

**MINISTRY OF HEALTHCARE OF UKRAINE
HSEEU "Ukrainian Medical Stomatological Academy"**

"Approved"
at the meeting of internal
medicine №1 department
Head of Department
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Protocol № 4 from 13.10.2016

**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in pulmonology clinic
<i>Study subject</i>	Management of the patients with pulmonary infiltrates
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

1. The aims of the training course:

To Know:

1. The main causes of infiltrative lung diseases.
2. Differential diagnosis of infiltrative lung diseases.
3. Test plan, the role of radiological, instrumental and laboratory methods of examination (radiography, CT, bronchoscopy, sputum crops).
4. Drug and non-medicamentous treatment.
5. Indications for surgical treatment.
6. Primary and secondary prevention.

To be able to:

Conduct surveys and examination of patients with major Pulmonological syndromes

- draft examination of patients with major Pulmonological syndromes
- justify the use of basic diagnostic methods in pulmonology, identify indications and contraindications for their conduct, possible complications
- prescribe treatment, determine prognosis and to conduct primary and secondary prevention in the major respiratory diseases
- diagnose and assist in respiratory distress
- Perform pikuometry

Demonstrate knowledge of moral principles

The contents of topic:

Text

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MANAGEMENT OF THE PATIENTS WITH PULMONARY INFILTRATES

The most common causes of pulmonary infiltration are pneumonias, pulmonary tuberculosis, lung cancer, lung infarction.

Classification of pneumonias:

Community-acquired pneumonia

Pneumonia in immunocompromised host

Nosocomial pneumonia

Pneumonia due to aspiration

Community-acquired pneumonia has become a major health problem throughout the world.

The etiology of community-acquired pneumonia is a long- and often-debated topic. Some researchers imply that outpatients contract different causative agents than do inpatients, while other investigators do not make major distinctions between the two categories. Other experts have attempted to elucidate the causes according to patient age. Even after examination of virtually every study completed on community-acquired pneumonia, it is extremely difficult to posit any useful probability of cause on the basis of age or outpatient versus inpatient setting.

The difficulty arises from a simple fact: in most patients with community-acquired pneumonia (about 98% of those treated as outpatients and 50% to 60% of those treated as inpatients), the

causative organism is not known. Even in studies at academic centers where every effort is made to culture samples from all conceivable sites, the success rate in determining a cause is only about 50%. In most cases with an "established" cause, testing has been done on expectorated sputum, and this source of sample material always has the potential of contamination with upper-airway organisms. Correlation is not high between findings in expectorated sputum and findings in specimens from lower in the respiratory tract, obtained by bronchoscopy with a protected brush or by fine-needle or transtracheal aspiration.

A variety of organisms can cause community-acquired pneumonia. A review of studies during the past 20 years that included more than 100 subjects (total, >4,900 patients) reveals that the following are the most common pathogens(1): *Streptococcus pneumoniae* (9% to 75%; mean, 33%), *Haemophilus influenzae* (0 to 50%; mean, 10%), *Legionella* species (0 to 50%; mean, 7%), and *Chlamydia pneumoniae* (0 to 20%; mean, 5%) (1,3,5,8). Other organisms reported, in no particular order, were *Mycoplasma pneumoniae*, other gram-positive organisms, gram-negative organisms, anaerobes, mycobacteria, fungi, and viruses. The incidence of so-called "atypical" (legionellal, chlamydial, and mycoplasmal) pneumonias is particularly difficult to ascertain, because diagnosis of these infections is usually made by serologic testing. This method indicates only whether there has been exposure to these organisms and an immunologic response; it does not necessarily establish that they are causative agents of the pneumonia under scrutiny.

Despite all the contradictory statistics on etiology, most investigators agree that *S pneumoniae* is the leading cause of community-acquired pneumonia in both inpatients and outpatients.

Considerations in choosing outpatient therapy

Perhaps the greatest debate concerning community-acquired pneumonia has been over therapeutic options. Because outpatient therapy must be chiefly empirical, antibiotics should be chosen that provide adequate coverage against the putative treatable organisms known to cause community-acquired pneumonia. The Infectious Diseases Society of America recommends selecting from among the macrolides erythromycin, clarithromycin (Biaxin), and azithromycin (Zithromax); the fluoroquinolones levofloxacin (Levaquin), trovafloxacin mesylate (Trovan), grepafloxacin (Raxar), sparfloxacin (Zagam), and any other fluoroquinolone with enhanced activity against *S pneumoniae*; and (in patients between the ages of 17 and 40) doxycycline.

Duration of therapy

The preferred duration of therapy for community-acquired pneumonia is an unresolved issue, and surprisingly, applicable prospective studies are not available. The Infectious Diseases Society of America recommends 7 to 10 days. However, one study found that clinical outcomes were as good with a 3- to 5-day course of azithromycin as with the usual 7- to 10-day course of comparable antibiotics. Outcome research is urgently needed, because both cost and resistance could be minimized by using shorter courses of antibiotic therapy.

Antibiotic resistance

Development of bacterial resistance has been a significant problem related to antibiotic use. The frequency of resistance among community-acquired pathogens is increasing and has been linked to inappropriate use of antibiotics, such as the following:

To treat viral infections

To treat resistant organisms

For longer periods than necessary

To treat a particular organism with a much-wider-spectrum agent than needed

Unnecessary use of antibiotics for viral illnesses is common and has led to increasing rates of antibiotic resistance among *S pneumoniae* and other community-acquired pathogens. In addition, boundaries between community and hospital environments are blurring, with potential negative consequences regarding resistance. Resistance genes occur in both pathogenic and commensal organisms to which people are exposed continually through food, the environment, and animals. The multitude of genetic mechanisms available for evolution and reassortment of antibiotic resistance genes virtually ensures that genes useful to survival of bacteria are rapidly disseminated.

On the bright side, resistance to newer fluoroquinolones (eg, trovafloxacin) may be slow to develop because bacteria might be required to mutate more than once to achieve a significant level of resistance. Encouragingly, one recent multicenter study found (theoretical considerations notwithstanding) that resistance to antibiotics did not parallel antibiotic use.

Many experts believe that empirical outpatient treatment of community-acquired pneumonia must include coverage for the common causative organisms, which include such gram-positive bacteria as *S pneumoniae* and such atypical organisms as *Legionella*, *Mycoplasma*, and *Chlamydia*. Since *S pneumoniae* is conceded to be the most common causative agent in community-acquired pneumonia, the organism deserves particular attention in therapeutic considerations.

In general, choosing antibiotics to which organisms are highly resistant should be avoided. However, there is little clinical evidence demonstrating that using antibiotics to which recovered organisms have high or intermediate resistance results in more treatment failures than using antibiotics to which the organisms are sensitive. In one recent study, a few clinical failures occurred among patients who had highly penicillin-resistant *S pneumoniae* infection. It seems intuitively obvious that treating infections with antibiotics to which organisms are highly resistant will eventually result in significant numbers of treatment failures.

Differences by location

Resistance to different antibiotics may vary by hospital and by locale, so the pattern of resistance in a geographic area of practice must be known to make a rational selection among antibiotics.

Information on resistance patterns can be obtained from each hospital's microbiology department and each state's board of health.

Surveillance studies show almost exponential increases in penicillin-resistant *S pneumoniae* over the past 3 years in the United States. This trend is also true worldwide. If a location has considerable (eg, more than 5% to 10%) resistance to *S pneumoniae*, use of another antibiotic should be considered. High-level resistance to penicillin is associated with high-level resistance to macrolides, cephalosporins, and doxycycline as well. In contrast, to date, high-level resistance to the newer

fluoroquinolones is less than 1%, and cross-resistance between these agents and penicillin has not, as yet, been recognized.

Minimizing resistance

Theoretically, choosing doses of antibiotics on the basis of pharmacodynamics should increase eradication of bacteria and thus minimize development of resistance. Preventing antibiotic resistance through rapid DNA-based testing is an emerging and potentially promising biotechnologic tool.

Additional new techniques under way to combat resistance include development of products that block bacterial adherence to tissues, design of drugs to fit model chemicals into the crystal structures of the catalytic sites of key enzymes from bacteria, and use of other highly sophisticated molecular biology tools.

More general solutions to the problem of increasing antibiotic resistance include intensive education of healthcare providers, enhanced education of patients, institution of mandatory surveillance programs, and funding of appropriate research.

Preventive measures

Virtually all experts on community-acquired pneumonia recommend use of polyvalent pneumococcal vaccine (Pneumovax 23, Pnu-Imune 23) in patients considered at increased risk. Some authors question the usefulness of pneumococcal vaccine, particularly in the elderly, but case-control and cohort studies have documented its efficacy. Prospective studies evaluating the impact of immunization on disease incidence, antibiotic resistance, and overall treatment cost are under way.

Summary

Most patients with community-acquired pneumonia are treated as outpatients, and choice of therapy is usually empirical because the etiologic agent is unknown. Therapy should include coverage for both typical and atypical organisms. In geographic areas with highly resistant *S pneumoniae*, one of the newer fluoroquinolones should be considered, since resistance to penicillin is associated with cross-resistance to macrolides and tetracyclines. Once-daily dosing should be given strong preference because more-frequent dosing results in poor compliance, which may lead to inadequate therapy and increased resistance. At present, the duration of therapy should probably be no less than 7 days.

Patients should be categorized for mortality risk with objective scoring methods, and the need for hospitalization should be decided accordingly. Greater use of observational and intermediate-care beds is encouraged, as is improved utilization of pneumococcal vaccine. The main types of pneumonia are presented.

PNEUMOCOCCAL PNEUMONIA

Essentials of Diagnosis

- Sudden onset of shaking chills, fever, chest pain, and cough with rust-colored sputum.
- X-rays show infiltration, often lobar in distribution, but sometimes patchy.
- Pneumococci are present in the sputum and often in the blood.
- Leukocytosis.

General Considerations

Pneumonia is an inflammatory process in lung parenchyma most commonly caused by infection. The consolidation of pneumonia must be differentiated from pulmonary infarction, atelectasis with bronchial obstruction, and congestive heart failure, but it may coexist with any of these conditions. The pneumococcus accounts for 50-80% of community-acquired bacterial pneumonias; types 1-9 and 12 are most commonly found in adults, whereas types 6, 14, 19, and 23 are most common in children. These bacteria frequently are in the normal flora of the respiratory tract. The development of pneumonia must therefore usually be attributed to an impairment of natural resistance. Conditions leading to aspiration of secretions include suppression of the cough or epiglottic reflex, impairment of upward migration of mucous sheets (propelled by cilia), and impairment of alveolar phagocyte function. Among conditions that predispose to pneumonia are viral respiratory diseases, malnutrition, exposure to cold, noxious gases, alcohol intoxication, depression of cerebral functions by drugs, and cardiac failure. Pulmonary consolidation may be in one or more lobes or may be patchy in distribution.

Clinical Findings

A. Symptoms and Signs: The onset is usually sudden, with shaking chills, "stabbing" chest pain (exaggerated by respiration but sometimes referred to the shoulder, abdomen, or flank), high fever, cough and "rusty" sputum, and occasionally vomiting. A history of recent upper respiratory illness can often be elicited.

The patient appears severely ill, with marked tachypnea (30-40/min) but no orthopnea. Respirations are grunting, nares flaring, and the patient often lies on the affected side in an attempt to splint the chest. Herpes simplex facial lesions are often present.

Initially, chest excursion is diminished on the involved side, breath sounds are suppressed, and fine inspiratory rales are heard. Later, the classic signs (absent breath sounds, dullness, etc) of consolidation appear. A pleural friction rub or abdominal distention may be present. During resolution of the pneumonia, the signs of consolidation are replaced by rales. Physical findings are often inconclusive, and repeated x-ray examination is helpful.

B. Laboratory Findings: Blood cultures are positive for pneumococci in 15-25% of cases early in the disease. In peripheral blood, leukocytosis (20-35 thousand/[^]L) is the rule, and a low white blood cell count carries a poorer prognosis.

Sputum must be examined by Gram's stain and by culture. In the smears, the presence of many squamous epithelial cells suggests heavy contamination with saliva, and such specimens are of no value. Typical sputum from pneumococcal pneumonia contains many red and white cells (PMNs) and many pneumococci. If good sputum specimens are not obtainable, a trans-tracheal aspirate may reveal the causative agent, but this procedure is not without risk. A microscopic "quellung" reaction with pooled antiserum rapidly identifies pneumococci in fresh sputum.

C. X-Ray Findings (picture 1): Initially, there may be only a vague haziness across the involved part of the lung field. Later typical consolidation is well defined either in lobar or in patchy distribution. Fluid shadows in the costophrenic angles may appear before pleural exudate can be detected by physical examination. During resolution of the consolidation, which may require 8-10 weeks, areas of radiolucency may appear, suggesting "pseudocavitation."

Treatment

A blood culture and a good sputum specimen for smear and culture should always be obtained before treatment is started. The dosage and route of administration of antimicrobial drugs are influenced to some extent by the clinical severity of the disease, the presence of unfavorable prognostic signs (see below), and the presence of complications.

A. Antibacterial Therapy: Penicillin G is the drug of choice. It is given initially in dosages ranging from 600,000 units of procaine penicillin every 12 hours intramuscularly for moderate illness to 1 million units of aqueous penicillin G given every 4 hours

rapidly into an intravenous infusion in severe cases. Only after there has been a definite response to treatment should oral penicillin V (400,000 units every 4-6 hours) be considered. All pneumococci are susceptible to penicillin at present, although strains requiring 4 units/mL of penicillin G have occurred in South Africa and, rarely, elsewhere. Some strains resistant to tetracyclines, erythromycin, or lincomycin have been encountered. Therefore, these alternatives to penicillin (eg, in patients with documented hypersensitivity) may fail, but they (or cephalexin or cephadrine, 0.5 g every 4-6 hours) can be tried orally in mildly ill patients. In more severely ill persons, cefazolin, 4 g intravenously daily, is a reasonable alternative. Treatment with an effective drug should be continued for 3 days after defervescence.

Sulfonamides are not in favor now because the therapeutic response is slower than with penicillin. However, sulfisoxazole diolamine or sodium sulfadiazine, 4-6 g intravenously, followed by maintenance doses intravenously or orally, is adequate (if not optimal) treatment for many cases of pneumococcal pneumonia.

B. General Supportive Treatment:

1. Ventilation and oxygenation-An adequate airway must be maintained—if necessary, by tracheal suction, endotracheal tube, or tracheostomy. Oxygen must be supplied to any patient with severe pneumonia, cyanosis with Pao₂ below 60, or marked dyspnea;

this will also help to prevent pulmonary edema. Oxygen may be supplied by nasal catheter, soft rubber mask, or oxygen tent. With masks, a 95% oxygen concentration can be maintained, whereas with nasal tubes or tents the concentration will reach only 40- 50%. However, masks are difficult to tolerate because of cough and expectoration. Oxygen must be humidified to prevent drying of secretions.

