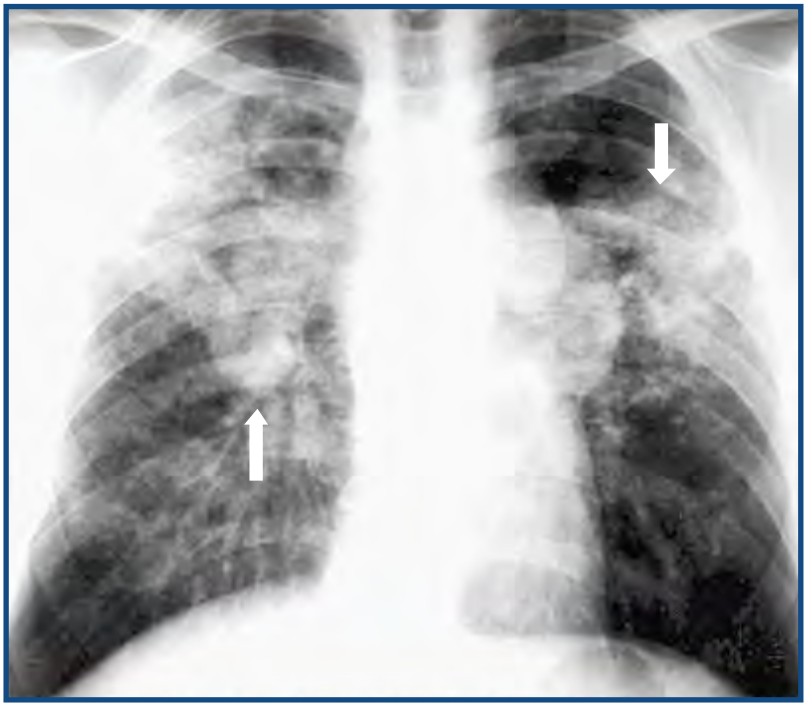


Figure 4-2.6: Chest radiograph showing Stage II Sarcoidosis with lymph node (arrow pointing up) and lung tissue involvement (arrow pointing down).

Several rarer forms of diffuse lung disease have been reported in fire fighters including case reports of chronic eosinophilic pneumonias with its own characteristic CT findings of patchy peripheral pulmonary opacities and pleural effusions which resolved after treatment with steroids.

Other chronic fibrotic lung diseases with particular importance for fire fighters include idiopathic pulmonary fibrosis, which is characterized by chronic progressive scarring of predominantly both lower lobes of lungs, which start at the periphery of the lung surfaces. On CT imaging, this is characterized by diffuse architectural distortion, ground glass opacities, reticular and nodular opacities, cystic lesions (honey combing) and traction bronchiectasis or any combination of these findings, but without lymph node involvement (refer to Figure 4-2.3). No proven medical treatment exists and currently when progressive, lung transplantation is the only therapeutic option.

Asbestos is no longer used in the United State but can be released from damaged insulation found in older houses and commercial buildings during renovation, fires and overhaul. Asbestos exposure may lead to a spectrum of disease ranging from pleural effusions, pleural plaques, pleural calcifications and fibrosis (usually 10 to 50 years after exposure). Chronic asbestos exposure (more so in combination with cigarette smoking) increases risk of lung cancer. Finally, chronic asbestos exposure may lead to malignant mesothelioma (usually 20 to 40 years after initial exposure to asbestos), a cancer affecting the outer lining of the lungs (pleura) and the inner lining of the abdomen (peritoneum). CT scanning of the lungs very well depicts all of these changes.

CT Angiography is a valuable tool used to diagnose diseases of blood vessels and circulation. This test involves injection of iodine-containing dye (contrast media) intravenously into the arm of a patient followed by appropriately timing the images taken with the help of a CT scanner to opacify the blood vessel of interest. The captured data can then be used to reconstruct thin sections with detail, which can help to diagnose disease within the arteries (pulmonary arteries, aorta) or the veins (systemic or pulmonary veins). The injected dye helps delineate blood vessels better by opacifying the vessels selectively and thus serving as effective contrast from non-vascular structures which are not opacified. Diseases such as clot formation within the pulmonary arteries (pulmonary embolism) and abnormalities of the aorta including tears (dissections) and dilatations (aneurysms) which can rupture, can be diagnosed effectively by this technique.

Benefits

- Painless, fast and easy to perform, making it ideal for use in medical emergencies.
- Able to accurately detect disease within the lungs when a CXR is non-diagnostic.
- Able to image bone and soft tissues including lungs simultaneously. Hence, a CT scan done for one indication may help diagnose unsuspected disease elsewhere.
- Can be fused with functional imaging in an attempt to differentiate benign from malignant cancerous disease.
- Can be used to guide needle biopsies (see section below).
- In many conditions, a CT scan eliminates the need for exploratory surgery by giving a definite diagnosis. In surgical cases, it often helps in pre-operative planning.

Risks

Risks from the procedure include those associated with radiation exposure and risks from injected dye (when contrast material is used in a study).

Effective radiation dose from a CT chest is roughly equal to that received by an average person from background radiation in three years (5mSv). This carries a slight increased risk of cancer, which needs to be weighed against the benefits of obtaining a diagnosis. Pregnant women have an increased risk to themselves and to the fetus from radiation exposure. Women referred for CT scanning should inform their physician or technologist if there is a possibility that they are pregnant.

Risks from the injected contrast material include an allergic-like reaction to dye and damage to kidney functions. Allergic reactions, like minor rashes occur with some frequency, while serious (anaphylactoid) reactions are exceedingly rare. A history of asthma or COPD confers an increased risk for a flare of these diseases.

When the risk-benefit ratio supports the use of contrast, patients can be pre-medicated with steroids and other medications before the study.

Risk of contrast induced kidney damage is more common in patients who have borderline or pre-existing impaired renal function. Certain medications and disease states predispose to development of contrast induced kidney disease and need to be stopped or the dosages modified after consulting a physician. Ample hydration and pre-medication with kidney protective agents has shown some value in preventing severe renal damage from injected radio contrast.

Limitations

- Very obese patients may not fit into the CT scanner.
- MRI may be superior to CT scan for diagnosis of vascular conditions (especially when injection of iodinated contrast material is contraindicated). Chest CT is superior to MRI for diagnosis of lung conditions (such as nodules, interstitial lung disease, and emphysema).

Future Advances

Advancement in detector technology has led to the development of new multi-slice CT scanners which allow thinner slice acquisition in a shorter time resulting in greater clarity of image. This is particularly useful in imaging of children and very sick, medically-unstable patients.

ROLE OF SPECIAL IMAGING MODALITIES: PET & MRI SCANS

PET Scan

PET is an abbreviation for Positron Emission Tomography. PET is a powerful, non-invasive imaging modality that focuses on biochemical changes that occur in diseased tissue like cancer, sarcoidosis, tuberculosis and certain infections. The rapid cell growth that occurs in tumor and infection leads to a higher

metabolic activity and more glucose consumption than in normal healthy tissue. PET scanners detects this increased metabolic activity as “hotspots” that light up on the image (Figure 4-2.7).

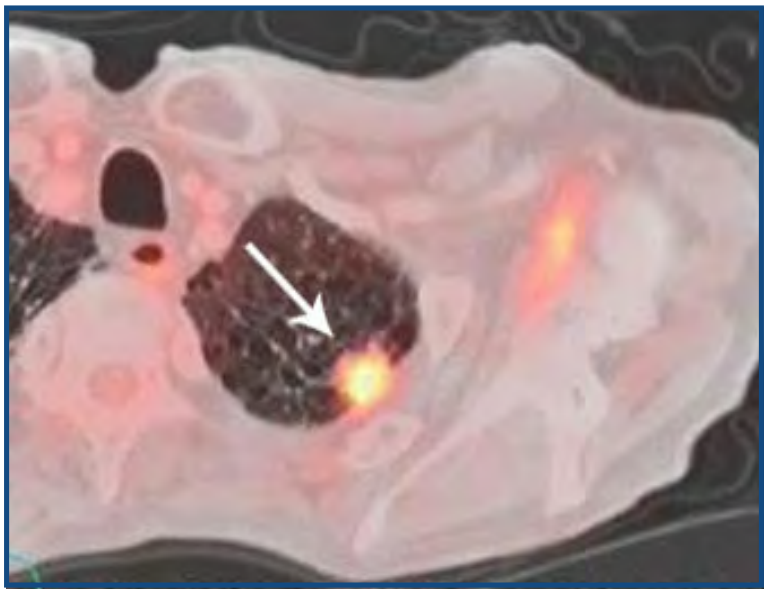


Figure 4-2.7: PET and CT fusion image showing hot area (arrow) is nodule subsequently proven to be a cancer.

PET scans are performed in the nuclear medicine laboratory. The imaging study involves injection of a radioactive glucose into the blood stream. The radioactive tracer accumulates in the organ system or body tissues which are most metabolically active. In these tissues, the radiotracer releases small amounts of energy in the form of gamma rays. These rays are then detected by a special camera, which converts the signal into computer-processed images of that part of the human body.

PET scanning can be combined with low dose CT scanning to form “fusion” images with a single machine. The two techniques complement one another. While a CT shows anatomical structures with detail, PET shows increased metabolic and biochemical activity in the affected regions. For example, a small nodule in the lung, which is barely noted on a plain CXR, is accurately detected and localized on CT scanning, and the PET study done on the same subject may highlight increased glucose consumption within that nodule as a “hot spot.” The fusion PET-CT images reveal the "hot spot" to be localized within the nodule, thereby suggesting tumor or infection as possible causes.

PET may help guide further management and treatment planning. The study may determine that a suspicious nodule is metabolically inactive and may be benign. A metabolically active lesion may be either due to infection or cancer and a decision on whether to biopsy the nodule can then be made. PET scanning is helpful in determining spread of tumor in distant organs and lymph nodes and thus in tumor staging. Similarly, response to treatment of cancer may be well depicted by performing a post treatment follow-up PET scan that may reveal residual or recurrent tumor.

Several caveats are important to note. First, certain benign conditions like active infection or inflammation (ex., sarcoidosis) may be PET positive,

while certain slow growing tumors (ex. Bronchoalveolar lung cancer) may not demonstrate PET positivity, owing to their relatively-slow metabolic rate. Second, PET scans are not accurate in their characterization of nodules less than eight millimeters in diameter. Third, PET scans are not accurate in their characterization of tumor spread to neurologic tissues (ex. brain and spinal cord). Of course, the technology continually improves and newer generation PET scans will hopefully overcome these diagnostic barriers. Finally, the use of PET radioactive tracers involves exposure to ionizing radiation (like gamma rays) with low risk for radiation-induced side effects. Lactating women must be instructed to stop breast feeding for 24 hours after the procedure.

MRI Scan

MRI is an abbreviation for Magnetic Resonance Imaging. It is a non-invasive imaging modality which uses a powerful magnetic field and radio waves to generate signals from different body parts, which are then processed by computer to generate detailed images of the human body. An MRI images of the chest provide increased soft tissue contrast. This is particularly useful in imaging the beating heart and the great blood vessels in the chest. Use of an MRI within the lungs is limited because air within the lungs is not well imaged with an MRI. The role of an MRI in the context of lung disease lies predominantly in the assessment of lung cancer when it can depict the relationship of the cancer to adjacent nerves, blood vessels and chest wall. Hence, an MRI for lung cancer is not useful in characterizing nodules but is of value if there are questions about metastatic spread to vessels, heart, or chest wall.

An MRI scan has some major drawbacks. The study is contraindicated in patients with cardiac pacemakers and defibrillators. Moreover, the limited availability of an MRI as compared to a CT, relative length of the scan time making it unacceptable for unstable patients and claustrophobia in selected patient groups may limit the role of this tool.

IMAGE GUIDED TISSUE SAMPLING

Imaging of lungs often leads to detection of abnormal findings such as nodules or masses. It is sometimes difficult to ascertain whether they are benign (such as a result of infection or scar) or malignant (cancerous). Image-guided needle biopsy or aspiration of the nodule or mass is a procedure by which a narrow-gauge, hollow needle is introduced using imaging such as a CT, fluoroscopy or ultrasonography to guide the path of the needle into the abnormality. A sample (not the entire nodule) is removed and examined directly under a microscope to look for signs of cancer or other diseases.

Preparatory Instructions

Patients are instructed to fast for at least six to eight hours before the procedure. They may, however, take certain medications with sips of water. It is important to inform the radiologist of all medications. Certain medications, like insulin, need dose adjustments, because of overnight fasting, while others like blood thinners may have to be stopped for days prior to the procedure. Any history of allergy and prior complication to anesthesia needs to be recognized. As with

all procedures that involve radiation exposure, women need to inform their physicians and radiologist if there is a possibility that they are pregnant. Most of these procedures are performed on an outpatient basis. Although all patients are given local anesthetic injections around the skin puncture site, some may need additional dose of intravenous sedation to alleviate anxiety and fear. Hence, it is important that all patients are accompanied by family or friend(s) who can accompany the patient or drive them home after the procedure.

Nature of the Procedure

Needles

A biopsy needle is a hollow needle, which varies in length (can be several inches in length) and in diameter, but is usually no wider than a paper clip. Two different types of needles may be used depending on the type of sample being obtained. One is a fine needle (thinner than a blood drawing needle) and the other is a core needle (slightly thicker and contains an inner needle attached to a spring device).

Image Guidance

Image guidance is usually provided by CT or fluoroscopy and rarely by ultrasonography. CT scanner details have been provided earlier. The fluoroscopy equipment consists of a radiographic table, x-ray tube and a monitor with screen. Real time video or still images are obtained. Ultrasound scanners use high frequency sound waves emitted from devices called transducers that are used to scan the body. These sound waves are reflected off different tissues within the human body and are captured by the transducer as they echo. A computer console then integrates these echo signals to process an image of the body parts, which are displayed on a video display screen. Several factors like the amplitude (strength), frequency and time it takes for the sound waves to return from the different depths of the tissues, influence the nature of the image. Ultrasound has a role in localizing and draining fluid collections in the pleural space. This is because of the ability of the sound waves to propagate through fluid. Fluid inside the pleural space appears dark and casts fewer echoes than air or solid tissues within the lungs. Ultrasound does not produce a radiation exposure.

Procedure

Using imaging guidance, the physician inserts the needle through the skin and into the abnormal tissue and collects samples, which are analyzed in the pathology laboratory for diseases. The process is usually performed on an outpatient basis. Written informed consent is obtained after explaining all probable risks, complications, and alternatives to the patient. An intravenous line is inserted into one of the veins of the hand or elbow. This is helpful in two ways. Some patients may need mild sedation before the procedure. More importantly, in case of any complications during the procedure, the venous access may save time administering medications into the veins. The patient may either be positioned lying down (usually the case) or rarely be sitting down (if procedure is performed under fluoroscopy or ultrasound). Sterile antiseptic precautions are obtained. Adequate local anesthetic is injected at the site of

the insertion of needle after preliminary imaging has localized the exact site of needle insertion. The patient is given proper breathing instructions and asked to hold the breath for a few seconds while the needle is inserted. The positioning of the needle may require multiple images to be taken to help guide the needle into the appropriate location. Once the lesion is reached, the radiologist aspirates samples from the lesion(s) and a cytopathologist technician prepares a microscopic slide of the sample in order to examine the material under microscope. If the sample seen under microscopy is not considered adequate to make a diagnosis, additional tissue can be collected.

After the procedure, pressure is applied to the injection site to control any local bleeding. The injection site is covered by sterile dressing and the patient is monitored usually in the radiology observation area for a few hours. A follow-up CXR is usually performed to rule out complications like lung collapse due to air leak (pneumothorax) or collection of blood within the chest (hematoma or hemothorax). After reviewing the follow up CXR and confirming patient stability, the patient is discharged home with instructions. Physical exertion like lifting heavy weights, running, and contact sports, as well as air travel, are prohibited for 24 hours after the procedure. Pain medications may be taken as instructed by the patient's physician. Patients are made aware that they should report to the emergency room if they experience increased shortness of breath, sharp chest pain, rapid pulse or excessive hemoptysis (coughing blood). Slight streaks of blood mixed with cough are not uncommon after the procedure and should not be a cause for alarm.

Benefits

- Reliable and relatively safe (in experienced hands), quicker and less invasive way of differentiating a benign (treated non surgically) from malignant lung lesion or nodule (treated by surgery, chemotherapy or radiation).
- Done on outpatient basis, with faster recovery time than open surgical biopsy.