2. Management of shock and pulmonary edema-These are the most frequent causes of death in pneumonia. Oxygen administration tends to prevent pulmonary edema; impending right heart failure must be managed, and digitalization is urgent.

3. Management of toxic delirium-Toxic delirium occurs in any severe pneumonia and may be particularly difficult to manage in alcoholics. Delirium, anxiety, and restlessness during waking hours may be treated with diazepam, 5 mg, or chlorthalidone, 10 mg, or phenobarbital, 15-30 mg orally 4-6 times daily. Pentobarbital, 0.1 g, or flurazepam (Dalmane), 30 mg, at bedtime helps to ensure adequate rest. If sedatives or tranquilizers are given, it is helpful to check the patient's sensorium frequently for any change suggestive of meningitis, which requires a diagnostic lumbar puncture.

4. **Fluids**-Patients with pneumococcal pneumonia may perspire profusely and lose much fluid and salt. Sufficient fluid must be given to maintain a daily urinary output of at least 1500 mL. Electrolytes must be kept in balance.

5. **Diet**-Initially, the dyspneic patient is anorectic, and a liquid diet is preferred. With improvement, a normal diet will be tolerated. If complications suggest a long illness, a high-protein, high-calorie diet with vitamin supplementation is indicated.

6. **Cough**-If cough interferes with sleep and rest, it may be suppressed with codeine phosphate, 15-30 mg every 3-4 hours subcutaneously or orally; or by elixir of terpin hydrate with codeine, 4 mL every 3—4 hours as necessary.

7. **Pleuritic pain**-For mild pain, spray ethyl chloride over the area of greatest pain for about 1 minute or inject a local anesthetic to anesthetize the involved dermatomes to provide temporary relief. Codeine phosphate, 15-30 mg, may be given as necessary for pain. For very severe pain, use meperidine, 50-100 mg subcutaneously, or morphine sulfate, 10-15 mg subcutaneously.

8. **Abdominal distention**-Abdominal distention is usually due to air swallowing in severe dyspnea and is a frequent problem in patients with pneumonia. Neostigmine methylsulfate, 1:2000, 1 mL subcutaneously, and insertion of a rectal tube will usually produce rapid initial decompression. Gastric dilatation can be relieved by suction through a nasal tube passed into the stomach.

9. **Congestive failure**- (Distinguish from shock and pulmonary edema.) In elderly patients or patients with preexisting heart disease, congestive failure may be precipitated by pneumonia. Rapid digitalization is indicated.

10. **Cardiac arrhythmias**-Extrasystoles usually require no treatment. If atrial fibrillation or flutter develops, rapid failure may be precipitated. Rapid digitalization is usually indicated in these cases.

C. Evaluation of Treatment: With proper selection of antimicrobial drugs, there should be marked improvement and defervescence in 72 hours or less. If this fails to occur, one must consider 3 main possibilities: (1) the presence of a serious complication such as empyema, pulmonary suppuration associated with bronchial obstruction, endocarditis, or meningitis; (2) infection by an organism other than the pneumococcus and resistant to the drug used; and (3) possible drug fever or other associated disease. If there is much pleural fluid, it must be aspirated promptly, smeared, and cultured to detect infection or empyema that requires drainage. If an organism other than the pneumococcus is shown to be the probable agent, treatment must be directed against it.

Complications

Complications of pneumococcal pneumonia occur with the following approximate frequencies: sterile pleural effusion (4-8%), empyema (0.5-2%), endocarditis and meningitis (0.1-0.3%), and pericarditis (0.1%). Other complications such as pneumococcal arthritis or lung abscess are even more rare. Fibrous organization of the pneumonia (in place of resolution) occurs sometimes but rarely causes disability. All pleural fluid collections must be aspirated and examined by smear and culture to permit early treatment of empyema.

Prognosis

Untreated pneumococcal pneumonia has a mortality rate of 20-40%. The following are unfavorable prognostic signs: age over 50 years, presence of underlying disease (eg, heart failure, cirrhosis), pregnancy, bacteremia, marked proteinuria, absence of leukocytosis, pulmonary edema, and shock. With early and adequate antimicrobial treatment, the fatality rate is about 5-8% but in bacteremic pneumonia it is 17-25%. Most fatalities occur in the age groups under 2 years and over 50 years. In untreated, uncomplicated cases, resolution by crisis (or more gradually) occurs 7-10 days after onset.

Prevention

A polyvalent vaccine containing polysaccharides from the 14 pneumococcus types that most frequently cause infection (1,2, 3,4,6, 8, 9, 12,14,19, 23,25, 51, and 56) is available. It has given significant protection against disease in persons at high risk: persons with sickle cell disease, splenectomized children, persons with chronic bronchopulmonary, cardiac, or renal disease, and elderly or debilitated persons. A single dose of 0.5 mL is given intramuscularly and may cause local erythema, soreness, or fever. It should not be given during pregnancy. Children at high risk can receive vaccine at age 6 months and again at 2 years. In addition, prophylactic penicillin may be required. Regrettably, some children under 2 years of age and some patients with myeloma or lymphoma have a poor antibody response to the vaccine. In adults, the need for revaccination is not established.

OTHER BACTERIAL PNEUMONIAS

Primary bacterial pneumonias caused by single bacterial species other than the pneumococcus may account for up to 25% of community-acquired and 80% of hospital-acquired pneumonias. All of these pneumonias may have somewhat similar physical findings and x-ray evidence of pulmonary infiltration or consolidation. For proper treatment, it is crucial to identify the causative agent by blood culture and by sputum examination with stained smear and culture. Transtracheal aspiration, fiberoptic bronchoscopy, or even lung biopsy may be needed for specific diagnosis and treatment.

Streptococcal Pneumonia

Pneumonia due to hemolytic streptococci occurs usually as a sequela to viral infection of the respiratory tract, especially influenza or measles, or in persons with underlying pulmonary disease. The patients are usually in a severely toxic condition and cyanotic. Pleural effusion develops frequently and early and progresses to empyema in one-third of untreated patients. The diagnosis rests on finding large numbers of streptococci in smears of sputum and culturing hemolytic streptococci from blood and sputum.

The treatment of choice is with penicillin G in a dosage similar to that for pneumococcal pneumonia (see above). If treatment is started early, the prognosis is good.

Staphylococcal Pneumonia (picture 2)

Pneumonia caused by *Staphylococcus aureus* occurs as a sequela to viral infections of the respiratory tract (eg, influenza) and in debilitated (eg, postsurgical) patients or hospitalized infants, especially after antimicrobial drug administration. There is often a history of a mild illness with headache, cough, and generalized aches that abruptly changes to a very severe illness with high fever, chills, and exaggerated cough with purulent or blood-streaked sputum and deep cyanosis.

There may be early signs of pleural effusion, empyema, or tension pneumothorax. X-ray examination reveals lung consolidation, pneumatoceles, abscesses, empyema, and pneumothorax. The demonstration of pyopneumothorax and of cavities with air-fluid levels by x-ray is highly suggestive of Staphylococcal pneumonia. The diagnosis must be confirmed by stained smear of sputum (masses of white cells and gram-positive cocci, many intra-cellular) and culture (predominantly *S aureus*), and also by means of cultures of pleural fluid and blood. The white count is usually more than 20,000//zL.

Initial therapy (based on sputum smear) consists of nafcillin, 6-12 g/d, or vancomycin, 2 g/d, given intravenously in divided doses as a bolus. If the staphylococcus proves to be penicillin-sensitive by laboratory test, penicillin G, 20-60 million units/d intravenously, is the antibiotic of choice. Drugs should be continued for several weeks. If empyema develops, drainage must be established. The prognosis varies with the underlying condition of the patient and the drug susceptibility of the organism.

Legionella Pneumonia

The eponym legionnaires' disease has been given to a serious pneumonia that afflicted people attending the American Legion Convention in Philadelphia in 1976. Other outbreaks have been diagnosed respectively at least since 1965, and sporadic infections have occurred at least since 1947 in many places.

Legionella pneumophila is a poorly staining gram-negative bacterium that grows slowly on special media (eg, charcoal-yeast extract) at 35 °C. There are at least 8 species of *Legionella*, some with multiple serotypes. These organisms can be recovered in human disease from sputum, bronchial washings, pleural fluid, lung biopsies, or blood. *Legionella* species occur in the environment and are acquired by humans from aerosols, dust from air-conditioning systems, water, or soil. The infection is not usually communicable from patient to contacts. Asymptomatic infection is common at all ages, whereas symptomatic infection is most often an opportunistic pneumonia in immunocompromised individuals.

Asymptomatic infection is evident only by a rise in specific antibodies. Symptomatic infection is observed mainly in elderly persons, smokers, and patients undergoing hemodialysis or renal transplant.

The incubation period is estimated to be 2-10 days. Initial symptoms are malaise, diffuse myalgias, and headache, followed in 12-48 hours by high, non-remittent fever and chills. Nausea, vomiting, and diarrhea are frequent early in the illness. On the third day a dry cough begins that is nonproductive or produces scanty mucoid, sometimes blood-streaked sputum. Dyspnea and hypoxia become marked as signs of consolidation develop. Pleuritic chest pain occurs in one-third of patients. Severe confusion or delirium may occur.

There is leukocytosis with a shift to the left, hyponatremia, abnormal liver function tests, and, occasionally, microscopic hematuria. Chest x-rays reveal patchy, often multilobar pulmonary consolidation, and, occasionally, small pleural effusions. The illness usually worsens for 4-7 days before improvement begins in those who recover. During severe outbreaks, the mortality rate has

been 10% in those with manifest disease. Death is attributed to respiratory or renal failure or shock, with disseminated intravascular coagulation.

The diagnosis is based on a clinical picture compatible with the specific features of the disease and on negative results of bacteriologic laboratory tests for other pneumonias. The organism can be identified by immunofluorescence in cultures, lung biopsy, and, rarely, sputum specimens. A retrospective diagnosis is based on a significant rise in specific serum antibodies detected by immunofluorescence.

The treatment of choice is erythromycin, 0.5-1 g every 6 hours intravenously or orally for 2-3 weeks. This usually results in improvement in 2-3 days. Rifampin, 10-20mg/kg/d, has been suggested for patients who fail to respond to erythromycin. Assisted ventilation and management of shock are essential.

Pneumocystis carinii Pneumonia

This parasitic infection occurs in debilitated children or immunodeficient adults. It has been a prominent opportunistic infection in AIDS patients. The diagnosis is made by lung biopsy and the demonstration of typical cysts of *P. carinii* in impression smears of lung tissue stained with methenamine-silver. Early treatment with sulfamethoxazole-trimethoprim can cure the pneumonia. The same drug has been effective in prophylaxis during immunosuppression. An alternative, more toxic drug is pentamidine isethionate (available through the Centers for Disease Control, Atlanta, GA 30333).

"MIXED" BACTERIAL PNEUMONIAS (Hypostatic Pneumonia, "Terminal" Pneumonia, Bronchopneumonia)

Essentials of Diagnosis

- Variable onset of fever, cough, dyspnea, expectoration.
- Symptoms and signs often masked by primary (debilitating) disease.
- Greenish-yellow sputum (purulent) with mixed flora.
- Leukocytosis (often absent in aged and debilitated patients).
- Patchy infiltration on chest x-ray.

General Considerations

Mixed bacterial pneumonias include those in which culture and smear reveal several organisms, not one of which can clearly be identified as the causative agent. These pneumonias usually appear as complications of anesthesia, surgery, aspiration, trauma, or various chronic illnesses (cardiac failure, advanced carcinoma, uremia). They are common complications of chronic pulmonary diseases such as bronchiectasis and emphysema. Old people are most commonly affected ("terminal" pneumonia). Patients treated with intermittent positive pressure breathing apparatus or immunosuppressive drugs may develop pneumonia caused by gram-negative rods.

The following findings in a debilitated, chronically ill, or aged person suggest a complicating pneumonia: (1) worsening of cough, dyspnea, cyanosis; (2) low-grade, irregular fever; (3) purulent sputum; and (4) patchy basal densities on a chest film (in addition to previously noted densities caused by a primary underlying disease, if any), sometimes with local necrosis and cavitation.

Clinical Findings

A. Symptoms and Signs: The onset is usually insidious, with low-grade fever, cough, expectoration, and dyspnea that may become marked and lead to cyanosis. Physical findings are extremely variable and may not be impressive against a background of cardiac or pulmonary disease. The signs listed under Other Bacterial Pneumonias may also be present.

B. Laboratory Findings: The appearance of a greenish or yellowish (purulent) sputum should suggest a complicating pneumonia. Smears and cultures reveal a mixed flora, often including anaerobes. Predominant types should be noted. Leukocytosis is often absent in the aged and debilitated patient presenting with a mixed infection.

C. X-Ray Findings: X-ray (Picture 3) shows patchy, irregular infiltrations, most commonly posterior and basal (in bedridden patients). Abscess formation may be observed. Careful interpretation will avoid confusion with shadows due to preexisting heart or lung disease.

Differential Diagnosis

Mixed bacterial pneumonias must be differentiated from tuberculosis, carcinoma, and other specific mycotic, bacterial, and viral pulmonary infections (to which they may be secondary).

Treatment

Clear the airway and correct hypoxia. Unless a probably significant etiologic agent can be identified, give one of the new cephalosporins (eg, cefotaxime, 12 g/d intravenously) as initial therapy. This will be modified according to clinical and laboratory results.

Prognosis

The prognosis depends upon the nature and severity of the underlying pulmonary disease and varies with the predominating organism.

ASPIRATION PNEUMONIA

Aspiration pneumonia is an especially severe type of pneumonia, often with a high mortality rate. It results from the aspiration of gastric contents in addition to aspiration of upper respiratory flora in secretions. Important predisposing factors include impairment of the swallowing mechanism (eg, esophageal disease), inadequate cough reflex (eg, anesthesia, postoperative state, central nervous system disease, drug abuse), and impaired gastric emptying (eg, pyloric obstruction). Pulmonary injury is due in large part to the low pH (< 2.5) of gastric secretions.

Scattered areas of pulmonary edema and bronchospasm occur, and the x-ray appearance (pictures 4-5) may be confused with that of pulmonary emboli, atelectasis, bronchopneumonia, and congestive heart failure.