Risks

- As high as a 25% risk of collapsed lung due to air leak (pneumothorax). This is usually self-limiting and treated with oxygen while the patient is positioned with the affected lung in the dependant position and monitoring of the patient's vital signs and CXR(s) over a period of time. Rarely, the air leak may be severe enough to require a chest tube insertion and hospital admission for several days. Warning signs include shortness of breath, cough, sharp chest and shoulder pain increased on breathing. In making the decision as to whether biopsy should be obtained by CT guided needle or surgery, it should be noted all surgical patients leave the operating room with chest tubes.
- Risk of bleeding: minor bleeding from the site is not uncommon as is minor coughing up of blood from the biopsied lung. Serious bleeding is rare.
- Infection at the biopsy site is rare.

Limitations

- The material obtained from a needle biopsy may not be sufficient to make a diagnosis.
- Needle may not be in an active site of lesion and thereby give a false negative result (false reassurance). This possibility must be carefully considered when the diagnosis appears to be non-cancerous.
- Small nodules less than one centimeter are difficult to diagnose on needle biopsy.
- Certain diseases like cystic lungs, emphysema, severe heart failure, bleeding disorders and patients with poor oxygenation may be contraindications for this procedure.

IMAGING OF PULMONARY ARTERIES AND VEINS

The pulmonary arteries carry de-oxygenated blood from the right ventricle of the heart to the lungs for oxygenation. The oxygenated blood is then returned by the pulmonary veins into the left atrium of the heart. The main pulmonary artery starts as a trunk approximately two inches long and slightly over one inch wide that arises from the right ventricle outflow tract. It then branches into right and left pulmonary arteries, which further divide to supply the corresponding lung.

The pulmonary arteries are involved in several disease processes. A pulmonary embolism (PE) is a sudden blockage of one or more pulmonary arteries, caused by a blood clot, which forms, usually in the leg or pelvic veins.

In fire fighters, probably the most common cause for a blood clot is leg trauma with subsequent prolonged inactivity (casting and or bed rest). See the separate chapter on pulmonary embolism for further details. Once the blood clot goes to the lung, the patient experiences sudden shortness of breath, chest pain and depending on the relative size of the clot, sudden death, if not promptly treated. Another vascular disease is pulmonary hypertension which is a more insidious disease of the pulmonary arteries, which occurs as a consequence of several chronic lung conditions including interstitial lung diseases and severe emphysema. It can also be caused by severe sleep apnea and certain cardiac conditions. It results in poor exercise tolerance and may lead to a progressive, fatal course.

Pulmonary Angiography

The classic test for imaging pulmonary arteries is pulmonary angiography. It involves injection of iodinated dye into the circulation with subsequent direct x-ray visualization (fluoroscopy) of the lungs. The test can be done in either invasively or in a non-invasive manner using CT scanning.

Conventional (Catheter) Pulmonary Angiography

Conventional pulmonary angiography is invasive because a catheter is introduced into the right heart through one of the thigh veins. Contrast or dye is then injected through this catheter into the pulmonary artery. Catheter pulmonary angiography is now infrequently performed as a CT pulmonary angiography, a non-invasive test has gained wide acceptance.

CT Pulmonary Angiography (CTPA)

CTPA is a non-invasive imaging test for visualizing the pulmonary arteries using CT with iodinated contrast. The contrast is injected through a small vein in the arm or leg. The scanning is optimally timed such that the contrast is within the pulmonary arteries at the time that the image is acquired. The scanning time is usually about five seconds and the entire time within the scanner is approximately five minutes. CTPA demonstrates normal pulmonary arteries as white (because these are opacified by radio contrast dye). A blood clot (pulmonary embolism) would show up as dark (filling defect) within the blood vessels (Figure 4-2.8). The size of the vessels can be accurately measured to see if these are dilated, which can be a sign of pulmonary hypertension.

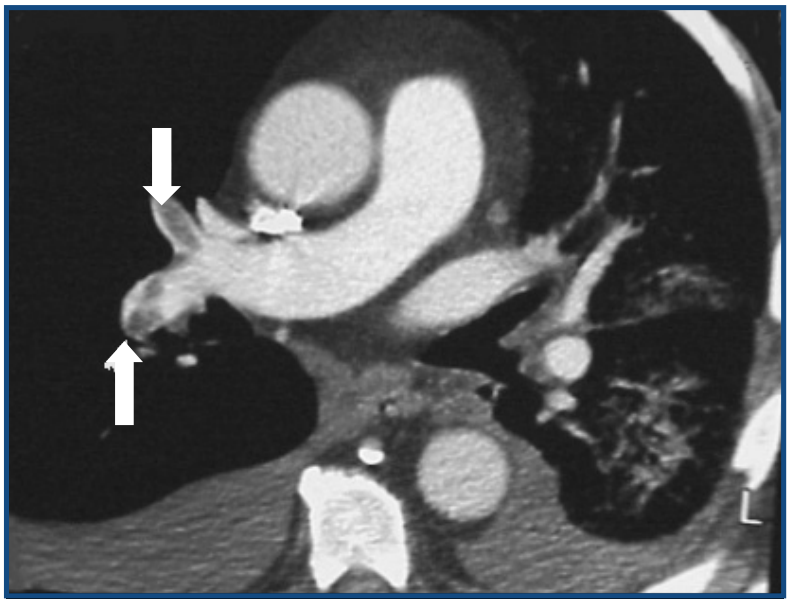


Figure 4-2.8: Chest CT Angiogram showing pulmonary artery emboli (blood clots) appearing as intravascular filling defects (arrows) in this contrast (dye) study.

Benefits

The advantages of CTPA are its non-invasive nature, fast speed, wide acceptability and availability for patients. CTPA can also depict disease elsewhere within the lungs or adjacent structures which can explain the symptoms. CTPA is a highly-effective and widely-used test for diagnosing PE and has the ability to identify PE in small branches of pulmonary arteries.

Limitations

The disadvantage of CTPA is the difficulty in detecting small peripheral blood clots. As technology improves this becomes less of a limitation as each newer generation CT scan has greater resolution.

Risks

See risks of CT with contrast (iodinated dye) (above).

Ventilation Perfusion Scintigraphy (VQ Scanning)

VQ scan is another non-invasive medical imaging test used to diagnose PE. This test is one of several nuclear imaging techniques used in medicine. It is less widely used owing to wider availability of CT technology. The test uses radioactive materials in relatively low doses, which are inhaled and injected into the human body. While passing through the human body, these radioactive materials emit certain rays such as gamma rays which can be detected by special cameras (gamma cameras) to create a computer generated image of that part of the body.

The test involves two phases, namely ventilation and perfusion phases. These two phases evaluate how well air and blood are able to circulate through the bronchial airways and the pulmonary circulation, respectively. The ventilation phase of the scan involves inhalation of a gaseous radionuclide like xenon or technetium DTPA through a mask or mouthpiece. Impaired uptake of these inhaled radiotracers due to airway obstruction or pneumonia leads to image voids from the corresponding lung on the ventilation scan. The perfusion phase of the scan involves injection of a radionuclide tracer (usually radioactive technetium tagged to macro aggregated albumin) into one of the arm veins. The tracer circulates through the lungs via the blood stream.

Blood clots within pulmonary arteries result in impaired circulation of the radionuclide in that lung or part of the lung without hampering ventilation or airflow. This is reflected in the perfusion scan classically as wedge-shaped area(s) of decreased uptake of radio tracer in that part of lung which has a normal ventilation image and is described as a mismatched defect.

In addition to using VQ scans for the diagnosis of PE, VQ scans are sometimes used for :

- Determining lung performance before and after lung surgery
- Determining extent of smoke inhalation injury (typically in a research setting).

Benefits

- Useful in patients whose CXRs are normal and in those with allergy to iodinated contrast or in renal failure where CTPA would be contraindicated.
- Lower radiation dose than CTPA
- Can detect smaller more peripheral pulmonary blood clots than can be done by current CTPA.

Limitations

The disadvantage of VQ scans is that a large number of the scans yield intermediate or non-diagnostic results. The scan is only useful if the result is negative or positive (high probability). Matched defects (abnormal ventilation and perfusion in the same area of the lung) are non-diagnostic because although they are mostly often due to pneumonia or obstructive airways diseases, they can less commonly be due to PE. Clinical judgment then determines whether additional testing is needed.

Risks

- Although the total amount of radiation exposure is low, it is not negligible.
- Lactating mothers must be warned to stop breast-feeding for 24 hours after the procedure.

Role of Ultrasonography in Imaging of Pulmonary Embolism

Most blood clots, which cause PE, arise from the lower limb veins in the thighs. Ultrasonography of the veins of the thigh and calves (Venous Doppler) can be performed to detect blood clot in these veins. A positive venous doppler test along with presence of a blood test call D-Dimer (a surrogate marker for blood clots), greatly increases the patient's probability of having a PE. These tests in isolation or when considered together, can dictate treatment with anti-clot medications without the need for further testing such as CTPA or VQ scans. This is particularly useful in cases like pregnancy where confirmatory tests such as CTPA or VQ scanning should be avoided when possible due to radiation risk to the fetus.

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Chapter 4-3
The Solitary Pulmonary Nodule

By Dr. David Ost, MD

An isolated nodule in the lung, often called a solitary pulmonary nodule, has long challenged physicians. At the heart of the dilemma, the question remains: "Is it cancer?" Bronchogenic carcinoma, a form of lung cancer, is the most common cancer (malignancy) found in solitary pulmonary nodules, and it remains the leading cause of cancer death in the United States. When faced with a solitary pulmonary nodule, the physician and the patient usually have one of three choices:

1. Observe it with serial chest computed tomography (CT) scans.
2. Perform additional diagnostic tests (imaging and/or a biopsy).
3. Remove it surgically.

The proper choice depends on radiographic appearance, assessment of probabilities based on epidemiology, assessment of surgical risk, and patient preferences. Surgical resection of an early solitary malignant lesion still represents the best chance for cure. On the other hand, unnecessary resection of benign nodules exposes patients to the morbidity and mortality of a surgical procedure. The aim of this chapter is to review what we know about the solitary pulmonary nodule in order to formulate a systematic approach to thinking about this common and often controversial problem. The goal will be to arrive at a solution that will facilitate prompt identification of malignant lesions so that they can be brought to surgery while avoiding surgery in patients with benign nodules. Finally, we will review the risk factors that are of particular relevance to fire fighters and related personnel with respect to solitary pulmonary nodules.

DEFINITION

A solitary pulmonary nodule is defined as a single discrete pulmonary opacity that is surrounded by normal lung tissue that is not associated with enlargement of the lymph nodes (adenopathy) or collapsed lung tissue (atelectasis). Previously there was controversy as to what constituted the upper size limit for defining a solitary pulmonary nodule. Some early series included lesions up to six centimeters in size. However, it is now recognized that lesions larger than three centimeters are almost always malignant, so current convention is that solitary pulmonary nodules must be three centimeters or less in diameter. Larger lesions should be referred to as lung masses and should be managed with the understanding that they are most likely cancerous. Prompt diagnosis and surgical resection if possible is usually advisable.

INCIDENCE AND PREVALENCE

The frequency with which a solitary pulmonary nodule is identified on chest x-ray is about one to two per thousand chest radiographs.[1] Most of these are clinically silent, and about 90% are noted as an incidental finding on radiographic examination. The percentage of these nodules that are cancerous (prevalence) varies widely, depending on the patient population; thus, many case series may not be directly comparable. Surgical series in the era before a CT, including both calcified and noncalcified nodules, reported an overall prevalence of cancer of 10 - 68%.

In younger patients the probability of cancer being present in a given nodule is less. In a Veterans Administration Armed Forces Cooperative Study in 1963 there was an overall 35% malignancy rate. This group included a significant number of young military recruits, and nearly half were under the age 50.[2] Of those over the age of 50, a 56% malignancy rate was noted, with a 30% incidence of benign granulomas. Of those under the age of 35, only three patients had a malignancy, only one of which was a primary lung carcinoma.

Today, a CT is used to screen out benign-appearing calcified nodules. Densely-calcified nodules are usually benign (discussed below). If we eliminate the densely calcified lesions, the probability of cancer in the remaining non-calcified lesions is significantly higher: 56 - 100% in various studies.[1, 3]

Importantly, most prior series were based on patients who had been referred to surgery for the lung nodule. When nodules are detected incidentally while looking for other problems, or as part of a lung cancer screening program, the probability of cancer is much less. In these instances, if the lesion is small (less than eight millimeters) then the overall prevalence of malignancy is under five percent.

Geographic region also matters. In some areas of the world, certain diseases are very common (endemic). For example, in the southwestern United States, a fungal infection of the lung, coccidioidomycosis, is quite common. This is usually a self-limited infection, also known as Valley fever. However, it can often leave a small scar on the lung, which appears as a solitary pulmonary nodule. Nodules detected in patients from this area can be expected to have a lower probability of malignancy, since many of the lung nodules seen are actually due to old infection. Other infectious diseases, such as tuberculosis (TB) and histoplasmosis, can cause old scars in the lung that appear as solitary nodules just like coccidioidomycosis. TB is common in some areas of the developing world. Histoplasmosis is common through the midwestern United States. As an example, in an Air Force Medical Center study from Illinois of 137 patients, only 22 (16%) had a malignancy. Granulomas were diagnosed in 103 patients (75%); 53 of them were attributable to histoplasmosis endemic to the area. Most of these patients (77%) were under age 45, and no malignant nodules were diagnosed in patients less than 35 years of age.

MALIGNANT SOLITARY PULMONARY NODULES

Risk factors for malignancy have been identified from studies of large series of solitary pulmonary nodules and include patient age, smoking history, nodule size, and prior history of cancer.

Age is one of the most consistent risk factors. Cancer is very rarely found in patients under the age of 35.[2, 4, 5] In a series of 370 indeterminate solitary pulmonary nodules, the incidence of malignancy increased from 63% for patients between the ages of 45 and 54 to 74% for ages between 54 and 64 and continued to rise with age to 96% for those above the age of 75.[3]

Smoking is closely correlated with the development of lung cancer, particularly squamous and small cell carcinoma. The Surgeon General's report of 1964 and subsequent studies have demonstrated that the risk of lung cancer increases with the duration of smoking and the number of cigarettes smoked. Average smokers have about a 10-fold risk, and heavy smokers a 20-fold risk of developing lung cancer when compared to nonsmokers. Smoking is responsible for about 85% of the cases of lung cancer. Cessation of smoking will reduce this risk after 10 to 20 years, but it now appears that former smokers have a slightly higher risk of cancer throughout their lifetimes. Overall, smoking avoidance or cessation is the single best preventive measure against lung cancer.

Nodule size is closely correlated to risk of cancer, with larger nodules having a higher probability of cancer than smaller ones. Nodules larger than three centimeters will be cancerous about 80 to 99% of the time, while those under two centimeters in size will be cancerous about 20 t 66% of the time.

A history of current or prior cancer in an organ other than the lung greatly increases the probability that a lung nodule is cancerous. Depending on the study, 33- 95% of such nodules are cancerous. Most of these represent spread of cancer from the other organ to the lung. This spread of cancer from one organ to another is called metastasis. So lung nodules in this case may represent metastasis of a previously-diagnosed cancer to the lung. The most common types of cancer that spread to the lung and cause nodules are cancers of the colon, breast, kidney, head and neck tumors, sarcoma, and melanoma. Because of the high likelihood of cancer, a nodule in a patient with an established diagnosis of cancer should be treated differently from other solitary nodules. If there is no other metastatic spread (cancer outside of the lung), one should consider proceeding directly to biopsy of the nodule. Even in the presence of a known cancer, some of these nodules may represent a second primary pulmonary malignancy. A second primary means that the patient has two cancers- one in the other organ system and a separate lung cancer. This is different than having a cancer in another organ which has spread to the lung (metastatic to the lung). Special microscopic techniques (immunohistochemistry) can be used to distinguish between these two possibilities. In either case, if cancer is demonstrated and there is no evidence of spread of the cancer outside of the lung, then resection of the nodule should be considered.

BENIGN SOLITARY PULMONARY NODULES

Non-cancerous (benign) solitary pulmonary nodules are more common in the young and in nonsmokers. They include both infectious and noninfectious granulomas, benign tumors such as hamartomas, vascular lesions, and rare miscellaneous conditions. Benign tumors are those that usually are not life threatening and do not spread to other organs (metastasize).

Hamartomas are the most common benign tumors presenting as solitary pulmonary nodules. They are believed to be developmental malformations composed mainly of cartilage, fibromyxoid stroma (connective tissue), and adipose tissue (fat). A review of six studies of resected solitary pulmonary nodules since 1974 shows five percent were histologically proven hamartomas. In a series of 215 hamartomas resected at the Mayo Clinic, the peak incidence was in the seventh decade of life; male-to-female ratio was 1:1; and the average size was one and one half centimers, although some were as big as six centimeters. Most hamartomas were asymptomatic (97%), and 17% were noted to grow slowly on serial radiographic examination. Hamartomas may be identified radiographically by a pattern of "popcorn" calcification, which is often intermixed with areas of low attenuation on a CT scan representing fat deposits within the nodule. A CT appearance will be diagnostic in about 50% of hamartomas.

Infectious granulomas make up more than 90% of all benign nodules. They arise as a result of healing after infection from a variety of organisms. The offending agents will vary, depending on geographic location. Among the most common causes are histoplasmosis, coccidioidomycosis, and tuberculosis. Other, less common causes are dirofilariasis (dog heartworm), mycetoma, echinococcal cyst, and ascariasis. A history of exposure is important in establishing a possible infectious origin. Clues such as prior travel history, places of residence, occupation, and pets may be invaluable in some instances.

Noninfectious granulomas sometimes occur as solitary pulmonary nodules in systemic diseases such as sarcoidosis. Sarcoidosis is an inflammatory condition which actually affects multiple organs but the lung is the most commonly affected. Sarcoidosis may cause lung nodules. When it does, the nodules are frequently accompanied by enlargement of the lymph nodes. Other signs and symptoms of sarcoidosis include uveitis (inflammation of part of the eye), skin problems, arthritis, and fevers. Other systemic diseases that may cause lung nodules include rheumatoid arthritis and Wegener's granulomatosis.

Miscellaneous causes of solitary pulmonary nodules have been described. Some of the more common conditions are lung abscess; pneumonia; pseudotumor (which represents fluid in a fissure that actually lies between lobes of the same lung); hematomas after thoracic trauma or surgery; and fibrosis or scars resulting from prior infections. Rarer conditions presenting as solitary pulmonary nodules include silicosis (often due to certain types of coal mining), bronchogenic cyst (a congenital abnormality), amyloidosis, pulmonary infarct due to a blood clot, and congenital vascular anomalies. Sometimes smaller blood vessels may form connections and these can appear as nodules as well. These connections are usually between arteries and veins, and are known as arteriovenous malformations. They often appear as a solitary pulmonary nodule, and they may grow slowly over years. They have a characteristic appearance on a contrast-enhanced CT scan that is usually diagnostic.

IMAGING TECHNIQUES

Imaging techniques are often helpful in distinguishing benign from cancerous causes of solitary pulmonary nodules, and as such they play a key role in evaluation and management. During the last decade, rapid advances in both

CT and positron emission tomography (PET) have dramatically changed the diagnostic approach to solitary pulmonary nodules. The primary technologies that need to be considered are plain chest radiography, CT, and PET.

Plain Chest Radiography

Most solitary pulmonary nodules are discovered on routine plain chest radiograph while asymptomatic. Malignant nodules are usually identifiable on chest radiograph by the time they are 0.8 to 1 centimeter in diameter, although nodules 0.5 to 0.6 cm can occasionally be seen.[1] Most will be identified on posteroanterior (PA) projection, but some will be seen only on lateral projection, so standard PA and lateral chest radiography should be obtained whenever possible. When a nodule can be seen only on one projection, the physician should question whether it is truly in the lung parenchyma. Structures overlying the skin of the chest wall—such as leads used for cardiac monitoring, nipple shadows, skin lesions, bone lesions, and pulmonary vessels on end—can all mimic pulmonary nodules.

Once it has been ascertained that a true nodule exists, the first step is to make every effort to obtain previous radiographs for comparison. Cancers have a typical growth rate. If a lesion does not grow it is not likely to be cancer. Conversely, if a lesion grows over days, then it is growing too fast to be cancer. As a rule of thumb, if a nodule has remained stable with no increase in size for two years, it is very probably benign and warrants no further investigation. Conversely, a large nodule that was not present on a comparable radiograph within the past two months is unlikely to be cancerous, since a cancer would not have grown so rapidly.

Computed Tomography

Computed Tomography (CT) is the main tool for diagnosis and follow-up of lung nodules. CT is indicated when one is assessing indeterminate nodules less than three centimeters in diameter. It can pinpoint the exact location of the nodule and provides three-dimensional images of the lesion. Thin-section high-resolution CT (HRCT) can better define the borders and the nodule's relation to adjacent structures, such as blood vessels and the pleura (the outside lining of the lung where it meets the chest wall). It is more sensitive than standard chest x-ray in detecting calcification patterns which are useful in determining if a lesion is cancerous or not. It can also detect fat within a nodule—which, when coupled with calcification, is highly suggestive of a benign hamartoma. A CT is also useful in looking for hilar or mediastinal adenopathy (enlargement of the lymph nodes), and in evaluating accessibility of nodules for biopsy or resection.

The morphology or shape of a nodule, in particular its borders, provides useful information and insight into whether or not the lesion is likely to be cancerous. Nodules that are very smooth and perfectly rounded are less likely to be malignant. Malignant nodules often have irregular or "spiculated" borders (Figure 4-3.1).

Another CT technique that may be helpful is incremental dynamic CT, which uses increasing doses of iodinated intravenous contrast to look for enhancement of nodules.[6] Malignant nodules enhance more than benign

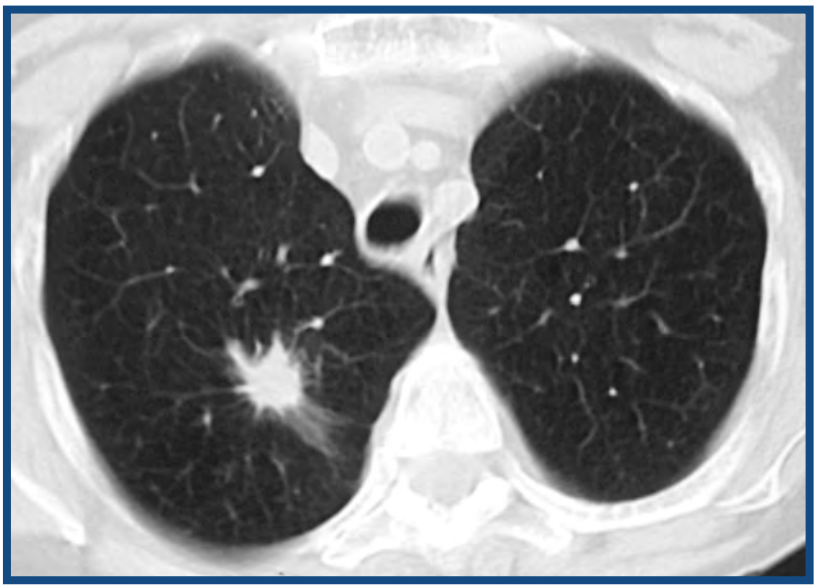

Figure 4-3.1: Spiculated lesion on CT highly suggestive of malignancy.

ones when given contrast. Occasionally, benign lesions, such as hamartomas and tuberculomas, may also enhance. In centers with expertise with this methodology, the sensitivity and specificity of this test is good. However, few centers at the present time are using this approach.

In summary, when using CT imaging, attention should be paid to the lesions size, location, shape of the border, density, and contrast enhancement if available. Nodules that are bigger than three centimeters or that have suspect characteristics in the right clinical setting (e.g., an older smoker, spiculated borders) should be considered for biopsy or resection.

Positron Emission Tomography (PET)

Newer imaging methods, such as PET, can be used to differentiate noninvasively between malignant and benign nodules. PET takes advantage of the fact that tumor cells have increased metabolism and therefore have higher glucose uptake. PET scanning uses a radioactive form of glucose, fluorine-18 radioisotope (FDG), which is injected into the patient, to measure metabolism. This radioactive glucose is not dangerous to the patient. After it is injected, it is taken up by the nodule. Malignant nodules, since they are more metabolically active, will take up more, while benign lesions will take up less. Since the glucose is radioactive, this can then be measured by a PET scanner. This system is both highly sensitive and specific. One review, combining the results of 13 different studies, estimated that PET scan was 94.3% sensitive detecting cancer in solitary pulmonary nodules and was also fairly specific at 83%.

However, a PET scan has some significant limitations. It appears to be less sensitive for lesions less than one centimeter in size, so its use should be limited to those lesions one centimeter or greater in size.[7] False negative findings have also been seen in patients with bronchioloalveolar cell carcinoma, carcinoid tumors, and mucinous adenocarcinomas.[8, 9] False positive results have been seen in patients with granulomatous infections, such as tuberculosis or endemic fungi, as well as in patients with inflammatory conditions, such as rheumatoid arthritis and sarcoidosis.[10, 11]

DISTINGUISHING BETWEEN BENIGN AND MALIGNANT NODULES

The goal of management algorithms for solitary pulmonary nodules is to bring to surgery all patients with potentially curable disease while avoiding unnecessary surgery in those who do not need it. As such, distinguishing between benign and malignant nodules is critical. Assessing image characteristics from a PET scan at a given moment in time is one method to help distinguish benign from malignant pulmonary nodules. However, there are other methods that can help. These include assessment of a nodule's shape and calcification pattern, the nodule's growth rate, and assessment of the probability of malignancy based on epidemiologic risk factors.

Nodule Shape and Calcification Patterns

Certain shapes make a nodule more likely to be malignant. Although nodules may appear to be spherical on a plain chest radiograph, further study by a CT may disclose irregular borders and shapes (Figure 4-3.2). The borders of benign nodules are often well circumscribed, with a rounded appearance. On the other hand, malignant nodules tend to have irregular, lobulated, or spiculated borders. A malignant nodule may have pleural tags or tails extending from its body, or a notch may be present in the border of the nodule (Rigler's sign). None of these radiographic signs is entirely specific for malignancy. As a general rule of thumb, the more irregular the nodule, the more likely it is to be cancer.

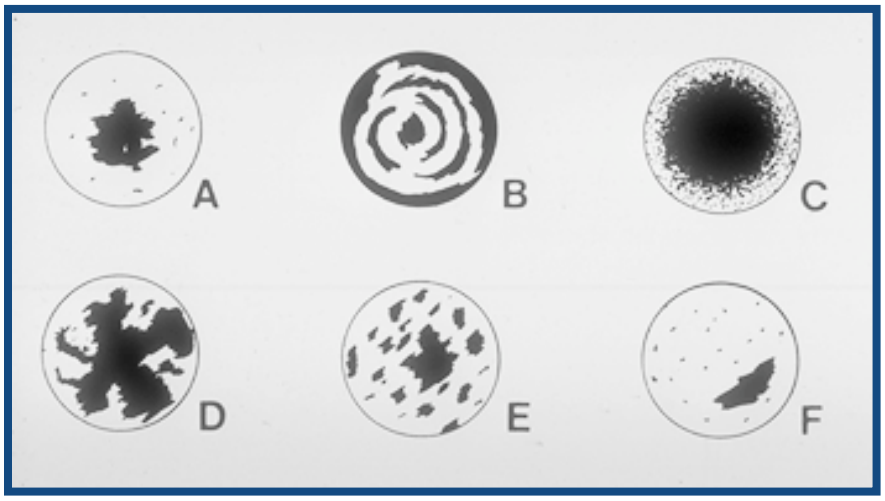

Figure 4-3.2: Calcification patterns. Patterns A-D are usually benign, E and F are indeterminate. A. Central, B. Laminated, C. Diffuse, D . Popcorn, E. Stippled, F. Eccentric.

Calcification is generally an indication of benignity in a solitary pulmonary nodule. Infectious granulomas tend to calcify with central, diffuse, or stippled patterns. Laminar or concentric calcification is characteristic of granulomas caused by histoplasmosis. Popcorn calcification, when present, is suggestive of a hamartoma. Eccentric calcification patterns should make one suspicious for malignancy. It should be noted that, in general, 6 - 14% of malignant nodules exhibit calcification. When present in cancerous lesions, calcifications are usually eccentric and few. Benign patterns of calcification (central, diffuse, laminar, or popcorn) are very rare in malignant nodules. Most nodules with a benign calcification pattern can be observed with serial CT scans.

Assessment of Nodule Growth Rate and Frequency of Follow-up Imaging

Assessing a nodule's growth rate can further assist in distinguishing between benign and malignant nodules, provided serial images over time are available for comparison. Determination of nodule growth is based on the assumption that nodules are more or less spherical. Growth of a sphere must be considered in three-dimensional volume, not in two-dimensional diameter. The formula for volume of a sphere is $4/3(\pi)r^3$, or $1/6(\pi)D^3$, where r = radius and D = diameter. A nodule originally one centimeter in diameter whose diameter is now 1.3 centimeters has actually more than doubled in volume. Similarly, a two centimeter nodule has doubled in volume by the time its diameter reaches 2.5 cm. A nodule that has doubled in diameter has undergone an eightfold increase in volume. When old radiographs are available, growth rate and nodule *doubling time* (i.e., the time for a nodule to double in volume) can be estimated. Accepting the assumption that a tumor arises from serial doublings of a single cancerous cell, we can estimate that it will take 27 doublings for it to reach one half a centimeter, the smallest lesion detectable on chest radiography. By the time a nodule is one centimeter in diameter, it represents 30 doubling times and about one billion tumor cells. Depending on the exact growth rate, this theoretical one centimeter nodule has probably existed for years before it is detected, as malignant bronchogenic tumors have doubling times estimated at between 20 and 400 days. The natural history of a tumor usually spans about 40 doublings, whereupon the tumor is 10 cm in diameter and the patient has usually died.[12] Squamous and large cell tumors have an average doubling time of 60 to 80 days. Adenocarcinomas double at about 120 days, and the rare small cell carcinoma that presents as a solitary pulmonary nodule can have a doubling time of less than 30 days. A nodule that has doubled in weeks to months is probably malignant and should be removed when possible.[13]

Benign nodules have doubling times of less than 20 days or more than 400 days. A nodule that doubles in size in less than 20 days is usually the result of an acute infectious or inflammatory process, while those that grow very slowly are usually chronic granulomatous reactions or hamartomas. Such nodules can be observed with serial radiographs.

Nodule growth rate and doubling times become clinically relevant when we have to decide how often to order follow-up imaging when observing a solitary pulmonary nodule. The question often arises whether observing a solitary pulmonary nodule for an extra three to six months increases the likelihood of metastatic disease, since that nodule has probably been growing for years. There is no convincing empiric evidence to support this hypothesis. Whether delays longer than three to six months are safe is unknown. However, estimating this hazard of delay is clinically relevant, since the optimal frequency of serial CT follow-up imaging to monitor nodules for growth is predicated on limiting this hazard of delay. The question is, how frequently do follow-up scans need to be done to minimize the hazard of delay while containing costs and avoiding excessive radiation exposure.

Traditional practice, based on little empiric evidence, recommended that when a careful observation strategy was warranted, repeat CT scans be done at 3, 6, 12, and 24 months. However, more recent data from lung cancer

screening trials using CT imaging suggests that a less aggressive practice may be reasonable in some patients with very small nodules.[14-17] Therefore, decisions about the frequency and duration of follow-up for patients with solitary pulmonary nodules need to consider multiple dimensions of the problem, including clinical risk factors, nodule size, the probable growth rate as reflected by CT morphology, the limits of imaging technology resolution and volume measurement (especially at sizes less than five millimeters), radiation dose, surgical risks, patient preferences, and cost.[18-20] All of these can affect the optimal frequency of CT follow-up significantly. For example, in patients who are not considered to be surgical candidates due to other comorbidities, such as severe emphysema, the utility of follow-up CT imaging is questionable and less aggressive approaches, such as no imaging at all, are reasonable.

Given this framework, it is reasonable to apply more recent expert consensus based guidelines to help guide the frequency of follow-up CT imaging for the solitary pulmonary nodule.[21] For follow-up studies, imaging should be performed with the lowest possible radiation dose that provides adequate imaging (with current technology between 40 and 100mA). The key variables that determine optimal imaging frequency are surgical risk, size and lung cancer risk. For patients who are potential surgical candidates with no lung cancer risk factors the frequency of repeat CT imaging is:

- Nodule size $\leq$ 4 mm: No follow-up needed.
- Nodule size > 4 mm but less then 6 mm: re-evaluate in 12 months. If there is no change then no additional follow-up is warranted.
- Nodule size $\geq$ 6 to 8 mm: followed in 6 to 12 months and then again at 18-24 months if there is no change.
- Nodules size > 8 mm: traditional schedule with serial CT imaging at 3, 6, 12, and 24 months if there is no change.