Removal of aspirated material by catheter suction or bronchoscopy may be attempted, but this usually fails to remove all aspirate completely. Corticosteroids (eg, prednisone, 100 mg orally on the first or second day) may reduce the intensity of the inflammatory reaction to acidic gastric secretion, but the value of corticosteroids in the treatment of aspiration pneumonia is not proved, and they increase the risk of superinfection. Some aspiration pneumonias have no bacterial component, but in many others a mixed bacterial flora is involved. Antimicrobial drugs directed against the latter (eg, penicillin G plus an aminoglycoside or the best available cephalosporin) are sometimes administered without waiting for evidence of progressive pulmonary infection. In doing so, however, there

is a risk of favoring the development of resistant microorganisms. Therefore, administration of antimicrobials should not continue without laboratory and clinical evidence of microbial infection. Assisted ventilation and supplementary oxygen are beneficial.

Infection in the immunocompromised host

Viral Pneumonias

Viruses are a common cause of serious infections of the lower respiratory tract among immunocompromised patients. Pathogens most commonly implicated are the herpesviruses--herpes simplex, varicella-zoster, and cytomegalovirus. These viruses belong to the family *Herpesviridae*, which consists of large, enveloped, double-stranded DNA viruses.

Herpesviruses vary widely in their ability to infect different types of cells. Further, they share the common ability to establish lifelong latent infection. This latter aspect is of particular concern for seropositive immunosuppressed persons, whose immune systems may be unable to contain the virus in its latent form.

Other viruses that cause significant lower respiratory tract disease in immunocompromised patients include adenoviruses and measles virus.

Epidemiologic, etiologic, and clinical characteristics

Immunocompromised patients are at particular risk for virus pneumonia. These include patients who are receiving cancer chemotherapy, those who are neutropenic, those infected with HIV, burn victims, those with congenital cell-mediated immunodeficiency, and those who are severely debilitated or malnourished as a result of prolonged hospitalization. Although the lung is often involved in disseminated HSV infection, disseminated disease seldom occurs among those with mucocutaneous HSV infections. Visceral dissemination develops in fewer than 10% of virus-seropositive transplant recipients with infection.

HSV pneumonia develops by two principal mechanisms. First, the presence of focal or multifocal infiltrates correlates with antecedent upper airway infection with virus. This pattern is most likely due to direct extension of viral infection from the upper to the lower respiratory tract, aspiration of infectious secretions, or reactivation of dormant HSV in vagal ganglia. Tracheitis or esophagitis and oral mucocutaneous lesions often precede development of pulmonary disease. Second, diffuse interstitial infiltrates may develop following viremia secondary to dissemination of HSV from genital or oral lesions or transfusion of HSV-infected blood. Early dissemination also may be reflected by other organ dysfunction, such as elevated liver enzyme levels.

The spectrum of respiratory diseases due to HSV infection ranges from oropharyngitis to membranous tracheobronchitis and diffuse or localized pneumonia. Usually the trachea and large bronchi are involved in creating a thick inflammatory membrane that can ultimately cause significant resistance to ventilation. Community-acquired pneumonia caused by HSV is uncommon, occurring usually only after a prolonged and complicated hospital stay.

Dyspnea and cough are the most common symptoms of HSV pneumonia. Fever, tachypnea, intractable wheezing, chest pain, and hemoptysis also occur. Cutaneous, genital, or oral lesions may herald pulmonary or disseminated disease.

Focal lesions on chest film begin as small nodules that are best seen in the periphery, away from normal vascular markings. As the disease progresses, the nodules may coalesce to form extensive infiltrates. HSV pneumonia may initially present as a focal or segmental pneumonia that has spread from upper airway lesions. However, it can ultimately extend to other areas of the lung, producing diffuse infiltrates similar to the pattern seen with viremic HSV infection.

Diagnosis

The diagnosis of virus pneumonia should be based on clinical suspicion, radiographic findings (picture 6), isolation of HSV from the lungs, and histologic findings of a necrotizing or hemorrhagic pneumonia. Since virus can be isolated from oropharyngeal secretions in 2% to 25% of normal hosts, positive sputum cultures are often difficult to interpret. The use of tracheal aspirates to bypass the upper respiratory tract can yield samples with significantly improved specificity. Bronchoscopy is especially useful for direct sampling of bronchial mucosal lesions and for obtaining bronchial brushings, washings, and biopsy specimens for histologic and cytologic examination. Scrapings from the base of ulcerated lesions can be examined with Wright or Giemsa stain for multinucleated giant cells and intranuclear inclusions. Specimens also can be examined by immunofluorescent staining with polyclonal- or monoclonal-specific antibodies or by electron microscopy. Appropriate viral cultures of mucosal lesions, blood, and respiratory secretions should always be obtained in cases of suspected herpetic pneumonia. Serologic assays are of little diagnostic use.

Treatment

Acyclovir (Zovirax), after it is metabolized to acyclovir triphosphate, inhibits viral DNA synthesis by competitively binding to viral DNA polymerase. Since oral acyclovir is poorly absorbed, intravenous acyclovir at a dosage of 250 mg/m² every 8 hours is currently the treatment of choice for HSV pneumonia (table 2). Adverse reactions are infrequent, but patients should be well hydrated to prevent renal impairment secondary to precipitation of acyclovir in the tubules, which occurs in 5% to 10% of patients. The dosage of acyclovir must be decreased in patients with underlying renal insufficiency.

Table 2. Treatment of severe viral infections of the lower respiratory tract

Virus	Therapy
Herpes simplex	Acyclovir (Zovirax)
Varicella-zoster	Acyclovir, VZIG
Cytomegalovirus	Ganciclovir (Cytovene), IVIG, foscarnet sodium (Foscavir)
Adenovirus	Supportive care, ribavirin (Virazole)*
Measles	Supportive care, IVIG, ribavirin*

IVIG, intravenous immunoglobulin; VZIG, varicella-zoster immune globulin.

*Currently not considered standard care or still under investigation.

More than half of all cases of viral pneumonia are complicated by other infections. Empirical broad-spectrum antibiotic therapy that includes an antistaphylococcal drug should be instituted in patients with progressive virus pneumonia that does not respond to antiviral therapy. If deterioration

continues despite the addition of antibiotics, a definitive diagnostic procedure such as bronchoscopy or open lung biopsy should be pursued to search for other opportunistic organisms, such as *Aspergillus*, *Candida*, and *Pneumocystis carinii*.

The role of adjunctive corticosteroids is still controversial. These agents should not be considered as standard care, especially in an already immunocompromised host. Ventilatory support is often required for severe hypoxemia. Fluid management is of special concern because fulminant pneumonia is often associated with pulmonary edema and alveolar hemorrhage.

Preventive efforts should be directed toward chemoprophylaxis of high-risk seropositive patients during induction of immunosuppression for transplantation. Passive or active immunization has not been proved to be helpful.

Summary

Three herpesviruses (herpes simplex, varicella-zoster, and cytomegalovirus) commonly cause respiratory tract infections in immunocompromised patients. Adenoviruses and measles virus are also significant causes of respiratory disease in this population.

Diagnosis of herpesvirus infections is difficult because these viruses can establish latency and are often shed intermittently in the absence of invasive disease. A positive respiratory tract culture of herpesviruses alone is not diagnostic of active invasive disease. Preventive measures should focus on limiting the patient's exposure to active infection, broad use of available vaccines in children and susceptible adults, and use of hyperimmune globulin and chemoprophylaxis in high-risk patients.

Adenovirus pneumonia is diagnosed by viral culture and rapid antigen detection assays, whereas measles pneumonia is often identifiable by the characteristic rash. Treatment of either adenovirus or measles pneumonia is primarily supportive.

SYSTEMIC FUNGAL DISEASES

(Systemic Mycoses)

General Diagnostic Principles

Several considerations are important in the diagnosis of the deep mycoses.

1. Many of the causative fungi are "opportunists," not usually pathogenic unless they enter a compromised host. Opportunistic fungus infections are particularly apt to occur and should be anticipated in patients after ionizing (x-) irradiation and during therapy with corticosteroids, immunosuppressives, or antimetabolites; they also tend to occur in patients with azotemia, diabetes mellitus, bronchiectasis, emphysema, TB, Hodgkin's disease or other lymphoma, leukemia, or burns. Candidosis, aspergillosis, phycomycosis, nocardiosis, and cryptococcosis are typical opportunistic infections.
2. Fungal diseases occurring as primary infections may have a typical geographic distribution. For example, in the USA, coccidioidomycosis is virtually confined to the southwest, while histoplasmosis occurs in the East and Midwest, especially in the Ohio and Mississippi River valleys. Blastomycosis is restricted to North America and Africa; paracoccidioidomycosis, often called South American blastomycosis, is confined to that continent. However, travelers can develop a symptomatic infection some time after returning from such endemic areas.

3. The major clinical characteristic of virtually every deep mycosis is its chronic course. Septicemia or an acute pneumonia is rare. Lung lesions develop slowly. Months or years may elapse before medical attention is sought or a diagnosis is made.

4. Symptoms are rarely intense; fever, chills, night sweats, anorexia, weight loss, malaise, and depression may all be present.

5. When a fungus disseminates from a primary focus in the lung, the manifestations may be characteristic. Thus, cryptococcosis usually appears as meningitis, progressive disseminated histoplasmosis as hepatic disease, and blastomycosis as a skin lesion.

6. Delayed cutaneous hypersensitivity tests and serologic tests are available for only 3 or 4 of the infections discussed in this chapter. Even in these, the tests become positive either so late (e.g., coccidioidomycosis) or so infrequently (e.g., blastomycosis) that they are of no diagnostic value for the acutely ill patient.

7. The diagnosis is usually confirmed by isolation of the causative fungus from sputum, bone marrow, urine, blood, or CSF, or from lymph node, liver, or lung biopsy. When the fungus is a commensal of man or is prevalent in his environment (e.g., *Candida*, *Aspergillus*), it is difficult to interpret its isolation from such specimens as sputum, and confirmatory evidence of tissue invasion is necessary to attribute an etiologic role to it

8. In contrast to viral and bacterial diseases, fungal infections can be diagnosed histopathologically with a high degree of reliability. It is the distinctive fungal morphology, not the tissue reaction to the fungus, that permits specific etiologic identification.

9. Even when the microorganism has been demonstrated histopathologically in tissues, the activity of the disease must be established before treatment is begun. Culture of the causative microorganism or such clinical and laboratory findings as fever, leukocytosis, elevated ESR, abnormal liver function, worsening of chest film findings, or elevated serum globulins are helpful as indications for therapy.

General Therapeutic Principles

General medical care, surgery, and chemotherapy constitute modes of treatment for systemic fungus infections. Ketoconazole, a new antifungal imidazole derivative, appears to have major advantages: oral dosage, broad antifungal activity, and minimal adverse effects; but testosterone synthesis may be blocked, usually transiently, and serious idiosyncratic hepatotoxicity may occur. Current usage is 200 to 400 mg orally once a day with a meal. It may be given for prolonged periods to establish and maintain clinical remission or to prevent reinfection. Because amphotericin B is used in many systemic mycoses, it is covered in detail here. Indications and directions for other therapeutic measures are given below in the discussions of specific mycoses.

Amphotericin B, a fungicidal and fungistatic antibiotic, has reversed the prognosis of many fungal infections. An initial IV dose of 0.1 mg/kg/day is increased by 0.05 to 0.10 mg/kg every day until 1.0 mg/kg (but not exceeding 50 mg/dose) is given *daily or every other day*. The antibiotic is dissolved in 5% D/W (optimal concentration, 0.1 mg/ml). (CAUTION: Saline solution precipitates

the drug and should not be used. Follow the manufacturer's instructions in preparing and storing solutions.)

The drug should be given over a 2- to 6-h period. Reactions are usually mild, but some patients may experience chills, fever, headache, anorexia, nausea, and, occasionally, vomiting, particularly with the initial injections. The severity of reactions may be reduced by giving aspirin or an antihistamine (e.g., diphenhydramine 50 mg) before, after 3 h, and at the end of treatment. If this therapy is ineffective, hydrocortisone 25 to 50 mg IV may be given at the beginning of the amphotericin B infusion.

Chemical thrombophlebitis may occur; adding heparin to the infusion (or into the tubing just prior to starting the injection) may lessen the incidence.

The BUN or serum creatinine should be determined before and periodically during treatment. A slight increase can be ignored. A moderate rise may be reversed by giving the drug on alternate days, but if not, treatment should be discontinued until the levels approach normal. If this requires only a few days, treatment can be resumed with the previous dose, but if a longer period is necessary, therapy should be restarted with a smaller dose. Serum potassium should be determined regularly, since hypokalemia is common and occasionally is dramatic and dangerous. Oral liquid supplements are usually sufficient; rarely, potassium IV (not added to the amphotericin B infusion) may be necessary. Intrathecal injection may be indicated in meningitis, but great care must be taken to ensure proper dose and volume: 50 mg of amphotericin B should be painstakingly dissolved in 10 ml of sterile water. The total volume should then be diluted in a 250-ml bottle of 5% D/W from which 10 ml has been removed. From 0.5 ml (0.1 mg) to 5.0 ml (1.0 mg) should then be drawn into a 10-ml syringe, further diluted to 10 ml with CSF, and injected *slowly* (over at least 2 min). A lumbar, cisternal, or ventricular site may be used.

HISTOPLASMOSIS

An infectious disease caused by *Histoplasma capsulatum*, characterized by a primary pulmonary lesion and occasional hematogenous dissemination, with ulcerations of the oropharynx and GI tract, hepatomegaly, splenomegaly, lymphadenopathy, and adrenal necrosis.

Etiology and Incidence

H. capsulatum in tissue is an oval budding cell 1 to 5 μ m in diameter. Infection follows inhalation of dust that contains the spores. Severe disease is more frequent in men.

Chest x-ray (picture 7-8) surveys in certain geographic areas have demonstrated many residents with symptomless, nontuberculous, occasionally calcified pulmonary lesions; delayed cutaneous hypersensitivity reactions to histoplasmin suggest widespread but subclinical infection. The highest incidence of such hypersensitivity is in the Ohio and Mississippi River valleys.

Symptoms and Signs

There are 3 recognized forms of the disease. The primary acute form causes symptoms (fever, cough, malaise) indistinguishable in endemic areas (except by culture) from otherwise undifferentiated URI or gripe-like disease. The progressive disseminated form follows hematogenous spread from the lungs and is characterized by hepatomegaly, lymphadenopathy, splenomegaly, and, less frequently, oral or GI ulceration. Addison's disease is an uncommon but

serious manifestation. The lesions in the liver are granulomatous, show the intracellular fungus, and may lead to hepatic calcification. Addison's disease of other etiology, lymphoma, Hodgkin's disease, leukemia, and sarcoidosis must be differentiated. The chronic cavitary form produces pulmonary lesions indistinguishable, except by culture, from cavitary TB. The principal manifestations are cough, increasing dyspnea, and eventually disabling respiratory embarrassment. That histoplasmosis is a cause of uveitis has been postulated but not proved.

Diagnosis

Demonstration of *H. capsulatum* by culture is diagnostic. Specimens for culture may be obtained from sputum, lymph nodes, bone marrow, liver biopsy, blood, urine, or oral ulcerations. Tissues may also be examined microscopically after staining (Goroori's methenamine silver, periodic acid-Schiff, or Gridley) pictures 9-10, Delayed cutaneous hypersensitivity and CF tests are of no diagnostic value, since they are usually negative early in the disease.

Prognosis and Treatment

The acute primary form is usually benign; it is fatal only in those rare cases with massive infection. The progressive disseminated form has a high mortality. In the chronic cavitary form, death results from severe respiratory insufficiency.

Primary acute disease rarely requires chemotherapy (see amphotericin B and also ketoconazole in General Therapeutic Principles, above). The disseminated form responds to amphotericin B; in the chronic cavitary form, the fungi disappear with therapy, but fibrotic lesions show little change.

COCCIDIOIDOMYCOSIS

(San Joaquin or Valley Fever)

An infectious disease caused by the fungus *Coccidioides immitis*, occurring in a *primary form* as an acute, benign, self-limiting respiratory disease, or in a *progressive form* as a chronic, often fatal, infection of the skin, lymph glands, spleen, liver, bones, kidneys, meninges, and brain.

Etiology, Incidence, and Pathology

The disease is endemic in the southwestern USA and occurs most frequently in men aged 25 to 55. Infection is acquired by inhalation of spore-laden dust. Individuals contracting the disease while traveling through endemic areas may not develop manifestations until later, after leaving the area.

The basic pathologic change is an acute, subacute, or chronic granulomatous process with varying degrees of fibrosis. Lesions may show central necrosis; the organisms are surrounded by lymphocytes and by plasma, epithelioid, and giant cells. Cavitation or granuloma ("coin lesion") formation may occur in chronic lung infection.

Symptoms and Signs

Primary pulmonary coccidioidomycosis, the more common form, may occur asymptotically, as a mild URI, as acute bronchitis, occasionally with pleural effusion, or as pneumonia. Symptoms, in descending order of frequency, include fever, cough, chest pain, chills, sputum production, sore throat, and hemoptysis. Physical signs may be absent, or occasional scattered rales and areas of dullness to percussion may be present. Leukocytosis is present and the eosinophil count may be

high. Some patients develop "desert rheumatism," a more recognizable form with conjunctivitis, arthritis, and erythema nodosum.

Progressive coccidioidomycosis develops from the primary form; evidence of dissemination may appear a few weeks, months, or, occasionally, years after primary infection or long residence in an endemic area. Symptoms include continuous low-grade fever, severe anorexia, and loss of weight and strength. Progressive cyanosis, dyspnea, and mucopurulent or bloody sputum are present in the pulmonary type. The bones, joints, skin, viscera, brain, and meninges may be involved as the disease spreads.

Diagnosis

Coccidioidomycosis should be suspected in a patient with an obscure illness who has been or is in an endemic area. Diagnosis is established by finding the characteristic spherules of *C. immitis* in sputum, gastric washings, pleural fluid, CSF, pus from abscesses, biopsy specimens, or exudate from skin lesions by direct examination or culture. In the tissues, the fungus appears as thick-walled, non-budding spherules 20 to 80 μ m in diameter.

A delayed cutaneous hypersensitivity reaction to coccidioidin or spherulin usually appears 10 to 21 days after infection, but is characteristically absent in progressive disease. Precipitating and CF antibodies are present regularly and persistently in the progressive form but only transiently in acute primary cases.

Prognosis and Treatment

For primary pulmonary Coccidioidomycosis, treatment is not needed and the outlook is excellent. The progressive type, however, is fatal in 55 to 60% of cases. Amphotericin B (see amphotericin B and also ketoconazole in General Therapeutic Principles, above) is indicated in all patients with the progressive form. Results are less satisfactory than in blastomycosis or histoplasmosis. Meningitis requires prolonged intrathecal administration, usually for years. Untreated meningitis is fatal.

SYSTEMIC CANDIDOSIS

(Candidiasis; Moniliasis)

Etiology and Incidence

The infections are usually caused by *C. albicans*. Superficial candidosis is universal, but patients with leukemia, or with organ transplants, or receiving immunosuppressive or antibacterial therapy are especially prone to *C. spp.* septicemia. *C. spp.* (frequently *C. parapsilosis*) endocarditis is related to intravascular trauma such as cardiac catheterization, surgery, or indwelling venous catheters.

Symptoms and Signs

C. spp. endocarditis resembles bacterial disease, with fever, heart murmur, splenomegaly, and anemia; large vegetations and emboli to major vessels are frequently present and are differential features. Renal involvement is usually found on laboratory and autopsy examination. *C. spp.* septicemia usually resembles gram-negative bacterial sepsis in frequency of fever, shock, azotemia, oliguria, renal shutdown, and fulminant course. *C. spp.* meningitis is chronic, like crypto-coccal

meningitis, but lacks the latter's usually fatal outcome when untreated. *C. spp.* pyelonephritis and pulmonary disease are less well characterized. Osteomyelitis is rarely encountered; it resembles that due to other microorganisms.

Diagnosis

Because *C. spp.* are commensals of man, their culture from sputum, mouth, vagina, urine, stool, or skin must be interpreted cautiously. To confirm the diagnosis, the culture must be complemented by a characteristic clinical lesion, exclusion of other etiology, and histologic evidence of tissue invasion. Isolation from blood or CSF, however, establishes the presence of *C. spp.* infection and supports the appropriate clinical impression: septicemia, endocarditis, or meningitis.

Treatment

Such predisposing conditions as diabetic acidosis must first be controlled. In systemic candidosis, amphotericin B IV is preferable therapy. As an alternative, flucytosine may be given as for cryptococcosis (see above) if the isolate is sensitive to it. Ketoconazole appears promising in investigational studies in this disorder.

ASPERGILLOSIS

Etiology, Symptoms, and Signs

The fungus, an "opportunistic," appears after antibacterial or antifungal therapy (to which it is usually resistant) in bronchi damaged by bronchitis, bronchiectasis, or tuberculosis. The "fungus ball" (aspergilloma), a characteristic form of the disease, appears on the chest film as a dense round ball, capped by a slim meniscus of air, in a cavity; it is composed of a tangled mass of fibrin, exudate, and a few inflammatory cells. Aspergillomas usually occur in old cavitory disease (e.g., tuberculosis) or, rarely, in patients with rheumatoid spondylitis. Symptoms (cough, productive sputum, dyspnea) and findings on physical examination or chest film are usually those of the underlying disease. However, hemoptysis has been a disturbing and even occasionally fatal complication. In the presence of leukemia, organ transplantation, or corticosteroid or immunosuppressive therapy, dissemination to the brain and kidneys may occur. The clinical picture in this form is a typical septicemia: fever, chills, hypotension, prostration, and delirium.

Diagnosis and Treatment

Because it is a commensal of man, culture of *A. spp.* from sputum, mouth, or bowel must not be considered diagnostic unless a clinically compatible illness is present, other causes have been eliminated, and tissue invasion has been demonstrated. In disseminated and pulmonary disease, amphotericin B should be given IV although tolerated doses are usually ineffective, since most strains are resistant.

ACTINOMYCOSIS

(Lumpy Jaw)

A chronic infectious disease characterized by multiple draining sinuses and caused by the anaerobic gram-positive microorganism Actinomyces israelii, often present as a commensal on the gums, tonsils, and teeth.

Incidence and Pathology

The disease is seen most often in adult males. In the cervicofacial form, the most common portal of entry is decayed teeth; pulmonary disease results from aspiration of oral secretions; abdominal disease, from a break in the mucosa of a diverticulum or the appendix.

The characteristic lesion is an indurated area of multiple, small, communicating abscesses surrounded by granulation tissue. Disease spreads to contiguous tissue and, rarely, hematogenously. Other anaerobic bacteria are usually also present.

Symptoms and Signs

There are 4 clinical forms of actinomycosis. (1) The abdominal form affects the intestines (usually the cecum and appendix) and the peritoneum. Pain, fever, vomiting, diarrhea or constipation, and emaciation are characteristically present. An abdominal mass with signs of partial intestinal obstruction appears, and draining sinuses and fistulas may develop in the abdominal wall. (2) The cervicofacial form usually begins as a small, flat, hard swelling, with or without pain, under the oral mucosa or the skin on the neck, or as a subperiosteal swelling of the jaw. Subsequently, areas of softening appear and develop into sinuses and fistulas with a discharge that contains the characteristic "sulfur granules" (rounded or spherical, usually yellowish, granules up to 1 mm in diameter). The cheek, tongue, pharynx, salivary glands, cranial bones, meninges, or brain may be affected, usually by direct extension. (3) In the thoracic form, involvement of the lungs resembles TB. Extensive invasion may occur before chest pain, fever, and productive cough appear. Perforation of the chest wall, with chronic draining sinuses, may result. (4) In the generalized form, hematogenous spread occurs to the skin, vertebral bodies, brain, liver, kidney, ureter, and (in women) the pelvic organs.

Diagnosis

This is based on clinical symptoms, x-ray findings (picture 12), and demonstration of *A. israelii* in sputum, pus, or biopsy specimen. In pus or tissue, the microorganism appears as tangled masses of branched and un-branched wavy filaments, or as the distinctive "sulfur granules." These consist of a central mass of tangled filaments, pus cells, and debris, with a midzone of interlacing filaments surrounded by an outer zone of radiating, club-shaped, hyaline and refractive filaments that take the eosin stain in tissue.

Lung lesions must be distinguished from those of TB and neoplasms. Lesions in the abdomen occur most frequently in the ileocecal region and are difficult to diagnose, except at laparotomy or when draining sinuses appear in the abdominal wall. Aspiration liver biopsy should be avoided because of the danger of inducing a persistent sinus. A tender, palpable mass suggests appendiceal abscess or regional enteritis. Nodules in any location may simulate malignant growths.

Clinical presentation:

53 year old man with left side pain and a lump in the left axilla, dullness to percussion in the left lower chest. Had been treated for an infection 3 and 25 years before. Works as a fitter, cutting insulation by hand. Smokes 10 cigarettes a day.

The view is taken central. The size of the left lobe is reduced and the margins of left hemidiaphragm, the lower left heart margin and the costophrenic recess are obscured by a density that has a clear central margin as it extends into the left axilla, implying a pleural density. There is shadowing at the apex of both lungs. This is well-defined and irregular with calcifications. The right hilar vessels are vertical and sparse in both upper zones with elevation of the hilar point on both sides, implying loss of upper lobe volume. There is coarse linear calcification immediately above the diaphragm, well shown on the right and a little obscured on the left. In this particular view, no rib erosion is identified.

Prognosis and Treatment

The disease is slowly progressive. Prognosis relates directly to early diagnosis, is most favorable in the cervicofacial form, and is progressively worse in the pulmonary, abdominal, and generalized forms.

Most cases will respond to medical treatment but, owing to the extensive induration and relatively avascular fibrosis, response is slow and treatment must be continued for at least 8 wk and occasionally for > 1 yr. Extensive and repeated surgical procedures may be required. Aspiration is indicated for small abscesses and drainage for large ones. Penicillin G, at least 12 million u./day IV, should be given initially; penicillin V 1 gm orally q.i.d. may be substituted after about 2 wk. Tetracycline 500 mg orally q 6 h may be given instead of penicillin. Treatment must be continued for several weeks after apparent clinical cure.

Lung atelectasis and middle lobe syndrome.

A shrunk and airless state of part or all of the lung; the disorder may be acute or chronic, complete or incomplete (partial atelectasis). Atelectasis is often accompanied by infection. The atelectatic lung or lobe is a complex mixture of airlessness, infection, bronchiectasis, destruction, and fibrosis.

Etiology

The chief cause of **acute or chronic atelectasis** in adults is bronchial obstruction (e.g., by plugs of tenacious bronchial exudate; foreign bodies; endobronchial tumors; tumors, lymph nodes, or an aneurysm compressing the bronchi; and bronchial distortions or kinkings). External pulmonary compression by pleural fluid or gas (e.g., due to pleural effusion, pneumothorax) may also cause atelectasis. Surfactant, a lipoprotein, covers the surface of the alveoli, reduces surface tension, and contributes to alveolar stability. Interference with its production may occur in O₂ toxicity, pulmonary edema, and other conditions that cause alveolar airlessness, and is probably important in the perpetuation of atelectasis.

Acute massive lung collapse is usually a postoperative complication, most frequently following surgery in the upper abdomen. Large doses of opiates and sedatives, very high O₂ concentrations during anesthesia, tight dressings, abdominal distention, and immobility of the body favor development of atelectasis, owing to limited respiratory movement, elevated diaphragm, accumulated viscid bronchial secretions, and suppressed cough reflex.

In the **middle lobe syndrome**, a form of chronic atelectasis, middle lobe collapse usually results from bronchial compression by surrounding lymph nodes. Partial bronchial obstruction in the presence of infection may also lead to chronic atelectasis and, ultimately, to chronic pneumonitis because of poor drainage of bronchial secretions. Acute pneumonia, usually with delayed and incomplete resolution, may also develop.

Pathology and Pathophysiology

Following obstruction of a bronchus, absorption of the gas in the peripheral alveoli by the circulating blood and consequent retraction of the lung produce the airless state within a few hours; lung shrinkage or collapse may be complete in the absence of infection. In the early stages, blood perfuses the airless lung, with consequent arterial hypoxia. Capillary and tissue hypoxia may result in transudation of fluid and pulmonary edema, filling the alveolar spaces with secretions and cells and preventing complete collapse of the atelectatic lung. The uninvolved surrounding lung distends, displacing the heart and mediastinum toward the atelectatic area; the diaphragm is elevated, and the chest wall flattens.

Hyperventilation and dyspnea are common. A decrease in Pao₂ is usual and, if the atelectatic area is large, may be considerable; Pao₂ often improves during and after the first 24 h, presumably as blood flow to the atelectatic area decreases. Paco₂ is usually normal or low as a result of the increased ventilation.

If the obstruction is removed, air enters the affected area, any complicating infection subsides, and the lung returns to its normal state in a variable length of time, depending on how much infection is present. If the obstruction is not removed and infection is present, airlessness and lack of circulation initiate changes that lead to development of fibrosis. If these conditions persist, the lung becomes fibrotic and bronchiectatic. In addition to bronchial obstruction, small areas of atelectasis may come about by inadequate regional ventilation and disturbances in surfactant formation from hypoxia, hyperoxia, and exposure to various toxins. Mild to severe disturbances in gas exchange may result.