For patients who are potential surgical candidates with one or more lung cancer risk factors, the frequency of repeat CT imaging is:

- Nodule size $\leq$ 4 mm: once at 12 months, no additional imaging if there is no change.
- Nodule size > 4 mm but less then 6 mm: initially at 6-12 months, and if no growth repeat again at 18-24 months if there is no change.
- Nodule size $\geq$ 6 to 8 mm: initially at 3 to 6 months and then again at 9-12 months, and then again at 24 months if there is no change.
- Nodules size > 8 mm: traditional schedule with serial CT imaging at 3, 6, 12, and 24 months if there is no change.

It should also be noted that controversy remains regarding how long follow-up should be continued. While traditional teaching has recommended observing lesions for a maximum of two years, it is now recognized that for some lesions, longer follow-up may be warranted. Long doubling times have been observed in malignant lesions that presented as ground-glass nodules or as partially-solid nodules.[22-24] As a consequence, longer follow-up extending over years may be appropriate in some special instances, especially if there is an antecedent history of lung cancer. For most nodules, two years of follow-up without evidence of growth is sufficiently long to warrant discontinuation of CT imaging.

Estimating Probability of Malignancy

Several authors have attempted to develop mathematical models to estimate the probability of malignancy of indeterminate solitary pulmonary nodules. Using clinical and radiographic characteristics of malignancy derived from the literature, these authors have analyzed some combination of malignant risk factors by Bayesian, neural network, and other methods to obtain a mathematical estimate of the probability of malignancy. Risk factors analyzed have included nodule size, location, growth rate, margin characteristics, age of the patient, smoking history, prevalence of malignancy in the community, and calcification on CT.[25-27]

One of the problems with these and other methods is the quality of the input data (i.e., the likelihood ratios), which may not be representative of all patient populations. In addition, Bayesian analysis presupposes that the likelihood ratios for a particular risk factor are not affected by the presence or absence of any other factor. It is not clear that this is true of the likelihood ratios. Therefore, although mathematical models to predict probability of malignancy may seem attractive, the complexity of the issue once again leaves us with an uncertain answer. This may explain why the above-described methods are not in widespread clinical use.

However, assessment of the pretest probability of malignancy is central to optimal strategy selection making when managing solitary pulmonary nodules.[28, 29] While formulas and neural networks may lack precision on an individual patient level, they can serve to inform decision making as to what risk factors to pay attention to and how important they are relative to each other. Risk factors associated with a low probability of malignancy include diameter less than 1.5 cm, age less than 45 years, absence of tobacco use, having quit smoking for seven or more years, and a smooth appearance on radiography. Risk factors associated with a moderately-increased risk of malignancy include diameter 1.5-2.2 cm, age 45-59, smoking up to 20 cigarettes per day, being a former smoker within the last seven years, or a scalloped edge appearance on radiography. Risk factors associated with a high risk of malignancy include a diameter of 2.3 cm or greater, age greater than 60 years, being a current smoker of more than 20 cigarettes per day, a history of prior cancer, and a corona radiate or spiculated appearance on radiography (irregular edge).

BIOPSY TECHNIQUES

The issue of whether it is useful to biopsy an indeterminate solitary pulmonary nodule and, if so, how to do it remains controversial. Most experts agree that in certain clinical circumstances, a biopsy procedure is warranted. For example, in a patient who is at high surgical risk, it may be useful in establishing a diagnosis and in guiding decision making. If the biopsy reveals malignancy, it may convince a patient who is wary of surgery to undergo thoracotomy or thoracoscopic resection of a potentially-curable lesion. Another indication for biopsy may be anxiety to establish a specific diagnosis in a patient in whom the nodule seems to be benign. Some chest physicians argue that all indeterminate nodules should be resected if the results of history, physical examination, and laboratory and radiographic staging methods are negative for metastases.

Others argue that this last approach exposes patients with benign nodules to the risks of needless surgery. In such cases, a biopsy procedure sometimes provides a specific diagnosis of a benign lesion and obviates surgery.

Once it has been decided to biopsy a solitary pulmonary nodule, the choice of procedure is a matter of debate but includes fiberoptic bronchoscopy, percutaneous needle aspiration, thoracoscopic biopsy (usually with video assistance), and open thoracotomy.

Bronchoscopy

Traditionally, bronchoscopy has been regarded as a procedure of limited usefulness in the evaluation of solitary pulmonary nodules. Studies have shown variable success rates, with an overall diagnostic yield of 36 - 68% for malignant nodules greater than two centimeters in size. In general, the yield for specific benign diagnoses has ranged from 12 - 41%.

For smaller nodules, the sensitivity of bronchoscopy is significantly worse. For example, for nodules larger than two centimeters in diameter, a sensitivity as high as 68% (average 55%) can be obtained. However, this dropped to 11% for nodules smaller than two centimeters. Location also matters: nodules located in the inner or middle one-third of the lung fields have the best diagnostic yield; nodules in the outer one-third have a much lower diagnostic yield and as such are probably best approached with percutaneous needle aspiration if biopsy is needed.

After an extensive evidence-based review of the various studies, it was concluded that bronchoscopy can play a role in the evaluation of the solitary pulmonary nodule under rare circumstances but that most of the time bronchoscopy will not be the best choice.[30] In those cases in which there is a bronchus leading to the lesion on a CT scan, or in cases in which there are very central lesions abutting the large airways, bronchoscopy may be of use. Similarly, if there is a suspicion for unusual infections, such as tuberculosis or fungal infections, then bronchoscopy may be warranted. However, for most patients bronchoscopy will not play a major role.[31, 32]

Percutaneous Needle Aspiration

Percutaneous needle aspiration can be performed under fluoroscopic or CT guidance, the choice often depending on the availability and the experience of the operator. It involves placing a very thin needle through the chest wall into the lesion to get an aspirate. It is most useful when nodules are in the outer third of the lung and in lesions under two centimeters in diameter. It can establish the diagnosis of malignancy in up to 95% of cases and can establish specific benign diagnosis (granuloma, hamartoma, and infarct) in up to 68% of patients. The use of larger-bore biopsy needles—such as a 19 gauge, which provides a core specimen in addition to cytology—improves the yield for both malignant and benign lesions.

The major limitation of percutaneous needle aspiration is its high rate of pneumothorax (10- 35% overall); pneumothorax is more likely when lung tissue lies in the path of the needle. Because of the high rate of pneumothorax and its possible complications, the following patients should not undergo percutaneous needle aspiration: those with limited pulmonary reserve (e.g.,

advanced emphysema); those with bullous emphysema or blebs in the needle path; and postpneumonectomy patients. Other general contraindications are: bleeding problems, inability to hold breath, and severe pulmonary hypertension.

Thoracotomy and Thoracoscopy

Lobectomy (resecting a lobe of the lung) using either open thoracotomy or video-assisted thoracoscopic surgery with lymph node resection and staging remain the standard of care for stage I bronchogenic carcinoma, the most common malignancy among solitary pulmonary nodules. Nodules greater than three centimeters in diameter have a greater than 90% chance of being malignant, and in the face of a negative metastatic workup and adequate pulmonary reserve, indeterminate nodules of this size should be resected. Smaller nodules that remain indeterminate after appropriate radiographic evaluation and possibly biopsy (bronchoscopic and/or percutaneous needle aspiration where indicated) either can be resected or can be observed with close serial CT follow-up. The decision will depend on the patient and on the physician, who must educate the patient on the alternatives and possible consequences.

Thoracotomy has a reported mortality of three to seven percent. It is higher in patients over age 70 and in patients with malignancy. These patients will usually have other coexisting illness, such as chronic obstructive pulmonary disease (COPD), coronary artery disease, etc. The mortality risk increases with the extent of the procedure. In one series by Ginsberg and coworkers, mortality was 1.4% for wedge resection (a small piece), 2.9% for lobectomy, and 6.2% for pneumonectomy (resection of a whole lung).[33] More recent observational studies of lung cancer surgery reported similar 30-day mortality rates.

Video-assisted thoracoscopic surgery (VATS) uses fiberoptic telescopes and miniaturized video cameras to facilitate biopsies and resection. VATS represents a complementary approach to traditional thoracotomy and can be very useful in some patients. This approach still requires general anesthesia but does not require a full thoracotomy incision or spreading of the ribs. VATS allows the experienced surgeon to identify and wedge out peripheral nodules in many cases with minimal morbidity and mortality. In a series by Mack and colleagues, 242 nodules were resected with no mortality and minimal morbidity.[34] Average hospital stay was 2.4 days. Video-assisted thoracic surgery can spare some patients with benign nodules the risks of open thoracotomy and can be useful for wedging out nodules in patients who have limited pulmonary reserve who cannot otherwise tolerate a lobectomy. However, in a significant percentage of cases, conversion from VATS to a mini-thoracotomy will still be required.

However resection is performed, whether by VATS or by thoracotomy, lobectomy remains the procedure of choice for malignant solitary pulmonary nodules. Wedge excisions or segmental resections for smaller cancers have been evaluated, but the role of these limited pulmonary resections in the management of lung cancer remains controversial. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy has been recommended as the surgical procedure of choice for patients with malignant solitary pulmonary nodules who have adequate reserve to tolerate the procedure.

For patients with insufficient pulmonary reserve to tolerate a lobectomy, segmentectomy or wedge resection remains a viable alternative. This involves resecting a part of a lobe (segment). At the present time, it is reasonable to recommend lobectomy for all patients with malignant solitary pulmonary nodules who have sufficient pulmonary reserve to tolerate the procedure, with consideration of segmentectomy for those patients with inadequate pulmonary function to tolerate a lobectomy.

DIAGNOSTIC APPROACH

As is often the case in medicine, it is unwise to presume that an infallible algorithm can be provided for the evaluation of all solitary pulmonary nodules. Since no consensus can be reached on the basis of available data, the best that can be done is to offer recommendations. The pathway to be taken and final decision will rest on the individual physician and patient. Individual patient preferences also play a key role. The following recommendations represent one possible approach to this complex clinical problem:

1. On discovering a solitary pulmonary nodule, the clinician should determine whether it is a true solitary nodule, spherical, and located within the lung fields. CT imaging should be part of the initial evaluation.
2. A thorough history and physical may provide clues about the nodule's possible cause. Most of the time, solitary pulmonary nodules are asymptomatic. The history should include an assessment of risk factors for cancer, including smoking history, occupational exposures, exposure to endemic fungi, and any history of prior malignancy. Patient risk preferences should be obtained as part of the discussion.
3. If it is established that the nodule is truly solitary, and a benign pattern of calcification is present, the nodule is considered benign and no further workup is necessary. Follow-up with serial CT imaging may be warranted based on the size of the lesion and risk factors for cancer as described above.
4. All prior chest radiographs and CT images should be obtained and compared with the present images.
    a. If prior chest radiographs are available, and the nodule has remained unchanged for two years or longer, no further workup is necessary. Follow-up with serial CT imaging may be warranted if there is a concern for a slow growing bronchioloalveolar cell carcinoma or there if there are other risk factors for cancer as described above.
    b. If the nodule has grown and the doubling time is more than 20 days but less than 18 months, it is considered malignant and should be resected. If the doubling time is more than 18 months, consideration of a slow growing bronchioloalveolar cell carcinoma or a carcinoid is warranted and, depending on the patient's preferences and surgical risk, a biopsy procedure may be useful to provide further reassurance to the patient. Alternatively, the nodule may be benign and close serial CT follow-up is also reasonable, perhaps every three months for the first year and every six months for the next year.

c. If old chest images are available but the nodule was not present on prior radiographs, an upper-limit doubling time is calculated. If the doubling time is again less than 18 months, it is considered to be malignant and resected. If the doubling time is more than 18 months, the nodule remains indeterminate. Nodules for which previous radiographs are unavailable are also indeterminate.

5. The physician should arrive at an estimate of the probability of malignancy based upon the history, physical, and CT imaging characteristics.
   a. Those with a low probability (under 10%) of malignant disease, such as those that have been demonstrated to be stable on serial CXR for two years or more, have a characteristic benign calcification pattern, or are present in patients less than 35 years of age in the absence of other risk factors, can be observed with serial CT scans depending on their size. The follow-up would be as described above, with surgery for those with evidence of progression.
   b. Those with a high probability of malignant disease who are surgical candidates should be considered for VATS or thoracotomy. Examples would be patients with a new nodule of large size in an older patient with a heavy smoking history and an irregular border (spiculated pattern) on CT. Staging would include a PET scan plus investigation of any other symptoms. When the probability of malignant disease is this high, even if the PET scan is completely negative, biopsy or resection is warranted. Note that PET in this instance is more of a staging tool (determine extent and respectability of cancer), rather than a diagnostic tool (determine whether or not there is cancer present).
   c. The third category, which many patients fall into, consists of those patients who are surgical candidates with nodules with a moderate probability (10-60%) of cancer. These nodules are considered indeterminate. The management of these nodules remains controversial. PET scanning for those with nodules measuring one centimeter or greater in size is warranted. Transthoracic fine needle aspiration, occasionally bronchoscopy, or a contrast-enhanced CT are reasonable options. If the results are positive, then surgery is warranted. If a specific benign diagnostic result (example: core biopsy demonstrates hamartoma or bronchoscopy demonstrates tuberculosis) is obtained then this is usually sufficient to guide management. However, a nonspecific nondiagnostic result should be interpreted with caution. Depending upon the patient's preferences, surgical risk, and probability of cancer, VATS or thoracotomy or careful follow-up CT imaging may be warranted.

Fire Fighters and Lung Nodules

The two main factors that should be considered when evaluating solitary pulmonary nodules in fire fighters are whether there is an increased risk of cancer associated with firefighting and whether there is an increased risk of developing benign nodules due to occupational exposure with subsequent inflammation and scarring. With respect to lung cancer, the evidence from large epidemiologic studies is conflicting. There is evidence for some association

between lung cancer and firefighting, but the magnitude of the risk is not strong. Specifically, the magnitude of the effect in terms of risk for lung cancer at an individual level is very small, such that it can be outweighed by other factors, such as smoking, age and the health-worker effect. The standards of evidence for occupational injury are different than those used for scientific consideration, and in taking care of patients, clinical decisions should be based on balancing science with individual exposure histories.

This is further complicated by the fact that firefighting and the nature of fires have changed over the decades, making comparisons between studies over time difficult. In studies relevant to the present day, the risk is only elevated in certain groups, mainly those with the highest and longest exposure histories. The introduction of synthetic polymers and building materials in the 1950s poses a theoretical basis for increased risk, but epidemiologic studies have not consistently demonstrated an association. This is further confounded by improvements in respiratory protective devices and the frequency of their utilization. The frequency of respiratory protective device utilization was suboptimal in the past and therefore the impact of these devices in older studies probably is too small to determine. However, as utilization rates have improved in recent years, it is likely that future studies may show the benefits of such devices in the form of even lower risks.

The other main clinical concern is whether or not fire fighters might develop more benign solitary pulmonary nodules due to intermittent minor lung injury. Solitary pulmonary nodules are not an uncommon finding among fire fighters. However, there is no rigorous data comparing the frequency of lung nodules in fire fighters as compared to that of the general population.

Based on the available evidence, the approach to a solitary pulmonary nodule, once it has been identified, is the same for fire fighters as it is for other individuals. The risk of cancer should be assessed based on traditional risk factors, such as age, smoking history, size of the nodule, and prior history of malignancy. In making clinical decisions whether a non-smoking firefighter has added risk similar to a cigarette-smoking non-fire fighter is a topic of great controversy and concern. Accordingly, it should be openly discussed between patient and clinician. Diagnostic strategies based on probability of cancer and patient preferences are also similar and would include careful observation, biopsy, or proceeding directly to resection as described above.

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Chapter 4-4
Where There's Smoke… There's Help!

Self-Help for Tobacco Dependent Fire Fighters and Other First Responders

By Matthew P. Bars, MS, CTTS

Although this chapter can be of use to many readers (tobacco users, non-user with family, friends and co-workers who use tobacco and health professionals), it is written to speak directly to you the tobacco user. Like every chapter on health and disease, we will introduce the topic with information on why tobacco use is unhealthy and we will stress those issues that are of primary concern to fire fighters and other first responders. But we will be brief because this information is well known to you. Most tobacco users already know the dangers and want to quit but have not been adequately informed that there are now modern quit methods with excellent success rates and minimal discomfort. In 2002, the Fire Department City of New York (FDNY) launched a free, voluntary, non-punitive, modern tobacco cessation program for all its employees and their families. This effort was funded in part by the IAFF's Counseling Service Fund. This chapter will describe to you that program and how you and your health care professional can use this approach to become tobacco free.

Tobacco smoke contains over 4,000 chemicals, 69 of which are known carcinogens, many more are known toxins. These chemicals are absorbed in the lungs and via the blood travel to virtually every organ, every tissue, and every cell in the human body. Tobacco can affect any part of the body but primarily and most directly affects the lungs and heart. Throughout this chapter the term "smoker" or "tobacco user" will refer to the use of any and all tobacco products including cigarettes, cigars, pipes, and all forms of smokeless tobacco, unless otherwise specified.