Symptoms and Signs

Most of the symptoms and signs are determined by the rapidity with which the bronchial occlusion occurs, by the size of the area of lung affected, and by the presence or absence of complicating infection. Rapid occlusion with massive collapse, particularly if infection is present, causes pain on the affected side, sudden onset of dyspnea and cyanosis, a drop in BP, tachycardia, elevated temperature, and shock. Chest examination reveals dullness to flatness over the involved area and diminished or absent breath sounds. Chest excursion in the area is reduced or absent. The trachea and heart are deviated toward the affected side. The patient tends to lie with the atelectatic area dependent. Slowly developing atelectasis may be asymptomatic or cause only minor pulmonary symptoms. The middle lobe syndrome is also often asymptomatic, though a severe, hacking,

nonproductive cough may be present because of irritation in the right lower and middle lobe bronchi. Physical examination discloses the same findings as in rapid occlusion.

Chest x-ray may show an airless area of lung, its size and location depending on the bronchus involved. If only segmental areas are affected, the shadow will be triangular, with its apex toward the hilum. When small areas are involved, distention of surrounding lung tissue causes the atelectatic area to appear curiously discoid in shape, particularly in subsegmental lower lobe atelectasis. If the atelectasis is lobar, the entire lobe is airless. The trachea, heart, and mediastinum are deviated toward the atelectatic area, the diaphragm on the affected side is elevated, and rib spaces are narrowed.

Diagnosis

Diagnosis is made from the clinical findings plus x-ray evidence of diminished lung size (indicated by retracted ribs, elevated diaphragm, and deviated mediastinum) and of a solid, airless mass. Bronchoscopy may reveal bronchial obstruction, but only a small number of bronchi are visualized, and examination may be negative unless the obstruction is in a main bronchus or in early divisions of the smaller bronchi.

Bronchogenic carcinoma, which may present with atelectasis, must be ruled out in all patients over age 35. Spontaneous pneumothorax produces clinical findings similar to those in atelectasis, but the percussion note is tympanitic, the heart and mediastinum are pushed to the opposite side, and x-rays are diagnostic. Massive effusion may also cause dyspnea, cyanosis, weakness, flatness over the involved area, and absent breath sounds, but the heart and mediastinum are deviated away from the involved area and the chest wall is not flattened.

Treatment

Acute atelectasis (including postoperative acute massive lung collapse) requires removal of the underlying cause. Acute massive atelectasis is best combated by prevention. Anesthetic agents with a long postanesthesia narcosis should be avoided, and narcotics should be used sparingly after surgery, since they depress the cough reflex. At the conclusion of anesthesia, the lungs should be left filled with air, not O₂. The patient must not be allowed to lie in one position for more than 1 h. Early ambulation is important. The patient should be encouraged to cough and breathe deeply. IPPB for 5 to 10 min/h during the postoperative period, using air and not O₂, may improve ventilation and bronchial drainage and prevent atelectasis. Nebulized bronchodilators and aerosols of water or saline may help to liquefy secretions and promote their easy removal. If bronchial obstruction is incipient, as indicated by wheezing or sharp, forced expirations, these measures are urgently required.

When a mechanically obstructed bronchus is suspected but relief is not obtained by cough or suction, bronchoscopy should be performed. Once bronchial obstruction is established, treatment is directed at the obstruction and at the infection invariably present. The patient should be (1) placed so that the uninvolved side is dependent, to promote increased drainage of the affected area, (2) given vigorous chest physiotherapy, and (3) encouraged to cough. If improvement is not evident in 1 or 2 h, bronchoscopy should be repeated to aspirate as much secretion as possible. Chest physiotherapy is then continued and the patient is encouraged to cough, move from side to side, and breathe deeply.

Periodic use of IPPB may be helpful. Penicillin 600,000 u. IM t.i.d. or a broad-spectrum antibiotic such as ampicillin 0.5 gm orally q 6 h or tetracycline 0.5 gm orally q 6 h should be given at the outset and modified appropriately if a specific pathogen is isolated from sputum or bronchial secretions.

Chronic atelectasis is treated by segmental resection or lobectomy. Since secondary atelectasis usually becomes infected regardless of the cause of obstruction, a broad-spectrum antibiotic, penicillin, ampicillin, or tetracycline should be given. Obstruction of a major bronchus may cause severe hacking or spasmodic cough. Treatment resulting in too great a reduction in the cough reflex may produce further obstruction and should be avoided.

THROMBOEMBOLISM AND INFARCTION OF LUNGS

Pulmonary embolism (thromboembolism): *Lodgement of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma.* **Pulmonary infarction:** *Hemorrhage consolidation (often followed by necrosis) of lung parenchyma resulting from thromboembolic pulmonary arterial occlusion.*

Etiology and Pathogenesis

The most common type of pulmonary embolus is a thrombus which usually has formed in the leg or pelvic veins. Most of those causing serious hemodynamic disturbances form in the iliofemoral veins, either de novo or by propagation from calf vein thrombi. Embolization of thrombi originating in the veins of the upper extremities or in the right cardiac chambers is infrequent. Amniotic fluid emboli and fat emboli following fractures are much less common types of pulmonary emboli in which the primary site of vascular obstruction is the pulmonary microcirculation (arterioles and capillaries rather than in the pulmonary arteries); the involvement of the microcirculation may result in the development of the so-called acute respiratory distress syndrome .

Pulmonary infarction is an infrequent (< 10% of cases) consequence of pulmonary embolism. It is sometimes due to thrombosis in situ of the pulmonary arteries as might occur in congenital heart disease associated with severe pulmonary hypertension or in hematologic disorders such as sickle cell anemia.

The pathogenesis of venous thrombosis involves stasis, increased blood coagulability and vascular wall damage (Virchow's triad). Factors predisposing to thromboembolic disease include prolonged bed rest with immobility, chronic congestive heart failure, the postoperative state, pregnancy, hip fracture use of oral contraceptives, chronic obstructive pulmonary disease, obesity, malignancy, hematologic disorders (e.g., polycythemia vera), vascular injuries resulting from minor trauma, and immobilization with stasis as may occur in chronic disease states. In many patients, no predisposing factor can be found.

Once released into the venous circulation, emboli are distributed to both lungs in about 65% of cases, to the right lung only in 20%. and to the left lung only in 10% The lower lobes are involved 4 times more frequently than the upper lobes. Most thromboemboli lodge in the larger or intermediate (elastic or muscular) pulmonary arteries; 35% or fewer reach the smaller arteries.

Pathophysiology

The pathophysiologic changes which occur following pulmonary embolism are complex, involving alterations in pulmonary hemodynamics, gas exchange, and mechanics. The extent of alteration in cardiopulmonary function is determined by the degree of pulmonary arterial obstruction, which varies with the size and number of thrombi embolizing and obstructing the pulmonary arteries, and by the patient's preembolic cardiopulmonary status. A consideration of the pathophysiology of pulmonary embolism must include the mechanisms responsible for the following: (1) pulmonary hypertension, right ventricular failure, and shock; (2) dyspnea with tachypnea and hyperventilation; (3) arterial hypoxemia; and (4) pulmonary infarction,

Pulmonary hypertension, a most important physiologic alteration following embolization, results from increased pulmonary vascular resistance. As a consequence the right ventricle must generate a higher pulmonary artery pressure to maintain normal cardiac output. Significant pulmonary hypertension (> 20 mm Hg mean pressure) usually occurs only when > 30 to 50% of the pulmonary arterial tree is occluded in the previously undiseased lung. Pulmonary hypertension may be further enhanced in the presence of preexisting cardiopulmonary disease, such as valvular dysfunction (e.g., aortic stenosis) or obstructive lung disease.

The primary mechanism of the increased resistance is obstruction of pulmonary arteries by the thrombi; i.e., a decrease in the total cross-sectional area of the pulmonary vascular bed. However, because some degree of pulmonary hypertension often develops with obstruction of $< 50\%$ of the vascular bed, pulmonary vasoconstriction appears to play a definite, but secondary, role. Vasoconstriction is partly mediated by hypoxemia, by serotonin release from platelet aggregates on the thrombi, and possibly by other humoral substances, including prostaglandins.

If pulmonary vascular resistance increases to the extent that the right ventricle is unable to generate sufficient pressure (about 40 mm Hg mean pulmonary arterial pressure) to maintain cardiac output, hypotension (in which the central venous and right atrial mean pressures are increased) develops. This occurs only following massive embolization involving at least 50% and usually 75% or more of the pulmonary vascular bed in the absence of pre-existing cardiopulmonary disease. With severe hypotension and shock, mean central venous pressure tends to fall.

2. Tachypnea, often with **dyspnea**, almost always occurs following an embolic episode. It appears to be of reflex origin, most likely due to stimulation of intra-pulmonary receptors in the alveoli (J receptors). This stimulation increases vagal afferent activity, which in turn stimulates medullary respiratory neurons. Consequent alveolar hyperventilation is manifested by a lowered arterial CO_2 tension.

Following pulmonary arterial occlusion, areas of the lung are ventilated but not perfused, resulting in "wasted ventilation" (the physiologic hallmark of pulmonary embolism). The degree of wasted ventilation can be estimated by measuring the physiologic deadspace or the arterial-alveolar CO_2 tension difference.

Alterations in lung mechanics with an increase in airway resistance and a decrease in lung compliance tend to occur. A decrease in the maximal expiratory flow rate results from diminished lung volume and possibly from bronchoconstriction. Heparin appears to lessen the degree of bronchoconstriction, when present, as evidenced by improved maximal expiratory flow rates. Reduced lung volume following thromboembolism sometimes is manifested on the chest x-ray by elevation of the diaphragm due to atelectatic infarcted segments. Since the changes in lung mechanics are usually transient and minor, they are unlikely to be important in the genesis of prolonged dyspnea. However, they probably contribute to development of arterial hypoxemia, described below.

3. Arterial hypoxemia: Arterial O₂ saturation is characteristically diminished (94 to 85% or lower), but may be normal. Hypoxemia is due to right-to-left shunting in areas of partial or complete atelectasis; characteristically, this atelectasis can be partially corrected by deep breathing, either voluntary or induced by a positive pressure ventilator. Ventilation/perfusion (VA/Q) imbalance probably also contributes to the hypoxemia. The mechanisms responsible for the VA/Q imbalance and atelectasis are not well defined. One explanation that has been offered is the release, after an embolic episode, of a humoral agent in the pulmonary arterioles that produces nonuniform constriction of distal airways and peripheral lung units with resultant underventilation of the units with respect to their perfusion; atelectasis results if these changes are severe. Tachypnea may augment the changes. In massive embolization, severe hypoxemia may result from right atrial hypertension that causes right-to-left shunting of blood through a patent foramen ovale.

4. Pulmonary infarction: Most pulmonary emboli do not produce infarction. When the bronchial circulation is intact and normal (i.e., in the absence of congestive heart failure or underlying chronic pulmonary disease), pulmonary infarction rarely develops. This suggests that collateral bronchial artery circulation adequately maintains viability of lung tissue despite the absence of pulmonary arterial flow. However, patients with previously abnormal pulmonary circulation are prone to develop pulmonary infarction. Pulmonary infarcts may heal by absorption and fibrosis, leaving a linear scar, or may resorb completely, leaving a normal lung (incomplete infarction).

Acute pulmonary thromboembolism is a dynamic process. The thrombi begin to lyse immediately after reaching the lung. Usually, complete clot lysis takes place within several weeks in the absence of preexisting cardiopulmonary disease, but, in some instances, even large thrombi may be lysed in a few days. The physiologic alterations lessen over hours or days as the pulmonary circulation becomes less obstructed. Massive emboli may cause death within a few minutes or hours without sufficient time for infarction to develop. Smaller emboli may produce infarction, which can heal with recanalization and restoration of blood flow through the occluded vessel. Infrequently, the embolic events recur for months or years, causing progressive pulmonary arterial obstruction with chronic pulmonary hypertension, increasing dyspnea, and cor pulmonale.

Symptoms and Signs

The clinical manifestations of pulmonary embolism are not specific. Diagnosis may be difficult without using special diagnostic procedures, the most important of which are radioisotope perfusion lung scans and pulmonary arteriography (see Diagnosis, below). The symptoms and signs vary in

frequency and intensity depending on the extent of pulmonary vascular occlusion, the development of pulmonary infarction, and the patient's preembolic cardiopulmonary function. There may be no symptoms with small thromboemboli.

Embolism without infarction is manifested by breathlessness, which may be the only symptom if infarction does not develop. Tachypnea is a consistent and often striking feature. Anxiety and restlessness may be prominent.

Pulmonary hypertension, if severe, may cause dull substernal chest discomfort due to pulmonary artery distention or possibly myocardial ischemia. It may be manifested by an increase in the intensity of the pulmonary component of the basal 2nd sound or abnormal splitting (i.e., widened with less variation of splitting during inspiration) of the aortic and pulmonary components of the basal 2nd sound. If pulmonary vascular obstruction is massive, acute right ventricular insufficiency may supervene, with distended cervical veins, right ventricular heave, right ventricular (protodiastolic) gallop, sometimes with arterial hypotension and evidence of peripheral vasoconstriction. Lightheadedness, syncopal episodes, convulsive phenomena, and neurologic deficits may be the presenting events in a significant number of patients, usually reflecting a transient fall in cardiac output with secondary cerebral ischemia. Cyanosis is usual in patients with massive embolism, but not in patients with lesser obstruction.

Examination of the lungs is usually normal in the absence of pulmonary infarction. Wheezing may sometimes be heard, particularly if underlying bronchopulmonary or cardiac disease is present.

In addition to the above symptoms and signs, the manifestations of pulmonary infarction include cough, hemoptysis, pleuritic chest pain, fever, and signs of pulmonary consolidation or pleural fluid. A pleural friction rub may be heard. A small, peripheral embolus may cause infarction but not obstruct the pulmonary arteries to the extent that pulmonary hypertension develops.

The manifestations of embolization usually develop abruptly over a period of minutes; those of infarction over a period of hours. They often last several days, depending on the rate of clot lysis and other factors, but usually decrease in intensity every day. In those patients with chronic, recurrent emboli, the symptoms and signs of chronic cor pulmonale tend to develop insidiously over a period of weeks, months, or years.

Diagnosis

The diagnosis of pulmonary embolism with or without infarction is often difficult to establish. In patients with massive pulmonary embolism, the differential diagnosis includes bacteremic shock, acute myocardial infarction, peritonitis, and cardiac tamponade. In the absence of pulmonary infarction, the patient's symptoms and signs may be attributed to anxiety with hyperventilation because of the paucity of objective pulmonary findings. When infarction occurs, the differential diagnosis includes pneumonia, atelectasis, congestive heart failure, and pericarditis. A systematic approach to diagnosis is possible as outlined below.

1. **The clinical symptoms and signs** should suggest the diagnosis.