The four major areas of tobacco's health effects on the human body involve cancers (and not just lung cancer), non-cancerous respiratory (lung) diseases, diseases of the heart and blood vessels and miscellaneous other effects. Under this miscellaneous category, smoking affects parts of the body not commonly thought of including hearing loss, erectile dysfunction, premature wrinkling of the skin, earlier menopause and more menstrual difficulties, and sleep/wake abnormalities, to name just a few.

While most people are aware that smoking causes lung cancer, most smokers do not know that tobacco increases the risk of a tremendous variety of cancers including colon, liver, cervix, brain, esophagus, throat, kidney and even penile cancer in men, to name just a few.

Smoking affects the lungs in other ways in addition to causing lung cancer. Chronic obstructive pulmonary disease (COPD) is the single largest non-cancer lung disease caused by smoking and, of course, these risks are greater for fire fighters who are exposed to smoke and chemicals as a matter of routine and who must maintain normal lung function to do their job safely. COPD includes emphysema, chronic bronchitis, asthma (asthma is also referred to as reactive airways disease) and several less common diseases. Further, many if not all lung diseases are made worse by tobacco smoke exposure.

As dramatic as the effects of lung disease and cancer are, the greatest impact on morbidity and mortality is tobacco caused cardiovascular disease. This includes heart and blood vessel disease such as atherosclerosis (hardening of the arteries), myocardial ischemia (poor blood flow and low oxygen to the heart muscle), myocardial infarctions (heart attacks), hypertension (high blood pressure) and peripheral vascular disease (poor blood flow and low oxygen to the peripheral tissues such as the legs, feet, hands and fingers). The fact that the number one cause of fire fighter deaths is myocardial infarction (heart attacks) makes tobacco cessation a priority for fire fighters and other first responders.

National statistics reveal several things. Anywhere from a third to half of all smokers die as a direct result of their tobacco use; many years sooner than if they didn't smoke. Many more become cardiac or respiratory cripples, eventually unable to do the simplest activities. These risks are even greater for fire fighters and other first responders who every day must depend on their own cardiopulmonary fitness and that of their coworkers.

While every smoker knows tobacco kills, most are not aware of new methods, new medications and the combinations of medications available to help smokers (and other tobacco users) quit. If you are a smoker, odds are you have tried multiple times to quit and chances are great that you wish you were successful. Some reports show that the average smoker makes between six to nine serious attempts until they enjoy success and that over 70% of all smokers, wish they could quit. Indeed, if the negative effects of tobacco abstinence such as "missing not smoking" could be eliminated, the percentage of smokers wanting to quit would climb dramatically.

FDNY has treated approximately 1,500 first responders (fire fighters, EMTs, and paramedics), retirees, civilian employees and family members since September 11, 2001. Indeed, it is now possible to help smokers quit with virtually no pain and little, if any, discomfort. At the FDNY, smokers were able to achieve one year quit rates of 40%. These successes are even more remarkable because they were obtained immediately after the devastating and traumatic effects of the terrorist attacks of 9/11. You can quit too! Here's how:

TOBACCO ADDICTION

First, it is important to realize that the addiction to tobacco is extremely powerful. Smoking is the fastest, most powerful way to deliver nicotine to the

human brain. After a puff, nicotine reaches the brain in only seven seconds. There it affects the brain like a shotgun blast, changing the brain's chemistry increasing the sensation of pleasure, altering mood, decreasing appetite, and enhancing performance. Other parts of the brain learn "that was really good, let's do that again soon." Studies show that for most people, tobacco addiction occurs after a remarkably few number of cigarettes.

Measuring Your Tobacco Addiction

Karl Fagerström, a renowned Swedish tobacco addiction researcher over 20 years ago, designed a simple six question test to measure the severity of a smoker's nicotine addiction. The Fagerström Test for Nicotine Dependence has also been adapted for smokeless oral tobacco as well (Tables 4-4.1 and 4-4.2).

Fagerström Test for Nicotine Dependence		
How many cigarettes per day do you usually smoke?	10 or less 11 to 20 21 to 31 31 or more	0 1 2 3
How soon after you wake up do you smoke your first?	Within 5 minutes 6-30 minutes 30-60 minutes More than 61 minutes	3 2 1 0
Do you find it difficult to not smoke in no-smoking areas?	No Yes	0 1
Which cigarette would you most hate to give up?	The first one Any other one	1 0
Do you smoke more frequently in the first hours after waking than during the rest of the day?	No Yes	0 1
Do you smoke if you are ill?	No Yes	0 1
Scoring: 0-1 Very Low 2-3 Low 5-7 Moderate 7-8 High 9-10 Very High		

Table 4-4.1: Fagerström Test for Nicotine Dependence

For you the patient, there are ways to determine how severe the level of nicotine addiction is. For example, has a doctor told you that your health is being damaged by your smoking and yet, you continue to smoke? Do you have a heart or lung condition? Even if smoking is not the direct cause of your illness, for most illnesses smoking is contributing to your continued deteriorating health and if despite knowing this you continue to smoke then your addiction is severe. Do you wake at night and smoke? Nocturnal smoking is common in severely-addicted smokers. This does not mean after a midnight run but rather if you wake up and smoke. Are you avoiding family members, friends or events because smoking is difficult or forbidden? Years ago, we had a smoking patient who refused to visit her grandchildren because her son-in-law forbade her smoking in the presence of the children. If you are avoiding significant people and events in your life so your smoking is undisturbed, your addiction is severe. If your workplace prohibits smoking and you are risking termination by smoking where it is forbidden, you are severely addicted.

Modified Fagerström Test for Smokeless Oral Tobacco Use		
After a normal sleeping period, do you use smokeless tobacco within 30 minutes of waking?	Yes No	1 0
Do you use smokeless tobacco when you are sick or have mouth sores?	Yes No	1 0
How many tins do you use per week?	2 or less >2 but <4 <4	0 1 2
How often do you intentionally swallow your tobacco juice rather than spit?	Never Sometimes Always	0 1 2
Do you keep a dip or chew in your mouth almost all the time?	Yes No	1 0
Do you experience strong cravings for a dip or chew when you go for more than two hours without one?	Yes No	1 0
On average, how many minutes do you keep a fresh dip or chew in your mouth?	<9 10 - 19 20 - 30 >30	0 1 2 3
What is the length of your dipping day? (total hours from first dip/chew in the AM to last dip/chew in PM)	≤ 14 ½ >14 ½ - ≤15 ½ >15 ½	0 1 2
On average, how many dips/chews do you take each day?	<1 1 - 9 10 - 15 ≥16	0 1 2 3
Scoring: 0 - 5 Mild	6 - 10 Moderate	11 - 16 Heavy

Table 4-4.2: Modified Fagerström Tolerance Questionnaire: Smokeless Tobacco Use

LET'S GET READY!

Realizing that nicotine is such a strong addiction and that help is available is the first step to a conquering addiction and enjoying a lifetime of freedom from tobacco and improved physical fitness and health. The good news is modern day tobacco cessation therapies can not only minimize the discomfort that occurs when stopping but can also help you even if you are not ready to put down your cigarettes today. While the vast majority of all smokers want to stop, it is completely normal to have mixed feelings and experience aborted efforts and missteps. Quitting is a process and much can be learned from previous efforts even if you feel they were less than successful. There are no failures. Each attempt is a step towards success, especially if we can work together to determine the reasons for past missteps in the journey towards tobacco freedom and then construct a plan that tries to remove those barriers.

For example, we recently saw a 30 cigarette-per-day fire fighter who had used a 21 mg transdermal nicotine patch and had reduced his cigarette consumption to seven cigarettes daily. During our evaluation, he reported a common response to this type of situation: "The patch didn't work.". In actuality, we informed

him that (to use firefighting language) the patch started to "knock down" his smoking addiction, it just did not go far enough.

Let's explain. The 21 mg nicotine patch which delivers nicotine s-l-o-w-l-y through the skin (compared to smoking nicotine), was not designed to replace 100% of the inhaled nicotine from all the cigarettes for every smoker. Think about this: Elephants and mice like all mammals can develop bacterial upper respiratory infections. Like humans, both elephants and mice can be treated with antibiotics. Does it make sense to give the same dose of medicine to an elephant as a mouse? Of course, it does not! Does it make sense to fight a fire with the same number of fire fighters that has involved an entire city block as it does to knockdown a simple mattress fire? Of course, it doesn't! Similarly, why would we want to treat a 30 or 40 cigarette per day smoker the same as, say, a person who smokes five cigarettes per day? It makes much more sense to treat every smoker individually.

Actually in our clinical experience there are a number of smokers who continued to smoke (but less than usual) after taking an US Food and Drug Administration's (FDA) tobacco treatment medication such as the nicotine gum, nicotine patches and lozenges, nicotine inhalers and nasal sprays, what used to be called Zyban® (i.e., wellbutrin, bupropion) and Chantix® (varenicline). At this point you are probably wondering "Isn't it unsafe to continue to smoke while using, say, the nicotine patch or gum?" In a word: No! In fact, this a great way to help ambivalent or less than fully ready smokers to start on the road to better health as long as they make the commitment to eventually become tobacco free.

Reduction to Cessation Treatments (Reduce then Quit)

Let's say you smoke 25 cigarettes per day and want to cut-down but you're not ready to quit. Perhaps you refuse to quit now or maybe prior quit attempts failed due to severe cessation anxiety (the anxiety that occurs when contemplating quitting). Such patients can benefit from a reduction to cessation treatment approach where medication is started prior to quitting. For example, if you smoke 20 to 30 cigarettes per day, do you think you could use a 21 milligram transdermal nicotine patch to cut-down gradually to 10-15 cigarettes daily?

In May 2008, the U.S. Public Health Service working out of the Office of the Surgeon General released new guidelines to help clinicians treat tobacco addiction. These researchers and clinicians, chaired by Michael Fiore, MD a world-renowned tobacco cessation expert from the University of Wisconsin Medical School, reviewed thousands of peer-reviewed, high quality scientific studies. They concluded, among other things, that Reduction to Quit treatment plans are not only safe and effective, but some studies show that they may even increase success rates. Certainly they can engage smokers who are not ready to stop smoking today.

Over the years, we have treated many hundreds of smokers with a Reduction to Cessation protocol. The number of smokers who experienced any problems with this type of plan could be counted on one hand. The most common difficulty was mild nausea. This was transient and usually eliminated by reducing the daily number of smoked cigarettes. Sometimes the smoker will continue to smoke fewer and fewer cigarettes spontaneously until they just stop. Other smoking patients may need to add additional medications such as

nicotine gum, inhalers, or nicotine nasal spray to reach complete abstinence. Combinations of these medications are also recommended by the new federal tobacco addiction treatment guidelines. We will discuss these medications in greater detail later in this chapter.

Whether you are ready to establish a Target Quit Date (TQD) now, start a Reduction to Cessation treatment plan, or contemplate your next move, there are several simple steps that you can take to move you closer to a lifetime of freedom from tobacco.

Keep a Cigarette Log

Below is an example of a cigarette log (Figure 4.4.1). If you, a member of your family, friend or co-worker smokes, photocopy this page, cut out the log and wrap it around your cigarette pack with a rubber-band and a small pencil or pen. The cigarette log serves several purposes. First, it is impossible to change a behavior if you are unaware of precisely what that behavior is.

Cigarette Use Log:			
M	M	M	M
Tu	Tu	Tu	Tu
W	W	W	W
Th	Th	Th	Th
F	F	F	F
Sa	Sa	Sa	Sa
Su	Su	Su	Su

Figure 4-4.1: Cigarette Log.

Here is an example of a smoker who recorded smoking 22 cigarettes on Monday (Figure 4-4.2).

Cigarette Use Log: January			
M 𝍸 𝍸 𝍸𝍸 =22	M	M	M
Tu	Tu	Tu	Tu
W	W	W	W
Th	Th	Th	Th
F	F	F	F
Sa	Sa	Sa	Sa
Su	Su	Su	Su

Figure 4-4.2: Sample Use of Cigarette Log.

Second, the action of recording a cigarette in real-time (as it is smoked) helps the smoker become more aware of the act of smoking and this can help eliminate those cigarettes smoked just out of habit. Many cigarettes are smoked automatically without much of a real desire. Keeping a cigarette log can help understand patterns and that in itself may reduce tobacco use and will certainly help you and your doctor/ healthcare professional and tobacco treatment specialist create an individualized cessation treatment program and gauge your progress.

No Ashtrays Instead Use a Cigarette "Coughee" Jar

Another good technique is to eliminate all the ashtrays from wherever you smoke and to substitute a "cigarette coughee jar". Just like it sounds take a clean clear glass or plastic jar with a screw-cap. Fill it about one-quarter of the way with water. Use this now as your one and only ashtray into which you deposit all your cigarette ashes and discarded butts. Especially if you live with small children or other non-smokers, it is best to bring your cigarette jar with you and smoke outside. All non-smokers are affected by tobacco smoke and the health of children is dramatically harmed by the smoking of adults.

Before lighting up a new cigarette unscrew the jar and inhale a deep whiff of all those stale butts and ashes. Doing this regularly, each and every time you smoke will help break the positive association to your cigarettes and help you to conquer your addiction. When not smoking, for example, when watching TV, eating a meal, or drinking coffee, keep your cigarette jar with you.

Increase the Inconvenience of Smoking

Buy only one pack at a time, no more cartons of cigarettes or multiple packs lying around. It is also helpful to keep your cigarettes in an inconvenient place such as the trunk of your car, behind pipes in your basement, or a little used room, cabinet, or closet. During a Reduction to Cessation plan, you can smoke up to your cut-down goal but you do not want to smoke automatically when you don't really want to, simply because they are lying around.

Take Inventory and Do a Balance Sheet

It is important to understand why you are thinking of quitting the smoking habit, trying to be as specific as you can. For example, don't just say you are "quitting for health", instead state "I am more short of breath climbing up stairs on a run or forcing entry than I was a few years ago" or "my doctor says my lungs and heart are being damaged by my smoking." Write these reasons down and carry this list with you. A great place to keep this list is in your cigarette pack itself or your wallet. Take the list out and review it frequently; a great time to review your list is while smoking. Figure 4-4.3 shows some common reasons fire fighters express for quitting tobacco.

A particularly good technique: One fire fighter who was quitting for his wife and family placed a picture of them without him between the cellophane and his pack of cigarettes. Every time he smoked, he imagined his family surviving without him after he died from a disease caused by tobacco.

Common Reasons Fire Fighters Express for Quitting Tobacco

Check all that apply:

- ☐ Increased risk for heart attack
- ☐ Expense of smoking
- ☐ Wife pregnant
- ☐ Shortness of breath
- ☐ Increased risk for lung disease
- ☐ To set example for my children
- ☐ To please spouse / co-workers / friends
- ☐ I get enough smoke and chemicals fighting fires
- ☐ I want to conquer my tobacco addiction and take control of my life
- ☐ My doctor told me to quit
- ☐ Cigarette money can be better spent: college educations, vacations, house
- ☐ I am not getting any younger
- ☐ Smoking lowers sexual energy and ability
- ☐ Other: _____

_____

_____

Figure 4-4.3: Common Reasons Fire Fighters Express for Quitting Tobacco

No reason to quit is a bad reason if it is your reason. It is also important to assess honestly why you smoke. Most people smoke for many reasons in addition to their addiction to tobacco. Are you smoking out of boredom? To deal with stress? Hunger? Do you smoke because you associate with other smokers (i.e., your spouse or members of your firehouse)? Do you feel cigarettes help you relax? Do you use cigarettes to pick you up? To stimulate you or organize your energies? Do you smoke as a work break or after a run?

Avoid People, Places, Things You Associate with Smoking

Take some time to detail the things that make you smoke automatically or more than usually. Check all that apply and/or add your own. Where possible, change these behaviors to make smoking inconvenient, difficult, or impossible. For example, if you smoke while drinking coffee simply hold the coffee cup in a different hand; stand instead of sitting (or vise-a-versa), and/or hold a handling substitute such as a pencil or pen or eating can help you disassociate coffee from cigarettes. If you always smoke while driving to and from work try taking a different route and use oral or handling substitutes such as sugarless chewing gum or cinnamon sticks. Figure 4-4.4 can be used for this purpose.

Likely Times for Smoking or Using Tobacco
Check all that apply:
☐ Alcohol
☐ Coffee / Other beverages
☐ After meals
☐ While driving
☐ Boredom
☐ Work break/After a run
☐ After awakening
☐ Before bedtime
☐ Before / during a bowel movement
☐ During stress / anxiety
☐ After sex
☐ With negative feelings (anger, sadness, etc.)
☐ Social activities (bowling, softball)
☐ Family gatherings
☐ Other: _____
_____
_____

Figure 4-4.4: Common Reasons Fire Fighters Express for Quitting Tobacco

Alcohol and Tobacco Use

A word to the wise: alcohol can be a trump card. Alcohol consumption can sabotage the most earnest individual's quit smoking attempt. This is true for both the occasional "partier" as well as the problem drinker. Many people smoke at bars or parties just because everyone is. This is not to say that a smoker must forever abstain from alcohol to quit, but it is probably a good idea to avoid alcohol while you are attempting to quit.

A comprehensive discussion of the relationship between alcohol and tobacco is beyond the scope of this chapter. That said, alcohol and fire fighter social activities often go hand and hand and the stress first responders experience in dealing with life and death events can lead to alcohol use, which then can trigger tobacco use in smokers and (even more unfortunate) can precipitate a return to tobacco in ex-smokers.

Sadness, Depression and Post Traumatic Stress

Unfortunately, first responders see things that civilians only dream about in their nightmares. Witnessing tragedy up close and personal can cause feelings of despondency and other emotional problems. While an in-depth discussion of depression and post-traumatic stress are beyond the scope of this chapter

and while anyone can temporarily experience one or a few of the symptoms described below, if the symptoms are recurrent and cause significant problems in your life, seek professional assistance. Both depression and post-traumatic stress can increase the difficulty of conquering your tobacco addiction.

- Difficulty sleeping.
- Loss of interest or the ability to enjoy oneself.
- Excessive feelings of guilt or worthlessness.
- Loss of energy or fatigue.
- Difficulty concentrating, thinking or making decisions.
- Changes in appetite.
- Observable mental and physical sluggishness.
- Thoughts of death or suicide.
- Recurrent and intrusive distressing recollections of a traumatic event, including images, thoughts, dreams or perceptions.

The Money You Save

Calculate how much you are saving by smoking less (or not smoking at all) and place this money in another clean clear jar. As you watch your savings grow, plan on what you will do with the money. If you smoke one pack per day at $6/ pack, the savings after one year can pay for a large ticket item such as a vacation. If you prefer more immediate gratification, you can use the money saved for something small each week such as an article of clothing, book, CD or dinner at a special restaurant with someone special. All that matters is that you are cognizant of the fact that you are rewarding yourself for this important step.

Exercise – Start Slow, Start with Your Doctor's Input, but Start!

Changing unhealthy habits and replacing them with healthy ones is always a great idea. Starting an exercise program or increasing the intensity and/ or session length of a current program is one of the best things you can do to help you quit tobacco. Studies show even small to moderate amounts of exercise can reduce the urge to smoke and help you remain tobacco free. If you were in the habit of lighting-up while watching TV, try doing a few minutes of push-ups or sit-ups during the commercial breaks. This is a new habit to take the place of the deadly habit and addiction of smoking. Even simple stretching exercises can work wonders and they feel great. Exercise naturally "burns off" tension and increases heart and respiration rates. Exercise increases endorphin and other brain chemicals that tobacco increase artificially. Exercise can also help reduce the weight gain (averages about five pounds) during tobacco cessation. Again we recommend anyone and everyone receive medical clearance regarding an exercise program.

Keep Oral Low-Calorie Substitutes Handy

Sugarless gum, candy, and mints, cloves, crunchy fruits and vegetables, cinnamon sticks or straws are all wonderful to keep your mouth and hands busy without cigarettes. Chewing gum works great while driving, around the house or at work. Fruits and vegetables are wonderful while sitting at home reading or watching TV. Again, healthy low-calorie substitutes will reduce the

few pounds of weight gain that may accompany tobacco cessation efforts. In addition, nicotine replacement medications have been found to be exceptionally helpful in reducing appetite and weight gain.

Associate Only with Non-Smokers for a While

We don't want you to abandon all your smoking associates but for a while it's a good idea to spend more time with the non-smokers in your life. This is especially true if you tended to smoke automatically or tended to smoke more around other smokers. If you must socialize with other smokers, advise all who know you that you have decided to no longer smoke. If feasible, ask them if they could refrain from smoking around you. In small groups of one or two, you may be pleasantly surprised by their response. Other smokers are probably interested in quitting as well. Instead of a cigarette, offer them a piece of sugarless chewing gum.

Unfortunately, sometimes smokers may attempt to sabotage your efforts to become tobacco free. We have found this is more common in firehouses where there are a sizable and vocal number of smokers. It is important to remember that for some smokers your success highlights their own difficulties in conquering the addiction to tobacco. Sometimes it is better to simply state, especially when offered cigarettes, "I don't smoke" rather than "I am trying to quit." Remember you can't control the behavior of others but you can control your own. If the situation becomes too tempting, simply walk away. You can return when cigarettes are extinguished.

Avoiding parties where smokers can smoke freely is certainly a good idea; especially where a large number of smokers would congregate. If that is not possible, make a commitment to your self that you will not smoke. Use of rescue medications (nicotine gum, nicotine spray or nicotine inhaler—see more information about these medications later in this chapter) can be extremely important in these settings. Use them instead of a cigarette. Remember the vast 75 - 85% of Americans do not smoke. At any social or work setting, you can find people who do not smoke.

MEDICATIONS ARE ESSENTIAL TO INCREASE YOUR CHANCES OF SUCCESS

Fortunately, as we discussed earlier, there are seven FDA-approved tobacco treatment medications. These include several strengths of nicotine gum, nicotine patches and lozenges, nicotine inhalers and nasal sprays, as well as Zyban® (i.e. Wellbutrin, Bupropion) and Chantix® (Varenicline).

There are hundreds of well-researched studies that prove without question that medications help you quit. However, many people don't believe that and choose not to use medications or they discontinue these medications too soon and/ or don't take enough to begin with. This is usually a mistake and sabotages many efforts.

For example, many smokers fear (incorrectly) that nicotine replacement medications are dangerous because they deliver nicotine into the human body. Actually, even in cigarettes nicotine is not the dangerous chemical. Nicotine, as we discussed earlier, makes and keeps the tobacco user addicted, but nicotine is not what kills. The 4,000 other chemicals are what damage the

heart and lungs, increasing the risk for cancers of many organs, while carbon monoxide (the odorless, colorless gas which kills many fire victims) robs the body of oxygen.

The only active ingredient in nicotine replacement medications is nicotine. Each of the five FDA-approved nicotine replacement medications are designed to deliver nicotine slower than a cigarette. Clean and slow nicotine is better than dirty cigarette-delivered nicotine. Nicotine replacement products have been used by millions of smokers in the last quarter century.

Not one smoker has know to have died from a nicotine replacement medication. Conversely, during the past 25 years, over 12 million Americans have been killed as a direct result of their tobacco addiction. That is about 1,200 each day, equaling about 50 smoker deaths each hour.

Every medication for every condition has certain risks associated with its use. The question is always do the benefits exceed the risks? Does the potential good outweigh the potential harm? According to some studies, more than half of all smokers will die many years or decades earlier than if they did not smoke. While no medication is right for everyone, every one of the FDA-approved medications is safe and effective. While four of the FDA medications are available only by prescription and the other three are over-the-counter, every smoker is advised to address medications with their physician or healthcare professional.

Chantix® (Varenicline) or Champix® (outside the United States)

Chantix® is the first new medication approved for the treatment of tobacco addiction in almost 10 years and it was specifically designed to simultaneously bind and block the nicotine receptors in the human brain. Chantix® is a prescription medication and must be prescribed by a physician or other licensed health professional. The effect of this tablet medication is to release the same pleasure neurochemical that nicotine stimulates while also preventing nicotine from having the same positive reinforcing effect on the smoker's brain.

Simply stated, the smoker does not get the same pleasure or "high" from their tobacco but also does not miss smoking as much. Research demonstrates that Chantix® allows the smoker to quit with greater ease. After 12 weeks of treatment, 44% of Chantix® users were tobacco free. The FDA product instructions recommend quitting within seven days of starting this medication. As with all tobacco treatment medications, smokers who have difficulty establishing a quit date can focus on reducing their tobacco consumption without a specific planned quit date as long as they are in a treatment program and are committed to eventually becoming tobacco free. Approved by the FDA in 2006, at the time of this writing there have been over five million Chantix® users. The most common side-effects are nausea, abdominal gas, constipation, insomnia and vivid dreams. Rare instances of depression have been reported. Many clinicians believe that this depression is most commonly due to nicotine withdrawal rather than Chantix® use but it rarely may be drug related. As we discussed previously, no medication is right for everyone. As always, discuss this and all medications with your physician. Your doctor should be an integral part of your tobacco treatment plan.

Bupropion® (Wellbutrin, Zyban)

In 1997, Bupropion®, an antidepressant, was the first non-nicotine medication approved for the treatment of tobacco addiction. Years before, Dr. Linda Ferry observed at the Jerry L. Pettis Veterans Administration Hospital in Loma Linda, California that the Bupropion® molecule was significantly more effective in helping her smoking military veterans quit. Every smoker and those of us in the tobacco treatment field owe Dr. Ferry a debt of gratitude. In our experience, Bupropion tablets are particularly effective in smokers, who after stopping, experience depression, dysphoria or sadness. Bupropion® is a prescription medication and must be prescribed by a physician or other licensed health professional. After years of using Bupropion®, we observed and subsequently demonstrated in a large placebo-controlled multi-center study that this medication reduces the amount of nicotine the smoker consumes prior to a quit date and even increases the motivation to quit. Side-effects include dry-mouth, headache, constipation, light-headedness, and a reported one in 1,000 risk for a seizure. Like every medication, Bupropion® is not right for every smoker. Talk to your physician to determine if Bupropion® is a wise choice for you.

Bupropion® works well with Chantix® and the nicotine replacement products. However, the correct use of multiple medications can require the assistance of a trained tobacco treatment specialist. For a listing of tobacco specialists in your area, see the resource section at the end of this chapter.

Nicotine Replacement Medications

The four other FDA-approved products are all Nicotine Replacement medications. Remember we cannot say it enough: clean nicotine is always better than dirty (4,000 chemicals, 69 of which are known to cause cancer) nicotine. All nicotine replacement medications are safe!

Nicotine Nasal Spray

The Nicotine Nasal Spray delivers clean nicotine to the inside of the smoker's nose. There, the nicotine is rather rapidly absorbed by the nasal mucus membranes (nasal mucosa) and delivered to the brain within 4-15 minutes (depending on the individual). In fact, other than by smoking a cigarette, this is the fastest way to deliver nicotine to the brain. This makes the Nicotine Nasal Spray an extremely effective tobacco treatment. It can be used repeatedly and on a regular schedule as a "continuous" tobacco cessation medication and/or intermittently as a "rescue" medication for severe tobacco cravings. One spray of nicotine nasal spray to each nostril delivers approximately the same amount of nicotine as the average smoker can receive from the average cigarette.

While the nasal spray can be irritating and can result in sneezing, runny nose, tearing eyes and less seldom an occasional bloody nose, these effects are usually minor and transient, easing or disappearing entirely after the nasal passages are acclimated. The ability to tolerate the nasal spray's side effect is quite dependent on the technique used in the application. First, direct the spray towards the sides of each nostril, rather than the center, and allow the sprayed fluid to coat the inside of the nostril rather than straight up into the sinus. Hold your breath while spraying and after administration continue to breathe through your mouth for a few minutes and avoid sniffing the solution deep into the nose. Nicotine Nasal Spray is a prescription medication. Talk to

your doctor, healthcare professional, and tobacco treatment specialist to help determine if the nicotine nasal spray is right for you.

Nicotine Inhaler

The nicotine inhaler is also a prescription medication. It consists of a nicotine gel cartridge, which is placed in a plastic tube vaguely resembling a cigarette. The nicotine gel releases a nicotine vapor, which is absorbed in the mouth's oral mucosa. Each puff delivers approximately one-tenth the amount of nicotine delivered in a cigarette puff. For some smokers, the cigarette shape and the use of the nicotine inhaler also helps in reducing tobacco cravings by simulating the hand to mouth ritual of smoking. Some users may experience a sore throat, nasal irritation, cough, heartburn, stomach upset, hiccups or nausea. The most common side effects being mild mouth or throat irritation and cough. These side effects are usually minor, do not occur for most users, and can be eliminated or minimized by correct use.

The nicotine inhaler, which is actually a puffer, should be puffed similar to a cigar so that the Nicotine Vapor is deposited onto the mouth's lining. Nicotine is absorbed by the mouth's lining rather than the lung so the most effective use of the nicotine inhaler is a series of shallow puffs. This also minimizes or eliminates side effects by avoiding inhaling the vapor into the back of the throat where it can irritate the vocal cords and the airways leading into the lungs. The inhaler cartridges are designed to deliver the most nicotine at roughly four puffs per minute for 20 to 30 minutes and then discarding the cartridge. Most smokers puff each cartridge too infrequently and use, on average, between one and two cartridges per day. This is far too little to receive an adequate amount of therapeutic nicotine. For use as a "continuous" tobacco cessation medication, the FDA product insert recommends using anywhere from 6 to 16 cartridges each day. The nicotine inhaler is also suitable for use as a "rescue" medication for severe tobacco cravings. Like all medications, correct use is essential for the desired therapeutic effect and increased quit rates.

Nicotine Polacrilex Gum

In the United States, nicotine polacrilex gum is an over-the-counter medication that does not require a physician's prescription and in 1983 was the first tobacco cessation medication ever approved by the FDA. Nicotine gum delivers nicotine in a resin matrix directly to the lining of the mouth, similar to the nicotine inhaler. Nicotine gum is not like regular chewing gum. Chewed like ordinary gum, nicotine gum will not work very well. It is important to chew the nicotine gum very slowly until you notice a peppery taste or slight tingling sensation (usually after about 15 chews, but can vary individual to individual) in your mouth. Then "park" the gum between your cheek and gums (below your teeth line) until the peppery or tingling sensation disappears, then keep repeating these steps. One piece, chewed correctly can be used for about one half hour. Chewing incorrectly can increase unpleasant side effects. Do not eat or drink immediately before gum use.

Although the gum is available in two and four milligram strength, The FDNY program recommended the four milligram gum. The consistency and flavors have improved significantly over the original gum and is now available in mint, orange, cinnamon, and fruit flavors. Begin by chewing at least one

piece every one to two hours. Side effects include mouth irritation, hiccups, nausea, and on rare occasion jaw pain. The nicotine gum is contraindicated in smokers with TMJ (temporal mandible joint) syndrome or significant dental work or numerous missing teeth. Like all FDA-approved medications, nicotine gum also significantly increases quit rates. It can be used frequently as a "continuous" tobacco cessation medication and/or intermittently as a "rescue" medication for severe tobacco cravings.

Nicotine Polacrilex Lozenges

Nicotine polacrilex lozenges are an over-the-counter medication that does not require a physician's prescription. Similar to the nicotine polacrilex gum, the nicotine polacrilex lozenge releases nicotine directly through the lining of the mouth, temporarily relieving craving and nicotine withdrawal symptoms. It is recommended to use one to two lozenges each hour and at least nine lozenges per day. We have found many smokers may need much more than this minimum. Unlike ordinary lozenges, these are not meant to be chewed or swallowed. Place the lozenge in your mouth and allow the lozenge to dissolve slowly over 20 to 30 minutes while trying to swallow minimally. It is important to minimize swallowing so the dissolved medicine can be absorbed in the mouth. Of course, the lozenges deliver a lower, slower level of nicotine than a cigarette. It is not surprising that side effects are similar to the nicotine polacrilex gum and that it can be used frequently as a "continuous" tobacco cessation medication and/or intermittently as a "rescue" medication for severe tobacco cravings.

Nicotine Patches

In the United States, the nicotine patch is an over-the-counter medication that does not require a physician's prescription. Nicotine transdermal patches deliver a steady dose of nicotine directly through the skin. There it enters the blood circulation and slowly enters the brain easing craving and tobacco withdrawal symptoms and increasing quit rates. A constant low dose of nicotine may be all that is needed to eliminate tobacco cravings in light smokers (e.g. , five to six cigarettes per day). For those with heavier tobacco use and/or more severe cravings, the other nicotine products (spray, inhaler, gum or lozenge) can be used in addition as "rescue" medications for breakthrough cravings.