2. **Appropriate clinical diagnostic studies**, including chest ECG (picture 15), x-ray (picture 16), CBC, and serum enzyme (AST [formerly SGOT], LDH) and serum bilirubin determinations may be helpful. With infarction, the chest x-ray frequently shows a peripheral infiltrative lesion,

often involving the costophrenic angle, with elevation of the diaphragm and pleural fluid on the affected side. Diminished pulmonary vascular markings in the embolized area may be noted in the absence of infarction. Dilation of the pulmonary arteries in the hilar area, the superior vena cava, and the azygos vein signal pulmonary hypertension and right ventricular strain. Since ECG changes are characteristically transient, serial tracings are often helpful in the diagnosis and in the exclusion of acute myocardial infarction. Changes most frequently seen in the ECG include P pulmonale, right bundle branch block, right axis deviation, and supraventricular arrhythmias. The sensitivity and specificity of serum enzyme studies have been disappointing and the studies are rarely helpful in diagnosis. The triad of elevated serum LDH and bilirubin and normal AST occurs in < 15% of patients with acute pulmonary embolism and infarction. Elevated LDH may be demonstrable in as many as 85% of patients with pulmonary infarction, but is not a specific finding, occurring also in cardiac failure, shock, pregnancy, renal and liver disease, anemia, pneumonia, carcinoma, and after surgical procedures. A profile of enzyme studies involving elevated LDH, normal CPK, normal hydroxybutyrate dehydrogenase (HBD) is more specific in the diagnosis of pulmonary infarction and may differentiate acute myocardial infarction, but is of little value in diagnosing embolism without infarction. Blood levels of fibrin split products appear to rise rather consistently after pulmonary embolism whether infarction occurs or not, but the temporal relation of this rise to the onset of symptoms, and its time course, vary considerably. The specificity of this finding is also questionable since the incidence of elevation in other diseases is not well defined.

3. Radioisotope perfusion lung scanning, sometimes combined with **ventilation scanning**, is very valuable in establishing the diagnosis.

4. Pulmonary arteriography: Demonstration of emboli by angiography remains the most definitive diagnostic test. Angiography should be performed if the diagnosis is in doubt and appears urgent. The 2 primary criteria for arteriographic diagnosis of thromboembolism are intraarterial filling defects and complete obstruction (abrupt cutoff) of pulmonary arterial branches. Other frequent findings include partial obstruction of pulmonary arterial branches with increased caliber proximal and decreased caliber distal to the stenosis, and persistence of dye in the proximal portion of the artery during the late (venous) phase of the arteriograms. In those lung segments with obstructed arteries, pulmonary venous filling with contrast medium is delayed or absent.

5. Additional diagnostic studies to establish the presence or absence of iliofemoral venous thrombotic disease may be useful in the management of pulmonary embolism, particularly when signs of recurrent embolization despite anticoagulant therapy or contraindications to anticoagulant therapy make vena caval interruption an important therapeutic consideration. Contrast venography appears to be the most reliable means of establishing the diagnosis of iliofemoral venous thrombosis, though noninvasive measures such as impedance plethysmography of the leg and assessment of femoral venous flow velocity by externally applied Doppler ultrasound flow probe have been found to be about 75 to 90% as sensitive as phlebography. Intravascular injection of technetium-labelled albumin and ¹³¹I fibrinogen with leg scanning may detect venous thrombi, but the latter technic is useful only in relation to deep veins of the calf.

Prognosis

Mortality following the initial thromboembolic event varies with the extent of embolization and the patient's preexisting cardiorespiratory status. A patient with markedly compromised cardiopulmonary function is at greater risk of developing thromboemboli, and the likelihood that he will die following significant embolization is high (probably > 25%). On the other hand, it is unlikely that a patient with normal cardiopulmonary status will die unless the degree of embolization is massive (i-e., the occlusive process involves > 50% of the pulmonary vascular bed). When the initial embolic event is fatal, death is often sudden, occurring within 1 to 2 h.

If a patient survives the initial embolic event but is not treated, the likelihood of a recurrent embolus is about 50%; as many as half of these recurrences may be fatal. Outcome is significantly modified by anticoagulant therapy, which reduces the rate of recurrence to about 5%; only about 20% of these will be fatal.

Prophylaxis

Pulmonary embolism can be prevented by preventing venous thrombosis. Therefore, the reduction of factors that predispose to venous thrombosis is of great importance, particularly those that minimize venous stasis. In postoperative (particularly elderly) patients, the use of elastic stockings to augment velocity of venous return in the legs, leg exercises, and early ambulation is widely used to lower the incidence of pulmonary embolism, but the usefulness of these measures has been questioned since they have little effect on the incidence of deep calf vein thrombosis. Intra- and postoperative pneumatic leg compression and electrical calf stimulation reduce the incidence of deep calf vein thrombosis, but their effects on iliofemoral vein thrombosis and pulmonary thromboembolic complications are not known.

Anticoagulant prophylaxis is effective in selected settings. Following hip or leg fracture in patients over age 50, immediate (preoperative) oral anticoagulation (using warfarin sodium), continued for 1 wk after the patient is ambulatory, significantly reduces the incidence of pulmonary embolism with about a 5% risk of hemorrhage. In the absence of contraindications to anticoagulant therapy, routine use of warfarin sodium has been advocated in patients (particularly the elderly) with congestive heart failure or debilitating disease of any kind that predisposes to immobility.

Low-dose heparin administration provides effective prophylaxis with reduced incidence of deep vein (calf) thrombosis and pulmonary embolism in patients undergoing a variety of major surgical procedures. At a blood level about 1/5 that required for therapeutic efficacy (prevention of thrombus propagation) heparin activates antithrombin III sufficiently to inhibit Factor X, which is required for conversion of prothrombin to thrombin at an early stage in the coagulation sequence. This results in preventing the initiation of clot formation, but is ineffective once Factor X has been activated and the coagulation process has started. No laboratory monitoring is required. Heparin 5000 u. s.c. is given 2 h preoperatively and q 8 to 12 h (q 12 h appears to be equally effective and perhaps somewhat safer) thereafter for 7 days. The risk of major hemorrhage does not appear to be increased, though more wound hematomas have been observed. Low-dose heparin is usually recommended for patients undergoing thoracic, abdominal, urologic, or gynecologic surgery who are over age 40 to 50 yr, or who have risk factors such as prior thromboembolism, estrogen therapy, or obesity. Low-dose heparin prophylaxis is commonly employed for hospitalized patients with

cardiac failure, acute myocardial infarction, stroke, paraplegia, or other debilitating disease, though its efficacy in these conditions is not clearly established. Use of low-dose heparin appears to be ineffective in patients undergoing hip surgery or abdominal prostatectomy, and is contraindicated in cerebral surgery.

Agents to prevent platelet aggregation (aspirin, dipyridamole) have been used to prevent venous thromboembolism, but results of these trials have been inconclusive or frankly negative. Dextran appears to be effective in reducing the incidence of thromboembolism in postoperative patients, but requires IV administration, is no more efficacious than warfarin, and has no fewer hemorrhagic complications.

Treatment

The management of pulmonary embolism involves treatment of the initial thromboembolic event and prevention of further thromboembolic episodes.

Treatment of the initial event is supportive. Analgesics are given if pleuritic pain is severe. Though anxiety is often prominent, sedation, particularly with barbiturates, should be undertaken with caution. O₂ therapy is indicated when appreciable arterial hypoxemia ($P_{aO_2} < 50$ to 60 mm Hg) is present. Continuous O₂ should be given, usually by mask, in a concentration sufficient to raise arterial O₂ tension and saturation to normal (85 to 95 mm Hg, 95 to 98%) or as near normal levels as possible (at least > 50 to 60 mm Hg).

In patients with clinical findings suggestive of pulmonary hypertension and acute cor pulmonale, particularly pending diagnostic procedures such as lung scanning and/or arteriography, adrenergic stimulation may be helpful in maintaining tissue perfusion by virtue of its pulmonary vasodilator and cardiotonic effects. Isoproterenol 2 to 4 mg/L of 5% D/W may be infused at a rate sufficient to maintain systolic BP at 90 to 100 mm Hg under continuous ECG monitoring. Appropriate pharmacologic agents may be useful in aborting and preventing supraventricular tachyarrhythmias. Digitalis should be avoided during acute hypoxemia unless absolutely necessary; e.g., for serious arrhythmia or heart failure. When given IV, a modest initial dose is usually desirable (digoxin 0.25 to 0.5 mg). Response to therapy in patients suspected of hemodynamic impairment with acute cor pulmonale may be monitored by serial measurement of arterial blood gases and hemodynamic parameters. Use of a flow-directed balloon (Swan-Ganz) catheter is valuable for determination of pulmonary artery and wedge pressures, as well as mixed venous blood O₂ saturation and/or content as an index of cardiac output.

Following massive embolism, particularly with hypotension, or submassive embolism and hypotension in patients with preexisting cardiorespiratory disease, 2 approaches to management may be considered: pulmonary embolectomy or thrombolytic therapy. In the event of cardiac arrest with massive embolism, the usual resuscitative measures are ineffective due to obstruction of blood flow through the lungs. In this setting, emergency partial (femoral venoarterial) bypass, pending pulmonary embolectomy, may be life-saving. In view of the considerable potential for diagnoses other than embolism, pulmonary angiography while on bypass is advisable in most cases prior to surgery.

Thrombolytic therapy may now be considered as an alternative to embolectomy when massive embolism is uncomplicated by hypotension or when systolic BP can be maintained at 90 to 100 mm Hg on moderate vasopressor dosage. Streptokinase and urokinase are equally effective fibrinolytic activators and exert their thrombolytic effect by enhancing conversion of plasminogen to plasmin, the active fibrinolytic enzyme. Contraindications to thrombolytic therapy include stroke within 2 mo, active bleeding from any source, preexisting hemorrhagic diathesis (as in severe liver or kidney disease), pregnancy, and surgery within the preceding 10 days—the latter representing a major limitation to its use. Therapy should be carried out within 3 days of the embolic episode, as organization of the thrombus will obviate the lytic effect.

Initially, a streptokinase resistance test is carried out, and if resistance levels are in excess of 1,000,000 IU, streptokinase should not be given. A loading dose of 250,000 IU streptokinase is given IV over a 30-min period, followed by a maintenance infusion of 100,000 IU/h for 24 h. Since antibodies to streptokinase develop, repeat administration should not be undertaken for 6 to 9 mo.

If the patient has been on heparin, prothrombin time should be permitted to fall to < 2 times control before initiating therapy. Similarly, for initiation of heparin therapy after thrombolytic treatment, it is desirable to wait until prothrombin time has fallen to < 2 times control. All patients on thrombolytic therapy have an increased bleeding risk, particularly from recent operative wounds, needle puncture sites, sites of invasive procedures, and the GI tract. Thus, invasive procedures should be avoided whenever possible; pressure dressings are usually required to stop oozing. Reversal of the fibrinolytic state is effectively brought about by giving ϵ -aminocaproic acid.

Preventing further thrombus formation with embolization then becomes the essence of treatment. Heparin may be given IV q 4 to 6 h, or by continuous IV drip with an infusion pump. Some evidence suggests that hemorrhagic complications are reduced by continuous infusion, which obviates the peaks and troughs of blood levels with bolus injection. By either method of administration, larger dosage may be required for the first 48 h.

Following a bolus loading dose of heparin 100 u./kg, it is given at a rate to keep the clotting time (CT) 2 to 2.5 times control or the partial thromboplastin time (PTT) 1.5 to 2 times control by checking the level 30 min prior to giving the next dose of heparin. The maintenance dose by continuous infusion is usually 10 to 50 u./kg/h. Once a therapeutic level is established with continuous infusion, CT and/or PTT need to be monitored only 1 to 2 times/day.

A hemorrhagic disorder or an active bleeding site is an absolute contraindication to heparin therapy; septic embolization is usually taken as a contraindication. Hemorrhagic complications of heparin therapy may require cessation of the drug;

if severe, protamine sulfate may be given in an initial dose of 50 mg IV. Hemorrhagic complications are frequent in patients over age 65, particularly women, and heparin should be given to these patients only for short periods—usually no more than several days—before changing to an oral anticoagulant.

After 7 to 14 days, or when the patient becomes ambulatory, oral warfarin sodium is given in addition to heparin. The oral agent and heparin should overlap for 5 to 7 days, allowing the oral

anticoagulant to take effect. Warfarin sodium may be given, usually in a dosage of 10 to 20 mg/day. When the prothrombin time rises to a level 1.5 to 2.5 times control, heparin is discontinued.

The use of any drug containing aspirin by patients taking anticoagulants should be avoided since aspirin can further impair hemostatic mechanisms. Drugs that interfere with protein binding or metabolism of the oral anticoagulants (e.g., barbiturates, quinine, phenylbutazone, clofibrate, chloral hydrate) should be used cautiously when given simultaneously with warfarin.

The duration of anticoagulation therapy is adjusted individually for each patient. In patients with a definable, reversible cause (e.g., the postoperative state), anticoagulation need be continued only until the condition is corrected (e.g., the patient is fully ambulatory). Otherwise, anticoagulation therapy may be continued empirically for 3 to 6 mo. A patient with a chronic medical disorder associated with high incidence of thromboembolism should be continued for long-term anticoagulant therapy.

Surgical venous interruption of the inferior vena cava should be considered in certain situations:

(1) contraindications to anticoagulation, (2) recurrent emboli despite adequate anticoagulation, (3) septic pelvic thrombophlebitis with emboli, and (4) in conjunction with pulmonary embolectomy. Venous ligation at the femoral level is accompanied by unacceptable mortality from postoperative pulmonary embolism. The optimum site of interruption is the inferior vena cava just below the entry of the renal veins together with the spermatic or ovarian veins. Various procedures to interrupt the vena cava partially or completely are used. Patients who have had vena caval interruption require anticoagulation for at least 6 mo following the procedure. Morbidity following such procedures is significant (10 to 15%), and recurrent embolization may occur in as many as 50% of patients from the site of interruption or through large collateral (lumbar) veins if interruption is complete.

Differential diagnosis of lung infiltrates

are presented in the next table:

Table 1. Differential diagnosis of lung infiltrates.