Some suggestions for proper application of the patch: after a shower or cleaning a non-hairy area of skin with a non-moisturizing soap, let the area dry completely. The upper arm is a good choice for most people, but the patch can be worn on almost any non-hairy area. It is important to avoid using lotions, cream, and skincare products on the area you choose. Try not to touch the sticky part of the patch. Firmly press the patch on your skin with the heel of your palm for at least 10 seconds. Wash your hands after applying or removing a transdermal nicotine patch. Safely dispose of any foil pouch, wrapping in plastic that protected the patch. Used patches should be folded in half and disposed of safely as well. Make sure these materials are out of reach of children and pets.

The nicotine patch can be worn for either 16 (removed at bedtime) or 24 hours. If you crave cigarettes when you wake up, or feel like you want extra

protection from tobacco cravings, wear the patch for 24 hours. Some patients can experience vivid dreams while wearing the patch after bedtime. In actuality, some patients enjoy the vivid colorful dreams. If vivid dreams present a problem, simply remove the patch at bedtime and apply a fresh patch first thing in the morning. Some smokers experience skin irritation caused by the adhesive. This can often be effectively treated with over the counter cortisone cream. Cortisone cream can be applied after the patch is removed. In more severe instances the area can be pre-treated the night before but, wash off the area of the remaining pre-treatment cortisone cream before applying the patch in the morning. Some patients may prefer one brand to another because of differences, real or perceived in effectiveness, stickiness and/or skin irritation.

Combination Medications

The FDNY Tobacco Cessation Program has used all of these medications in every possible combination safely and effectively with first responders and their families. Tobacco users who have a specific target quit date or those that prefer a reduction to cessation treatment plan can use each one of these medications, individually or in combination. Again, you should discuss medications, combination of medications or treatment plan with your physician or healthcare provider.

Tobacco Treatment Decision Guidelines

The first thing to examine is your readiness to quit now. Are you on fire to quit now or are you ambivalent? Are you concerned about "failing" (remember there are no failures, only smokers who have not yet quit) or are you experiencing "cessation anxiety?" If you are concerned, it has been recommended to use a reduction to cessation (RTC) plan that will eventually lead to a quit date.

Another consideration: Have you made serious quit attempts in the past? Do you consider those attempts successful? Partially successful? Did you quit or significantly reduce your tobacco consumption for a period of time during those attempts? Did you use an FDA-approved medication during that attempt and did you use it correctly? Depending on your results, it may make sense to re-challenge your tobacco addiction with the same medication (assuming of course it did not cause any significant problems) or to add an additional "rescue" medication.

If you reduced your cigarette consumption significantly (for example from 20 or 25 cigarettes per day down to 15 or less) or even if you were totally abstinent but you experienced craving and tobacco withdrawal symptoms, it may be helpful to consider multiple tobacco treatment medications that combine "continuous" medications with "rescue" medications. When considering multiple medications, it is important to add only one medication at a time.

While it is always recommend that every smoker consult with his or her physician, healthcare provider and a tobacco treatment specialist, we realize that this is not always possible. The simplest treatment plan for many smokers may to rely only on over-the-counter medications. In the FDNY program, recommendations were made to members to use a transdermal nicotine patch (for most a 21 mg patch) that provided continuous nicotine in an attempt to reduce cigarette consumption by approximately 50%, if not more. Then for "breakthrough" cravings, the program recommended "rescue" medication using

either gum or lozenge; four milligram nicotine polacrilex gum or lozenges can address further reductions in cigarettes per day toward total cessation as well as breakthrough cravings. Remember to begin only one medicine at a time.

Some smokers prefer to add the nicotine inhaler to a nicotine transdermal patch. This is often helpful with smokers who enjoy (or would miss) the hand-to-mouth ritual of smoking or benefit from the oral stimulation or the cigarette handling aspects of smoking. Collaborating with a licensed health care provider is required because the nicotine inhaler is a prescription medicine. Forming a partnership with a concerned healthcare provider, knowledgeable in the stressful demands regularly placed on fire fighters and other first responders can have many other beneficial effects both in designing an effective cessation program, preventing or treating any adverse effects that may have occurred from prior tobacco use and ultimately in improving cardiopulmonary fitness.

A number of well-designed research studies have shown that high-dose multiple nicotine patches can increase quit rates. For those with intermittent rather than constant cravings, "rescue" medications are a better option. For severe urgent cravings, we recommend the nasal spray for "rescue" therapy. For less urgent cravings, we recommend the inhaler, gum or lozenge depending on patient preferences.

While multiple patches are safe and almost universally produce no difficulties or side effects (other than occasional and mild skin irritation), these combination treatment plans are complicated and require the assistance of trained healthcare professionals.

U.S. Federal and State Programs

The National Network of Tobacco Cessation Quitlines is a state/federal partnership that provides tobacco users in every state with access to the tools and resources they need to quit smoking; ensuring the highest level of assistance to tobacco users who want to quit. The toll-free number 1-800 QUIT NOW (1-800-784-8669) serves as a single point of access to all state-based programs. The federal government website, Smokefree.gov, is maintained by the Tobacco Control Research Branch of the National Cancer Institute (NCI) and provides choices that best fit the needs of tobacco users.

The site provides assistance in the form of:

- An online step-by-step cessation guide;
- Local and state telephone quitlines;
- NCI's national telephone quitline and instant messaging service; and
- Publications, which may be downloaded, printed, or ordered

IAFF: A TOBACCO FREE UNION

The IAFF and Pfizer are collaborating to help the IAFF become the first smoke-free union. This initiative, modeled after the successful FDNY program, was begun to encourage all IAFF members and their families to take on healthier lifestyles by quitting smoking. This program provides information on the health risks of smoking and the benefits of quitting as well as tips on how friends and family can help a smoker quit. Information is also provided on how to encourage health insurance plans to make sure they cover smoking

cessation. The entire program is accessible on the IAFF website at: http://www.iaff.org/smokefree/.

A FINAL WORD

Smokers often say that quitting tobacco is the hardest thing they have ever done. Tobacco cessation programs, like the one offered at FDNY and now by the IAFF, make the battle easier and often pain free. If you are a first responder who has been on the job for more than a few years, you have probably tried to force an entry or knock down a fire that was difficult and didn't go as planned. Sometimes you have to reassess a situation and try again. Living a tobacco-free life can be a lot like that. That said, nothing should be more important to you, your family, and your friends than eliminating tobacco from your life.

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7. Information regarding Nicorette® nicotine polacrilex gum can be found at: www.nicorette.com.
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11. Information regarding the International Association of Fire Fighters' Campaign for a Smoke-Free Union can be found at: http://www.iaff.org/smokefree/.

Chapter 4-5
Respiratory Failure, Assisted Ventilation, Mechanical Ventilation and Weaning

By Dr. Thomas K. Aldrich, MD

The respiratory system is built to accomplish gas exchange, bringing air into close proximity of blood, so as to allow oxygen to diffuse from air to blood and carbon dioxide to diffuse from blood into air. Respiratory failure occurs when the respiratory system cannot adequately maintain gas exchange, most commonly because of a failure to provide and maintain adequate ventilation (the movement of air into and out of the lungs).

The major structures of the respiratory system and the processes that determine the adequacy of their functioning is illustrated in Figure 4-5.1. Respiratory

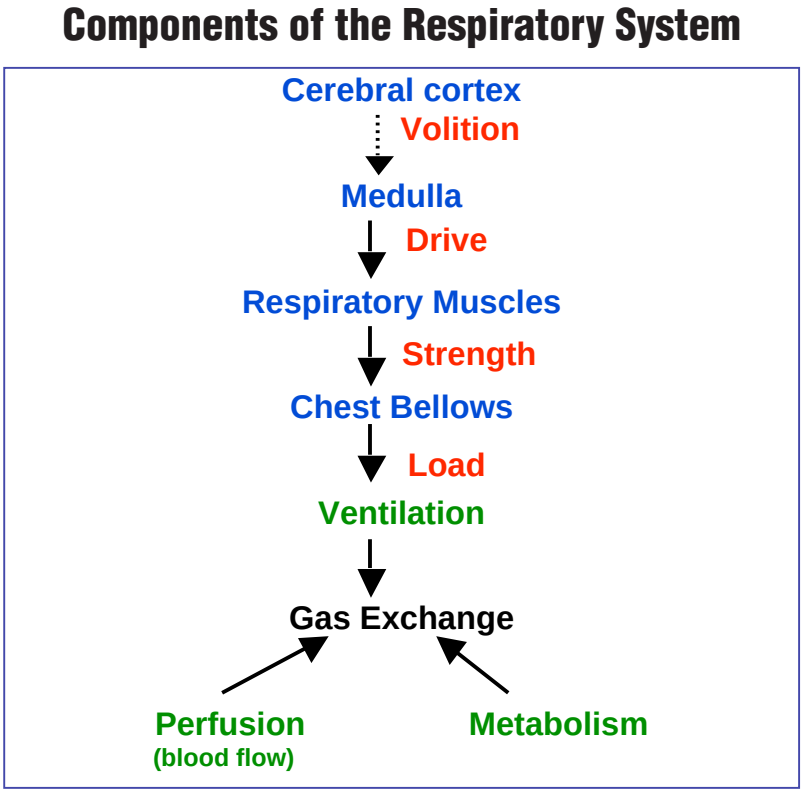

Figure 4-5.1: Structures and functions of the respiratory system (*structures are in blue, functions in red*). The goal is exchange, determined by the balance of ventilation, perfusion and metabolism

drive, the neural control of breathing, originates in the brainstem (primarily the medulla), and proceeds unconsciously, but can be influenced by higher structures for voluntary control of breathing (e.g., during breath-holding, playing musical instruments, etc.). The respiratory muscles, depending on their strength and endurance, enlarge (and sometimes contract) the volume of the chest (the "chest bellows"). It is more difficult to inflate the lungs if they are stiff (e.g., pneumonia, pulmonary fibrosis, etc.) or if airways resistance is increased (e.g., asthma, chronic bronchitis, etc.). Normally, the load faced by the chest bellows is so low that ventilation occurs effortlessly. Stiff lungs or increase airway resistance results in an increased workload and depending on the magnitude of the load and other factors, the chest bellows may fail resulting in respiratory failure.

TYPES OF RESPIRATORY FAILURE

Two types of respiratory failure can occur: hypoxemic (low oxygen) or hypercapnic (high carbon dioxide)[1] (Table 4-5.1). Normally room air is 21% oxygen and the partial pressure of oxygen in arterial blood (PaO_2) at sea level is ~90mmHg. For practical purposes, hypoxemic respiratory failure is considered to be present if PaO_2 cannot be corrected to >50mmHg on a nontoxic level of supplemental oxygen (<50%). Hypercapnic respiratory failure is characterized by elevated levels of carbon dioxide in arterial blood. It is often accompanied by hypoxemia, though typically not as severely as is the case in hypoxemic respiratory failure.

Types of Respiratory Failure	
Hypoxemic Characterized by Hypoxemia (arbitrarily <50mmHg)	**Hypercapnic** Characterized by Hypercapnia (>46mmHg) and hypoxemia (usually)
Typical Causes	
• Pneumonia • Pulmonary edema • Pulmonary embolism • Pulmonary hypertension • Interstitial lung disease • Atelectasis	• Lower airways obstructive disease (asthma, COPD) • Upper airways obstruction • Kyphoscoliosis • Neuromuscular disease • Rarely central hypoventilation • Obesity hypoventilation syndrome

Table 4-5.1: The Two Types of Respiratory Failure.

The two types of respiratory failure also differ as to the conditions or diseases that typically produce them.

Hypoxic Respiratory Failure

The common causes of hypoxemic respiratory failure are diseases of the lung or the pulmonary blood vessels (see Table 4-5.1), impairing gas exchange because there is not adequate exposure of the perfusing blood to ventilating gas. In such cases, the ventilatory pump is able to increase overall ventilation adequately to prevent a rise in carbon dioxide partial pressure (pCO_2), but the continuing maldistribution of ventilation prevents full correction of the hypoxemia.

Hypercapnic Respiratory Failure

The common causes of hypercapnic failure are diseases of any of the components of the respiratory system leading up to the lungs: the brainstem, the respiratory muscles, the chest wall, or the airways (see Table 4-5.1). In hypercapnic respiratory failure, relatively mild hypoxemia occurs, primarily for the same reason that hypercapnia occurs: the level of ventilation is not adequate to refresh the oxygen within the lungs, just as it is not adequate to eliminate a normal amount of carbon dioxide.

Hypercapnic respiratory failure results when the ventilatory pump is inadequate to meet the metabolic and ventilatory demands because of reduced central drive (brain), impaired respiratory muscle function (nerves or muscles), excessive respiratory workload, or some combination of these three factors[2] (Table 4-5.2). Of the three potential causes of hypercapnic respiratory failure, the least common is impaired central drive. It occurs in drug overdose, rarely in hypothyroidism, and even less commonly in brain lesions, such as catastrophic bilateral brainstem strokes or central alveolar hypoventilation syndrome (Ondine's curse), an exceedingly rare congenital impairment in brainstem function. Most brain lesion (strokes, tumors, etc) and most metabolic disorders (cirrhosis, uremia, and other deliriums) are associated with hyperventilation rather than hypoventilation and do not cause respiratory failure.

Causes of Hypercarbia (CO_2 Retention)
Ventilatory pump failure
• Reduced central drive • Impaired ventilatory muscle endurance • Increased respiratory workload
Contributing factors
• Increased CO_2 production • Increased dead space • Impaired intrapulmonary gas exchange

Table 4-5.2: The Causes of CO_2 Retention.

Thus, most cases of hypercapnic respiratory failure are due to impaired respiratory (mostly inspiratory) muscle strength and endurance and/or excessive respiratory workload (Figure 4-5.2). In chronic obstructive pulmonary disease (COPD), for example, the major problem is excessive workload, due mostly to

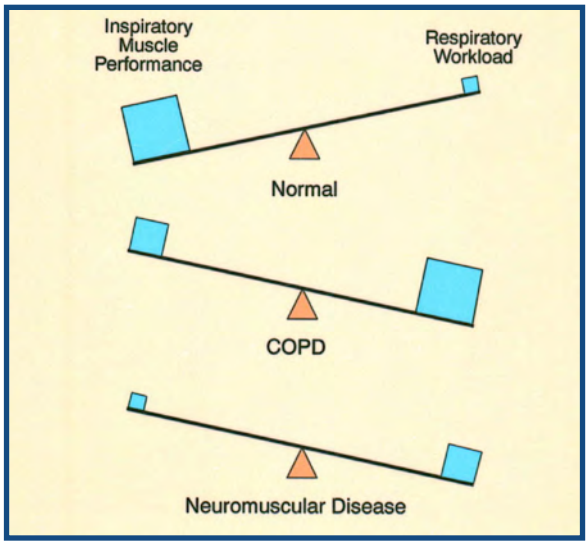

Figure 4-5.2: The balance between inspiratory muscle performance (strength and endurance) and respiratory workload.

increased airway resistance. But, in COPD, inspiratory muscle strength is also commonly impaired by a number of concomitant mechanical and metabolic conditions. Similarly, in neuromuscular diseases, although inspiratory muscle weakness is the major problem causing ventilatory pump failure, a number of factors increase inspiratory workload, such as increased airways resistance and lung stiffness caused by recurrent aspiration pneumonia.

CLINICAL ASSESSMENT OF RESPIRATORY FAILURE

Symptoms and signs of both types of respiratory failure are primarily those of the underlying disease. There may be shortness of breath, cough, and/or chest pain. Unfortunately, symptoms correlate poorly with the severity of respiratory failure. Findings on physical examination might include evident labored breathing and, depending on the type of underlying disease, prolonged expiratory phase (in COPD or asthma), diminished breath sounds (in COPD), crackles (in pulmonary edema, pneumonia, or pulmonary fibrosis), wheezing (primarily in asthma, but occasionally in COPD), or bronchial breath sounds (in pneumonia). Stridor, a harsh or musical wheeze-like sound, most prominent in or confined to the inspiratory phase of ventilation, strongly suggests upper airway obstruction, often a medical emergency. Cyanosis of the mucous membranes and nail beds is an unreliable sign of hypoxemia. Somnolence (falling asleep inappropriately) can be an important clue to the presence of inadequately compensated CO_2 retention, but, of course, there are many other possible causes of somnolence.

Laboratory Findings

Arterial blood gases (measurements of pH, $PaCO_2$, and PaO_2 in arterial blood) are the definitive tests to diagnose both types of respiratory failure. They allow for precise assessment of the adequacy of oxygenation, along with determination of acid/base status and of the adequacy of ventilation. Drawbacks are the painful nature of the necessary arterial puncture, the small risk of arterial injury, and the fact that they provide only a "snapshot" look at the status of respiratory function.