Signs and symptoms	Tuberculosis (infiltrative)	Pneumonia	Lung infarction	Eosinophilic Infiltrate	Lung cancer
Anamnesis	Contact with tbc patient	Colds, tonsillitis, flu	Surgery, trauma, thrombophlebitis, heart diseases	Allergy, helminths	Men > 40 years, smoker
Follow-up	Slow beginning and regress after therapy	Acute beginning and regress after therapy	Acute beginning	Slow beginning	Slow beginning and progressive worsening

Symptoms	Moderate intoxication, subfebrile fever, perspiration, cough,. Minimal auscultative changes (wet rales after cough)	High temperature, dyspnoe, cough. Rich and changeable auscultative picture (rales, crepitation)	Pain in chest, blood in sputum, dyspnoe. On zone of infarction–dullness and bronchial breath.	Frequently no complains. Sometimes cough with sputum, unstable and different rales.	Pain in chest, blood in sputum, dyspnoe. In some cases–local dullness, dry rales
X-ray	Nonhomogenous infiltrate in 1,2 or 6 segments. Way to the root, dessimination	Homogenous or lineal opacity in middle or lower parts of lungs.	Triangle homogenous opacity with peak to the root. Sometimes round or oval opacity. High position of diafragm.	Rapid appearing and disappearing of infiltrate with irregular margins.	In case of peripheral tumor– in anterior part homogenous opacity with ways to the root. In case of central tumor – opacity connected with root and frequently associated with atelectasis
Laboratory	Leucocytosis < $15 \cdot 10^9/l$, limphopenia, increased ESR, MBT+	High leucocytosis, deviation to the left, increased ESR, MBT–	Increased ESR, leucocytosis, hypercoagulation	Eosinophilia (50-60%) for two-three weeks. Eosinophilia in sputum.	Increased ESR, leucocytosis, anemia, atypical cells in sputum.
Other	Positive Mantoux test, specific endobronchitis on bronchoscopy.	Nonspecific endobronchitis on bronchoscopy	Right ventricle overloading on ECG.	Positive skin tests with allergenes	Signs of tumor on bronchoscopy

SARCOIDOSIS

A multisystem granulomatous disorder of unknown etiology, characterized histologically by epithelioid tubercles involving various organs or tissues, with symptoms dependent on the site and degree of involvement.

Ethiology and incidence

The cause is unknown. A single provoking agent (e-g., a slow virus) or disordered defense reactions triggered by a variety of insults may be responsible; genetic factors may be important. Sarcoidosis occurs predominantly between ages 20 and 40 and is most common among northern Europeans and American blacks. The incidence in some advanced countries exceeds that of TB.

Pathology

The characteristic histopathologic findings are multiple noncaseating epithelioid granulomas, with little or no necrosis, that may resolve completely or proceed to fibrosis. They occur commonly in mediastinal and peripheral lymph nodes, lungs, liver, eyes, and skin, and less often in the spleen, bones, joints, skeletal muscle, heart, and CNS.

Symptoms and signs

Symptoms depend on the site of involvement and may be absent, slight, or severe. Function may be impaired by the active granulomatous disease or by secondary fibrosis. Fever, weight loss, and arthralgias may be initial manifestations. Persistent fever is especially common with hepatic involvement. Peripheral lymphadenopathy is common and usually asymptomatic. Even insignificant nodes may contain characteristic tubercles.

Skin lesions (plaques, papules, and subcutaneous nodules) frequently are present in patients with severe chronic sarcoidosis. Nasal and conjunctival mucosa granulomas may occur. Erythema nodosum with fever and arthralgias is a frequent manifestation in Europe, but less common in the USA.

Mediastinal adenopathy often is discovered by routine chest x-ray. X-ray findings of bilateral hilar and right paratracheal adenopathy are virtually pathognomonic; adenopathy occasionally is unilateral. Diffuse pulmonary infiltration may accompany or follow the adenopathy; this infiltration may have a diffuse ground-glass appearance on x-ray, may occur as reticular or miliary lesions, may be present as confluent infiltrations or large nodules that resemble metastatic tumors. Pulmonary involvement, which may also occur without visible adenopathy, is usually accompanied by cough and dyspnea, but these symptoms may be minimal or absent. Pulmonary fibrosis, cystic changes, and cor pulmonale are results of longstanding progressive disease.

Hepatic granulomas are found in 70% of patients examined by percutaneous biopsy, even if patients are asymptomatic with normal liver function tests. Hepatomegaly is noted in fewer than 20% of patients; progressive and severe hepatic dysfunction with portal hypertension and esophageal varices is rare.

Granulomatous uveitis occurs in 15% of cases; it is usually bilateral, and may cause severe loss of vision from secondary glaucoma if untreated. Retinal panphlebitis, lacrimal gland enlargement, conjunctival infiltrations, and keratitis sicca occasionally are present. Myocardial involvement may cause angina, congestive failure, or fatal conduction abnormalities. Acute polyarthritis may be prominent; chronic periarticular swelling and tenderness may be associated with osseous changes in the phalanges. CNS involvement is of almost any type, but cranial nerve palsies (especially

facial paralysis) are most common. Diabetes insipidus may occur. Hypercalcemia and hypercalcfuria may cause renal calculi or nephrocalcmosis with consequent renal failure, but prednisone therapy has reduced the frequency and importance of disordered calcium metabolism.

Laboratory Findings

Leukopenia frequently is present. Hyperglobulinemia is common among blacks. Elevated serum uric acid is not uncommon, but gout is rare. Serum alkaline phosphatase may be elevated as a result of hepatic involvement. Depression of delayed hypersensitivity is characteristic, but a negative second-strength tuberculin reaction reliably excludes a complicating TB.

Pulmonary function tests show restriction, decreased compliance, and impaired diffusing capacity. CO₂ retention is uncommon, since ventilation rarely is obstructed except in patients with endobronchial disease or in late stages with severe pulmonary fibrosis. Serial measurements of pulmonary function are a guide to treatment and to the course of the disease.

Diagnosis

A clinical diagnosis may be made in asymptomatic patients with typical chest x-ray findings, but the diagnosis must be considered in the presence of the symptoms and signs described above even if (as in about 10% of patients) the chest x-ray is normal. Tissue biopsy, with microbiologic as well as histologic examination, is essential if symptoms are present and corticosteroid therapy seems indicated. When superficial or palpable lesions (e.g., in skin, lymph nodes, palpebral conjunctiva) are present, biopsy is positive in 87% of specimens.

When physical examination is negative, transbronchial biopsy by fiberoptic bronchoscope is the best initial procedure for securing histologic evidence of sarcoidosis. This technic has shown granulomas in 60 to 90% of patients, whether the chest x-ray reveals pulmonary infiltration or hilar adenopathy alone.

If this approach is not available or fails to show granulomas, other possible biopsy sites include the mediastinum, which can be approached by mediastinotomy or mediastinoscopy; the lungs, approached by intercostal biopsy; or random biopsies of skeletal muscle and conjunctiva. Liver biopsy shows granulomas in 70% of cases, and can be useful. Scalene fat-pad biopsy is obsolete in view of the higher yields of other methods.

Local sarcoid reactions in a single organ and granulomas due to infection or hypersensitivity must be excluded. In questionable cases, histologic evidence of granulomas should be sought in more than one site. The Kveim reaction, a granulomatous reaction appearing 4 wk after intradermal injection of extracts of spleen or lymph node, is positive in 50 to 60% of patients, but reliable antigens are not available in the USA.

Angiotensin converting enzyme (ACE) is elevated significantly in sera of patients with sarcoidosis, presumably reflecting macrophage activity. Tissue levels are highest in sarcoid lymph nodes rather than in pulmonary tissues. Elevations greater than 2 standard deviations occur in 60% of patients with sarcoidosis, but these elevations are also seen in 10% of patients with TB or

lymphoma; therefore elevated ACE has limited diagnostic value, but may prove useful in following the course of sarcoidosis.

TB still must be distinguished from sarcoidosis, but aspergillosis and cryptococcosis are now more frequent complications of sarcoidosis. Hodgkin's disease also must be excluded. It is uncertain whether the typical sarcoid granulomas found in 5% of liver biopsies done for staging of Hodgkin's disease indicate 2 concurrent diseases or a sarcoid reaction to the neoplasm.

Course and Prognosis

Evaluating treatment is difficult, since spontaneous improvement or clearing is common. Massive hilar adenopathy and extensive infiltrates may disappear in a few months or years. Mediastinal adenopathy persists without change for many years in about 10% of cases. In 1/3 of the patients, complete clearing of the disease occurs; another 1/3 recover, but with minor residua; in the remaining 1/3, progressive disease requires treatment. Mortality is < 5%. Gradual pulmonary fibrosis, leading to pulmonary insufficiency, pulmonary hypertension, and cor pulmonale, is the leading cause of disability and death; pulmonary hemorrhage from aspergillosis is the second most common cause of death.

Treatment

No available therapeutic agents have been shown to prevent progressive tissue damage and fibrosis of the lungs. Corticosteroids accelerate clearance of symptoms, physiologic disturbances, and roentgenographic changes; but after 5 yr no difference is demonstrable between treated and untreated patients. Asymptomatic hilar or peripheral adenopathy needs no treatment. Corticosteroid therapy should be given to suppress troublesome or disabling symptoms such as dyspnea, severe arthralgia, or fever, and should be started promptly if active ocular disease, respiratory failure, hepatic insufficiency, cardiac arrhythmia, CNS involvement, or hypercalcemia is present. Prednisone therapy is required by 1/3 of white patients and 2/3 of black patients with sarcoidosis.

Prednisone 40 to 60 mg/day orally may be given when a prompt effect is desired, but doses of 10 to 15 mg/day by mouth usually are adequate to control the inflammatory reaction. If doses > 15 mg/day are given, alternate-day schedules should be employed. Treatment may be needed for weeks, for years, or indefinitely. Maintenance doses of 5 to 10 mg/day are surprisingly effective in controlling symptoms and radiologic changes in many chronic cases. Clinical examination, x-rays, and pulmonary function studies should be made at frequent intervals when dosage is being reduced or medication terminated. Serious complications of corticosteroid therapy are infrequent with low-dose therapy in this disease. Concomitant isoniazid therapy, 300 mg/day for a year, is indicated only for the few patients given corticosteroids who have positive tuberculin skin tests.

Methotrexate and chlorambutil occasionally are effective in sarcoidosis, but dramatic improvement with these agents is rare. They deserve a trial only when corticosteroids fail or are contraindicated.

IDIOPATHIC INFILTRATIVE DISEASES OF THE LUNGS

A spectrum of disorders with different etiologies but similar clinical features and diffuse pathologic changes that affect primarily interalveolar interstitial tissue. Interstitial infiltration is characterized in its acute phase by abnormal accumulation of histiocytes, lymphocytes, plasma cells, eosinophils, and exudate in alveoli and bronchioles. Hyperplasia of bronchiolar or alveolar epithelium may be present at a later stage. If the disorder progresses, the exudate may become organized, and necrosis, scarring, and reepithelialization of alveolar septae may take place. The whole process may ultimately lead to extensive fibrosis, progressive destruction of lung and formation of cysts ("honeycombing").

Idiopathic pulmonary fibrosis (usual interstitial pneumonia [UIP], diffuse fibrosing alveolitis, Hamman-Rich syndrome): when the etiology leading to pulmonary fibrosis cannot be defined (about 50% of cases), the term "idiopathic" is used.

Desquamative interstitial pneumonia (DIP) resembles idiopathic pulmonary fibrosis, but the histology tends to be more uniform: the cellular infiltrate is more sparse and less pleomorphic. There is striking hyperplasia of type II pneumocytes and filling of air spaces with macrophages. It has been argued that the separation of DIP from idiopathic pulmonary fibrosis is artificial because both histologic patterns can be found frequently in the same lung (probably representing different phases of the same process). However, the clinical recognition of DIP is important because the process is associated with a better prognosis and a better response to systemic corticosteroids.

Symptoms and Signs

Symptoms and signs vary with the extent of pulmonary infiltration, its rate of progress, and with the presence of complications such as pulmonary infections or cor pulmonale. Pulmonary symptoms may be few, but exertional dyspnea of insidious onset is almost invariably present. Cough is usually not prominent, but it is more likely to be present when there is secondary bronchial infection. Anorexia, weight loss, fatigue, weakness, and vague chest pains are common. Physical signs may be absent early in the course, but, as the disease progresses, tachypnea and labored breathing are observed and chest examination reveals prominent breath sounds and end-inspiratory crackles at lung bases. With progression, cyanosis, cor pulmonale, and clubbing may appear.

Laboratory Findings

Routine laboratory studies are not helpful. Polycythemia may be present secondary to chronic hypoxemia. **Chest x-rays** may be normal even in the presence of significant symptoms or functional abnormalities. X-ray changes tend to be more prominent at the bases and may include diffuse or patchy "ground-glass" haziness, linear markings, rounded opacities, small cystic lesions (honeycombing), evidence of reduced lung volumes, and signs of pulmonary hypertension. **Pulmonary function** studies reveal a restrictive ventilatory defect with reductions in both vital capacity and residual volume. The coefficient of retraction (maximum static transpulmonary pressure/total lung capacity) can be increased. Arterial blood gases show a low P_{aCO_2} denoting hyperventilation at rest and a decrease in P_{aO_2} . The abnormal increase in P_{aCO_2} at rest may be exacerbated during

exercise. The diffusing capacity for CO is usually reduced. These functional abnormalities can worsen as the disease progresses.

Diagnosis

Diagnosis is made by recognizing the clinical features, demonstrating the presence of a diffuse interstitial disorder, and excluding a specific etiology. Because the amount of tissue obtained by transbronchial biopsy is frequently insufficient, open lung biopsy is recommended for the identification of DIP. Open pulmonary biopsy is not indicated when there is radiographic honeycombing.

Prognosis

The outcome varies with the etiology and the rate of progression. Some patients may die within a month, while others survive many years. The mortality is smaller and the mean survival greater when histologic features of DIP are present on open lung biopsy.

Treatment

A trial of systemic corticosteroids is indicated in patients without evidence of extensive fibrosis. Prednisone 40 to 60 mg/day usually is given with gradual reduction of the dose to maintenance levels (10 to 30 mg every other day). The response to therapy is followed by serial chest x-rays and appropriate lung function tests. Gallium citrate Ga 67 lung scanning and serial analysis of cellular content of bronchoalveolar lavage fluid may prove to be useful to detect and follow the response of the inflammatory process to therapy. A few patients who have not improved on prednisone have shown improvement with azathioprine 3 mg/kg/day, but experience with this agent is limited. Other treatment is supportive and palliative. O₂ in high concentrations may help combat hypoxemia. Antibiotics are required if secondary bacterial infection occurs. Digitalis and diuretics are used to treat heart failure.

Differential diagnostics of lung injuries in connective tissue disease

In connective tissue disease symptoms may include: shortness of breath, especially with exertion, fatigue and weakness, loss of appetite, loss of weight, dry cough, that does not produce phlegm, discomfort in chest, labored breathing, hemorrhage in lungs.

Examinations of lungs reveals:

Pleuropulmonary manifestations are common. The incidence varies from 20-85%.

Pleuropulmonary complications include pleural effusion, interstitial pulmonary fibrosis, pulmonary arterial hypertension, pulmonary vasculitis, pulmonary thromboembolic phenomena, aspiration pneumonia, serositis, and hypoventilatory failure.