Other non-invasive tests can be of value. The venous bicarbonate (often identified as "CO2" on blood electrolyte reports), rises in compensation for rising pCO_2. Thus, although bicarbonate measurements without blood gases do not rule in or rule out respiratory failure, a normal venous bicarbonate can be reassuring, especially when the pulse oximeter reading is normal and the patient's mental status is well preserved.

Pulse oximetry is a noninvasive technique to allow measurement and monitoring of blood oxygen (SpO2). A patient's fingertip is transilluminated by two wavelengths of light, typically 660nm (red) and approximately 900 nm (infrared), in rapid alternation. Changes in absorbance of each of the two wavelengths, caused by pulsing arterial blood is measured, and the ratio of the two is used to calculate percent oxygen saturation.

Pulse oximetry has become an indispensable vital sign for all emergency rooms (ER), operating rooms and procedure rooms, and it is fast becoming a part of emergency medical service (EMS) evaluations and even routine medical visits. It is rapid, painless, inexpensive, and (generally) accurate. It can quickly rule in or rule out most cases of hypoxic respiratory failure and those cases of hypercapnic respiratory failure where the oxygen level is also low. The only drawbacks are (1) false negative results in cases of carbon monoxide poisoning (and even those may soon be routinely covered by multiwavelength models that measure carboxyhemoglobin as well as oxyhemoglobin), (2) a few cases of failure to achieve estimates of oxygenation when the pulse is too weak, usually due to shock or peripheral vascular disease, and (3) although it can perhaps screen for hypercapnia (significantly hypercapnic patients will not have normal S_pO_2 when breathing room air), it cannot rule out hypercapnia in a patient breathing oxygen, so it may provide a false sense of security.

Pulmonary function testing is usually valuable in the evaluation of the underlying pulmonary condition(s) that cause or contribute to respiratory failure. Forced expiratory volume in one second (FEV1, the maximal amount of air that can be exhaled in one second) is a good overall estimate of the ability of the respiratory system to accomplish ventilation. The pattern of impairment in pulmonary function may also be revealing; if FEV1 and the forced vital capacity (the maximum total volume exhaled in one breath, FVC) are down in proportion, that suggests a restrictive pattern of respiratory dysfunction – pulmonary parenchymal (pneumonia, pulmonary fibrosis, etc.), chest wall (rib fractures, chest surgery, etc.), or respiratory neuromuscular impairment (Guillain Bare Syndrome, Lou Gehrig's disease, etc.). When FEV1 is more severely impaired than is the FVC, then this suggests an obstructive airways disease (COPD or asthma). Another common pulmonary function test, the diffusing capacity for carbon monoxide (DLCO), can be of use. Severe reductions suggest pulmonary parenchymal disease (pneumonia, pulmonary fibrosis, etc.) or pulmonary vascular disease (pulmonary embolism or pulmonary hypertension). The DLCO can also be low if the blood carbon monoxide level is elevated due to either smoke inhalation of any type including tobacco smoke.

TREATMENT OF RESPIRATORY FAILURE

Treatment of both types of respiratory failure normally hinges on treatment of the underlying condition. Thus, central drive impairment due to drug overdose can often by treated by specific antidotes (e.g., naloxone for opioid overdose), pulmonary edema with cardiac medications, pneumonia with antibiotics, and asthma with bronchodilators and corticosteroids. Adjunctive treatments, especially the administration of supplemental oxygen, can be beneficial, while awaiting improvement in the underlying disease or in the situations in which the underlying disease cannot be corrected.

Supplemental oxygen is normally provided by one of three delivery systems, all of which are routinely available in all Fire/EMS units. They are nasal cannula, Venturi mask, and non-rebreather mask. Some EMS units are also able to supply oxygen at elevated continuous positive airway pressures (CPAP), which is discussed later in this chapter. The fractional concentration of oxygen (FIO2) in room air is 21 percent. The FIO2 actually delivered by nasal cannulae is quite variable and not reliably predictable by the liter per minute flow rate, in part because of variable amounts of mouthbreathing, but more importantly because inspiratory flow rates and consequent entrainment of room air are tremendously variable. The Venti-mask uses a jet of oxygen at high flow rate (5-15 liters per minute) through a delivery device shaped to entrain predictable amounts of room air (using the Venturi principle), so that FIO2 can be adjusted relatively precisely. The Venti-mask results in more predictable FIO2 than does nasal cannula, but it still suffers from entrainment of variable amounts of room air around the edges of the mask and through the holes that are built into the mask to allow egress of excess flow. The non-rebreather mask provides 100% oxygen from a bag reservoir into the mask and uses one-way valves to direct exhaled gases out of the mask. Even a non-rebreather mask, however, entrains a variably small but not negligible amount of room air around the mask and through one of the expiratory one-way valves, which is routinely left open so as to avoid suffocation if the reservoir runs dry.

Supplemental oxygen is the major adjunctive treatment for respiratory failure, and in patients with hypoxic respiratory failure, it can be used safely (for short periods) at any dose and for indefinite periods at "nontoxic" concentrations (FIO2 <50%). For the hypoxemia that often accompanies the hypercapnic type of respiratory failure, however, oxygen must be used with more caution. Especially when CO_2 retention has been present over long periods of time, persons in hypercapnic respiratory failure lose their ability to regulate minute ventilation based on pH and PCO_2. Consequently, their ventilatory drive is based primarily on oxygenation with low levels of oxygen stimulating increased breathing. If excessive oxygen is administered to such a person, there is a risk that further hypoventilation will occur, worsening respiratory acidosis, causing somnolence or even coma, and potentially resulting in respiratory arrest. For that reason, in hypercapnic respiratory failure (and in persons suspected of having hypercapnic respiratory failure in whom blood gases have not been measured), oxygen must be administered at low enough flow rates or FIO2 to avoid over-oxygenation. In practice, pulse oximetry is used to guide oxygen therapy, aiming for a pulse oximetriy reading (SpO2) that is safe but less than normal, 88 - 93% in persons with hypercapnic respiratory failure.

Mechanical Ventilation

Mechanical ventilation is of obvious benefit in people undergoing surgery, anesthetized and paralyzed, unable to breathe for themselves, and in people in respiratory arrest or severe intractable hypercapnic respiratory failure. Mechanical support is most clearly indicated in hypercapnic respiratory failure, but it can also be beneficial for hypoxemic respiratory failure, by "blowing open" collapsed regions of the lung and by improving the distribution of ventilation even in regions already open.

In addition to correcting hypoxemia and hypercapnia, there are other benefits of mechanical ventilatory support , including:

- Maintenance of oxygenation and acid/base balance
- Comfort
- Improved sleep
- Prevention of inspiratory muscle fatigue

Perhaps most important is the comfort issue. Dyspnea (shortness of breath) comes in many different varieties and has many potential physiologic causes, but in hypercapnic respiratory failure, one of the main problems appears to be the perception of the need for excessive respiratory effort. Although mechanical ventilation does not totally take over the work of breathing, it can substantially reduce the load on the respiratory muscles, especially if adequate inspiratory flow rates are used.

Mechanical ventilatory support also has a clear and established role in obstructive sleep apnea, being able to "splint" the upper airways open, preventing the upper airway collapse that is the major pathophysiologic cause of obstructive sleep apnea.

Noninvasive vs. Invasive Mechanical Ventilatory Support

Ventilatory support can be accomplished by noninvasive or invasive means, the latter via endotracheal intubation or tracheostomy. The most common noninvasive techniques deliver positive pressure support (continuous or bilevel positive pressure breathing [CPAP or BiPAP], or volume ventilation), by a tight-fitting nasal mask or full face mask[3]. The noninvasive techniques have the advantages of (usually) less discomfort, preserved ability to talk and to cough, less risk of airway (laryngeal and tracheal) injury and of ventilator associated pneumonia and the likelihood that the duration of support will be shorter (Table 4-5.3). The invasive methods have the advantage that ventilation is more effective. When respiratory failure is severe, noninvasive methods are just not adequate to provide the necessary volumes to correct it. With invasive mechanical ventilation, although secretions can still be aspirated alongside the endotracheal or tracheostomy tube, the risk of massive aspiration is considerably less than with noninvasive techniques. There is also easier access to secretions, both for culture and for therapeutic purposes. And, finally, aerophagia (swallowing air), a common complication of noninvasive nasal or face-mask positive pressure breathing, is not a problem in patients invasively ventilated via an endotracheal tube or tracheostomy.

Mechanical Ventilatory Support Factors	
Noninvasive	***Invasive***
• Less discomfort • Less risk of tracheal or laryngeal injury • Less risk of ventilator-associated pneumonia • Shorter duration of support • Preserved ability to talk/cough	• More effective • Less need for minute to minute monitoring • Less risk of aspiration • Easier access to secretions • No risk of aerophagia

Table 4-5.3: Mechanical Ventilary Support Advantages and Disadvantages

Types or Modes of Mechanical Ventilation

Assist/Control

The simplest mode of mechanical ventilation in general use is known as "Assist/Control." It is perhaps more accurately described as it is used in practice as "volume ventilation, triggered by assist efforts, with back-up timed triggering if needed." The ventilator is triggered to deliver a breath, either when its computer senses the patient's effort by detection of an abrupt decline in airway pressure (assisted ventilation), or when a set period of time has passed without a patient effort (controlled ventilation). The ventilator then delivers a set volume of a set mixture of air and oxygen at a set inspiratory flow pattern and rate and a set level of positive end-expiratory pressure (PEEP). The advantage over the previously-available pressure ventilation, is that the ventilator adapts to changing mechanics by essentially guaranteeing the delivery of a reasonable tidal volume, thereby avoiding the unexpected hypoventilation that were problems of the old pressure ventilation mode. A disadvantage is that over-ventilation is a constant threat; every effort by the patient results in a full tidal volume, so patients with severe shortness of breath often are found to "over-breathe" or over-ventilate, with consequent respiratory alkalosis (hypocapnia), elevated pressures and subsequent difficulties with weaning. Another disadvantage is that patients who are not sedated often find the set flow rates too low to satisfy their perceived need, so shortness of breath and discomfort may persist, despite mechanical ventilation.[4]

Pressure Support and CPAP (PS/CPAP)

PS/CPAP is a technique to reduce the effort required to take spontaneous breaths. CPAP (continuous positive airway pressure) is the pressure that the ventilator's computer maintains in the airway during the expiratory phase by providing sufficient inflow of the set air/oxygen mixture (essentially the same as positive end-expiratory pressure or PEEP). When the patient makes an inspiratory effort, the ventilator switches to the higherpressure support (PS) level of airway pressure maintenance and provides a higher and constantly adjusted level of inflow, so as to maintain the set PS level. When the patient terminates the inspiratory effort, the abrupt increase in airway pressure (occurring because

air is no longer entering the lungs) is sensed by the ventilator, which switches back to the CPAP level of airway pressure for the expiratory phase.

Originally developed as a technique to ease the transition from mechanical ventilator to spontaneous breathing (weaning), PS/CPAP is now used both as a weaning tool and as a primary mode of mechanical ventilation, especially for patients who do not have impaired mental status. As such, because patients are able to control their own flow rate, PS/CPAP may be a more comfortable mode of ventilation than is Assist/Control for some patients. A disadvantage is that staff may be lulled into a false sense of security; the fact that a patient breathes comfortably on PS/CPAP 15/5 cm H_2O does not mean that he or she can tolerate lower levels of PS/CPAP.

Synchronous Intermittent Mandatory Ventilation (SIMV)

In the SIMV mode, the ventilator delivers a set number of breaths per minute at a set volume, flow rate and pattern, and PEEP, but, when the patient makes an inspiratory effort between ventilator breaths, instead of triggering another ventilator breath, as in the Assist/Control mode, the patient breathes "on his own" (usually assisted to some degree by pressure support). As with PS/CPAP, SIMV was originally developed as a weaning tool. SIMV has generally fallen out of favor for weaning but can be used for relatively-stable respiratory failure patients.

Specialized Modes

A number of specialized modes of mechanical ventilation have been developed but are beyond the scope of this chapter. They include Inverse Ratio Ventilation (IRV), Airway Pressure Release Ventilation (APRV), High Frequency Ventilation (HFV) and other modes that could be useful in patients with severe lung disease. To date, none has been unequivocally demonstrated to improve outcomes over conventional modes. The only mechanical ventilation strategy that has proven better outcomes than its competitors is ventilating at low volumes (<7 ml/kg tidal volumes) in severe acute lung injury[5].

Types / Modes of Mechanical Ventilation	
Mode	*Key Settings*
Assist/Control	Backup rate, volume, flow rate & pattern, FiO2, PEEP, trigger sensitivity
SIMV	Rate, volume, flow rate & pattern, FiO2, PEEP, PS for spontaneous breaths
PS/CPAP	PS level above PEEP, PEEP, FiO2
Specialized Modes	(IRV, pressure release, high frequency ventilation)

Table 4-5.4: Types or Modes of Mechanical Ventilation

WEANING OR REMOVING A PATIENT FROM MECHANICAL VENTILATION

In this situation, medical dictionaries define "weaning" as the gradual withdrawal of a patient from dependency on mechanical ventilation life-support systems. The vast majority of patients do not need weaning. They were intubated for surgical procedures or for a clearly temporary medical condition (ex., seizures, asthma exacerbation, drug overdose, etc.). Shortly after the anesthesia wears off or the acute medical condition resolves, the patient is assessed and in most cases, the patient is breathing well, mechanical ventilation is discontinued and the endotracheal tube removed. However, in a minority of cases, the condition responsible for the respiratory failure is complex (COPD, sepsis, severe trauma, etc.) and is often complicated by multiple other medical problems. In these cases, weaning may be necessary to help re-train the patient's muscles or more likely to provide repetitive assessments to allow both the patient and medical team to gain confidence that the underlying condition has improved to the point where spontaneous ventilation could be successful.

Weaning can be accomplished by daily trials of spontaneous breathing (usually using low-level PS and CPAP). Some clinicians favor one daily trial with gradually lengthening duration, while other favor several daily trials of shorter duration. SIMV can also be used, with gradual reductions in the frequency of ventilator breaths. In practice, at least at the beginning of the weaning process, most clinicians wean patients primarily during the day and return them to a more comfortable mode of mechanical ventilation during the night. No technique for weaning has been unequivocally shown to be better than any other.[6,7]

In my view, only three elements are required for weaning:

- Nurse (or Respiratory Therapist)
- Pulse Oximeter
- Enthusiasm

As long as progress is being made, any technique can be used. The patient should be observed for evidence of discomfort, airway secretions, myocardial ischemia, hypoxemia, and hypotension, and returned to a comfortable mode of ventilation if such problems occur.

THE DECISION TO USE INVASIVE VENTILATORY SUPPORT AND THE IMPORTANCE OF ADVANCE DIRECTIVES IN PATIENTS WITH CHRONIC DISEASE

In patients with clearly-reversible respiratory failure, not adequately managed by noninvasive means, intubation and mechanical ventilation are almost always indicated. On the other hand, for patients with terminal illnesses, facing the onset of respiratory failure from which they are not expected to recover, especially when there is no substantial likelihood of meaningful cognitive function in the future, mechanical ventilation would simply prolong the process of dying. In most jurisdictions, intubation and mechanical ventilation can legally be withheld in such cases on the basis of medical futility.

The decision is more difficult when the results of ventilatory support cannot be accurately predicted, but when intubation (or tracheostomy) is necessary to prevent immediate death or in cases when chronic mechanical ventilation is necessary but death is not imminent. For most patients, life on long-term chronic mechanical ventilation is difficult and unpleasant, so many patients with chronic disease prefer to issue written advance directives documenting their desire not to be intubated ("do-not-intubate" or "DNI" directives). Decisions regarding DNI directives are optimally made prior to the emergent need for mechanical ventilation,[8,9] but the majority of patients unfortunately do not make such advanced decisions and are forced to make these decisions when respiratory failure is imminent or to rely on a family member or legal guardian to determine their wishes. All patients with chronic disease and their families should be encouraged to avoid this stress and instead to make their wishes known early on, before the threat of respiratory failure. They should not be concerned that DNI decisions are set in stone. They remain empowered to change their decision at any time as their condition, circumstances or outlook changes.

CONCLUSIONS

Respiratory failure is a common serious, life-threatening consequence of many other pulmonary and non-pulmonary conditions. It is defined as a failure of gas exchange, either for oxygen, for carbon dioxide, or both. Treatment is most satisfactory when the underlying cause can be corrected, but is otherwise focused primarily on supplemental oxygen, and, in severe cases, mechanical ventilation. Considerable progress has been made in improving the delivery of ventilatory support, especially in the relatively recent development of safe and effective forms of "noninvasive ventilatory support." Nonetheless, respiratory failure, especially when the underlying cause is chronic respiratory disease, remains a major cause of death in this country.

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