Pulmonary injuries are characterized by the presence of ground-glass attenuation, nonseptal linear opacities, and peripheral and lower lobe predominance.

- Ill-defined centrilobular opacities may be evident.

Chest radiography may depict pleural thickening, fibrosis, and pericarditis

- Pulmonary function tests may reveal ventilation disorders of the restrictive type.
 - These include a diminished vital capacity, a normal residual volume, and a diminished total lung capacity.
 - Respiratory function abnormalities usually are coexistent with the radiographic findings

The main role in differential diagnostics based on clinic of multiorgan involvement, immunological and histological findings, that are very specific in case of connective tissue diseases.

LUNG ABSCESS

Essentials of Diagnosis

- Development of pulmonary symptoms about 1-2 weeks after possible aspiration, bronchial obstruction, or previous pneumonia.
- Septic fever and sweats, and periodic sudden expectoration of large amounts of purulent, foul-smelling, or "musty" sputum. Hemoptysis may occur.
- X-ray density with central radiolucency and fluid level.

General Considerations

Lung abscess develops when necrosis and liquefaction occur in an area where necrotizing pneumonia is present (picture 1-3). Symptoms and signs occur 1-2 weeks after the following events: (1) massive-aspiration of upper respiratory tract secretions and microbial flora, especially during profound suppression of cough reflex (eg, with alcohol, drugs, unconsciousness, anesthesia, brain trauma); (2) bronchial obstruction (eg, by atelectasis, foreign body, neoplasm); (3) presence of pneumonias, especially those caused by gram-negative bacteria or staphylococci; or (4) formation of septic emboli from other foci of infection, or, during bacteremia, with pulmonary infarcts. Abscess is more commonly in the lower dependent portions of the lung. The main etiologic organisms are related to the underlying condition, but a dense mixed anaerobic flora is often prominent, particularly when aspiration has occurred.

Clinical Findings

A. Symptoms and Signs: Onset may be abrupt or gradual. Symptoms include septic fever, sweats, cough, and chest pain. Cough is often nonproductive at onset. Expectoration of foul-smelling brown or gray sputum (anaerobic flora) or of purulent sputum without odor (pyogenic organism) may occur abruptly and in large quantity. Blood-streaked sputum is also common.

Pleural pain, especially with coughing, is common because the abscess is often subpleural. Weight loss, anemia, and pulmonary osteoarthropathy may appear when the abscess becomes chronic (8-12 weeks after onset).

Physical findings may be minimal. Consolidation due to pneumonitis surrounding the abscess is the most frequent finding. Rupture into the pleural space produces signs of fluid or pneumothorax.

B. Laboratory Findings: Sputum cultures are usually inadequate in determining the bacterial cause of a lung abscess. Transtracheal aspirates should be obtained with the proper technique

employed to culture anaerobic organisms in addition to the usual aerobic cultures. Special methods of transporting specimens are required for anaerobic organisms, and appropriate culture media and methods must be employed.

Smear and cultures for the tubercle bacilli are required, especially in lesions of the upper lobe and in chronic abscess.

C. X-Ray Findings: A dense shadow is the initial finding. A central radiolucency, often with a visible fluid level, appears as surrounding densities subside. Computerized tomography can supply the detailed localization of the abscess and may also reveal primary lesions (eg, bronchogenic carcinoma) and provide guidance for contemplated surgery. Various x-ray procedures also permit localization of pleural involvement to facilitate drainage.

D. Instrumental Examination: Fiberoptic bronchoscopy may help to 'diagnose location and nature of obstructions (foreign body, tumor), obtain specimens for microbiologic and pathologic examination, and, occasionally, aid drainage.

Differential Diagnosis

Differentiate from other causes of pulmonary cavitation: tuberculosis, bronchogenic carcinoma, mycotic infections, and staphylococcal or gram-negative bacterial pneumonia.

Treatment

Postural drainage and bronchoscopy are important to promote drainage of secretions.

A. Acute Abscess: Intensive antibacterial therapy is necessary to prevent further destruction of lung tissue. While cultures and sensitivity tests are pending, treatment should be started with penicillin G, 2-6 million units daily. In penicillin hypersensitivity clindamycin and chloramphenicol are alternatives. If the patient improves on antimicrobial drugs (and postural drainage), the drugs should be continued for 4—8 weeks. If the patient fails to respond significantly to the initial treatment, laboratory results may suggest other antimicrobials, eg, nafcillin for staphylococci, cefotaxime for *Klebsiella*, cefoxitin or metronidazole for mixed anaerobes. Postural drainage is important adjunctive treatment. Percutaneous catheter drainage has been used successfully in selected cases. Surgical therapy is indicated mainly for severe hemoptysis and for the infrequent abscesses that fail to respond to antimicrobial management. Failure of fever to subside after 2 weeks of therapy, abscess diameter of more than 6 cm, and very thick cavity walls are all factors that lessen the likelihood of success with nonsurgical treatment alone.

B. Chronic Abscess: After acute systemic manifestations have subsided, the abscess may persist. Although many patients with chronic lung abscess can be cured with long-term treatment with antibacterial agents, surgery may occasionally be required.

Complications

Rupture of pus into the pleural space (empyema) causes severe symptoms: increase in fever, marked pleural pain, and sweating; the patient becomes "toxic" in appearance. Adequate drainage of empyema is mandatory. In chronic abscess, severe and even fatal hemorrhage may occur. Metastatic brain abscess is a well-recognized complication, and the infection may seed other organ sites. Bronchiectasis may occur as a sequela to lung abscess even when the abscess itself is cured.

Prognosis

The prognosis in acute abscess is excellent with prompt and intensive antibiotic therapy. About 80% of patients are healed within 7-8 weeks. The incidence of chronic abscess is consequently low; In chronic cases, surgery is curative.

BRONCHIECTASIS

Essentials of Diagnosis:

- Chronic cough with expectoration of large amounts of purulent sputum; hemoptysis.
- Rales and rhonchi over lower lobes.
- X-ray of chest reveals little; bronchograms show characteristic dilatations.

General Considerations

Bronchiectasis is a dilatation of small and medium-sized bronchi resulting from destruction of bronchial elastic and muscular elements. It may be, caused by pulmonary infections (eg, pneumonia, pertussis, tuberculosis) or by a bronchial obstruction (eg, foreign bodies or extrinsic pressure). In many patients, a history of onset following one or more episodes of pulmonary infection, usually in early childhood, is obtained. However, since infection does not regularly produce significant bronchiectasis, unknown intrinsic host factors presumably are present. The incidence of the disease has been reduced by treating pulmonary infections with antibiotics.

Clinical Findings

A. Symptoms and Signs: Most patients with bronchiectasis have a history of chronic cough with expectoration of large volumes of sputum, especially upon awakening. The sputum has a characteristic quality of "layering out" into 3 layers upon standing, a frothy top layer, a middle clear layer, and a dense particulate bottom layer. It is usually purulent in appearance and foul-smelling.

Intermittent hemoptysis, occasionally in dangerous proportions, is often combined with intercurrent respiratory infections. Symptoms occur most often in patients with idiopathic bronchiectasis (ie, childhood respiratory infections). However, patients who have bronchiectasis secondary either to tuberculosis or chronic obstruction may not exhibit characteristic symptoms. Idiopathic bronchiectasis occurs most frequently in the middle and lower lobes and posttuberculous bronchiectasis in the upper lobes. Hemoptysis is thought to result from erosion of bronchiolar mucosa with resultant destruction of underlying blood vessels. Pulmonary insufficiency may result from progressive destruction of pulmonary tissue.

Physical findings consist primarily of rales and rhonchi over the affected segments. If the condition is far-advanced, emaciation, cyanosis, and digital clubbing may appear.

B. Laboratory Findings: There are no characteristic laboratory findings. If hypoxemia is chronic and severe, secondary polycythemia may develop. There may be either restrictive or obstructive pulmonary function defects associated with bronchiectasis. Hypoxemia and hypocapnia or hypercapnia may also be associated with the disease, depending on the severity of the underlying condition. .

C.X-Ray Findings: Plain films of the chest often show increased bronchopulmonary markings in affected segments; in severe cases there may be areas of radiodensities surrounding portions of radiolucency. Early in the course of bronchiectasis, however, the chest x-ray may be normal.

Iodized contrast media instilled into the bronchial tree (a bronchogram) demonstrates saccular, cylindric, or fusiform dilatation of small and medium bronchi with consequent loss of the normal branching pattern. Cylindric changes of bronchiectasis that may result from acute pneumonia will revert to normal after 6-8 weeks, but saccular dilatations represent long-standing damage and permanent disease.

Differential Diagnosis

The differential diagnosis includes other disorders that lead to chronic cough, sputum production, and hemoptysis, ie, chronic bronchitis, tuberculosis, and bronchogenic carcinoma. The diagnosis of bronchiectasis is suggested by the patient's history and can be confirmed only by bronchographic examination or histopathologic examination of surgically removed tissue.

Complications

Recurrent infection in poorly drained pulmonary segments leads to chronic suppuration and may cause pulmonary insufficiency. Complications include hemoptysis, respiratory failure, chronic cor pulmonale, and amyloidosis. There is also an increased incidence of brain abscess, which is thought to be secondary to abnormal anastomoses between bronchial (systemic) and pulmonary venous circulation. These anastomoses produce right-to-left shunts and allow for the dissemination of septic emboli.

Treatment

. A. General Measures and Medical Treatment:

1. Environmental changes- The patient should avoid exposure to all common pulmonary irritants such as smoke, fumes, and dust and should stop smoking cigarettes.

2. Control of bronchial secretions (improved drainage)-

a. Postural drainage often gives effective relief of symptoms and should be utilized in every case. The patient should assume the position that gives maximum drainage, usually lying on a bed in the prone, supine, or right or left lateral decubitus position with the hips elevated on several pillows and no pillow under the head. Any effective position should be maintained for 10 minutes, 2-4 times a day. The first drainage should be done upon awakening and the last drainage at bedtime. Family members can be trained in the art of chest percussion to facilitate drainage of secretions.

b. Liquefaction of thick sputum may be promoted by inhaling warm mists and, in some cases, mucolytic agents such as acetylcysteine or 5% sodium bicarbonate given by aerosol may also be helpful.

3. Control of respiratory infection-Exposure to respiratory infections should be minimized and the patient should be vaccinated against influenza and pneumococcal pneumonia. Antibiotic therapy is indicated for acute exacerbations (ie, increased production of purulent sputum, hemoptysis, etc).

Long-term or prophylactic antibiotic therapy is controversial, since it has not been conclusively shown to be of lasting benefit. Therefore, it seems rational to treat acute exacerbations in order to control infection but minimize the emergence of resistant strains. Because the bacteria most commonly involved are *H influenzae* and *S pneumoniae*, the drug most commonly employed is ampicillin, 250-500 mg orally every 6 hours for 5 days. Alternative therapies for the penicillin-allergic patient are erythromycin, given in the same dosage schedule as ampicillin, or trimethoprim-sulfamethoxazole, 2 double-strength tablets twice a day for 5 days.

B. Surgical Treatment: Surgical treatment is most often employed when hemoptysis with bronchiectasis is recurrent and severe. Despite antibiotic therapy, localized bronchiectasis (eg, in a lower lobe or segment) with progressive uncontrolled infection and sputum production may be an indication for surgical removal of the affected segments.

Other Considerations

Bronchiectasis is also associated with mucoviscidosis. It is thought to be secondary to the thick viscid secretions that cannot be cleared by normal cough mechanisms and that lead to stasis of sputum and chronic infection. This disorder, usually associated with sinusitis, may be accompanied by other manifestations of mucoviscidosis. Its most common organisms are *S aureus* or *Pseudomonas aeruginosa*.

Bronchiectasis is also associated with certain abnormalities of cellular ciliary function, the most common of which is Kartagener's syndrome, a combination of sinusitis, situs in versus, and bronchiectasis. Patients with this disorder show immotile cilia secondary to ultrastructural abnormalities, stasis of sputum, failure to clear secretions, and chronic pulmonary infection that results in bronchiectasis.

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Self preparation at class:

Listen information;

Work with patients;

Ask about the problems that have not been found in information given.

Self preparation at home:

Compose the plan of your answer;

Answer the questions to the topic;

Do the test given above.

1. Histologic examination of lung tissue reveals multiple suppurative, neutrophil-rich exudates that fill the bronchi and bronchioles and spill over into the adjacent alveolar spaces only. The majority of lung tissue is not involved in this inflammatory process. Hyaline membranes are not found. This histologic appearance best describes
 - a. Bronchiectasis
 - b. Bronchopneumonia
 - c. Lobar pneumonia
 - d. Interstitial pneumonitis
 - e. Pulmonary abscess

2. A 44-year-old male alcoholic presents with fever and a productive cough with copious amounts of foul-smelling purulent sputum. Physical examination finds that changing the position of this individual produces paroxysms of coughing. Which one of the following is most likely responsible for this patient's signs and symptoms?
 - a. Esophageal cancer
 - b. Esophageal reflux
 - c. Myocardial infarction
 - d. Pulmonary abscess
 - e. Pulmonary infarction

Recommended literature:

A. Main:

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1. The answer is b. Pulmonary infections may be caused by bacteria, fungi, viruses, or mycoplasma. Bacterial infections generally result in a polymorphonuclear (neutrophil) response. Bacterial infection of the lung (pneumonia) results in consolidation of the lung, which may be patchy or

diffuse. Patchy consolidation of the lung is seen in bronchopneumonia (lobular pneumonia), while diffuse involvement of an entire lobe is seen in lobar pneumonia. Histologically, bronchopneumonia is characterized by multiple, suppurative neutrophil-rich exudates that fill the bronchi and bronchioles and spill over into the adjacent alveolar spaces. In contrast, lobar pneumonia is characterized by four distinct stages: congestion, red hepatization, gray hepatization, and resolution.

2. The answer is d. A pulmonary abscess is a localized suppurative process within the pulmonary parenchyma that is characterized by tissue necrosis and marked acute inflammation. Possible causes of a lung abscess include aerobic and anaerobic streptococci, *Staphylococcus aureus*, and many gram-negative organisms. Aspiration more often gives a right-sided single abscess, as the airways on the right side are more vertical. Antecedent pneumonia gives rise to multiple diffuse abscesses. The abscess cavity is filled with necrotic suppurative debris unless it communicates with an air passage. Clinically an individual with a lung abscess will have a prominent cough producing copious amounts of foul-smelling, purulent sputum. Changes in position evoke paroxysms of coughing. There is also fever, malaise, and clubbing of the fingers and toes. With antibiotic therapy 75% of lung abscesses resolve. Complications of a lung abscess include pleural involvement (empyema) and bacteremia, which could result in brain abscesses or meningitis.

Methodical recommendations consisted by

Kulishov S.K.