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Office Management of Lower Respiratory Infections in Adults

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The office management of lower respiratory infections in adults is a common major challenge to the practicing physician. The patient almost always has a cough, may have various other symptoms, and expects appropriate treatment. Appropriate treatment is related not to the patient's presenting symptoms but to the etiologic agent. The etiologic agent or agents may be determined with great accuracy, but frequently only after extensive, expensive testing. The test results may arrive too late to be helpful in the treatment—results of many cultures arrive after treatment should have been started, and results of acute and convalescent serologic tests are known only after the illness has ended.

Most physicians would appreciate the availability of a complete evaluation for patients with lower respiratory infection, including bacterial, fungal, acid-fast, *Legionella*, mycoplasmal, and viral cultures, and serologic tests for viruses, mycoplasma, fungi, and agents causing Legionnaires' disease and Q fever. A tuberculin skin test, chest roentgenogram, complete blood count, transtracheal aspiration, and bronchoscopy could be performed. However, in most cases, the cost of such a work-up would be prohibitive. Usually, the physician performs a careful history and physical examination and orders a few "appropriate" laboratory tests.

This challenge is followed by another, the choice of which, *if any*, antimicrobial agent or agents should be administered. If the physician chooses to administer an antimicrobial agent, the cost to the patient must be considered, as well as the efficacy and toxicity of the drug (Table 1).

Prevention, including immunizations, is discussed elsewhere in this issue. However, each physician must have a practical and efficient system for screening patients for immunization. Immunizations may prevent such lower respiratory infections as influenza, pneumococcal pneumonia, diphtheria, and atypical measles.

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Table 1. *Estimated Cost to Patient of Various Oral Antimicrobial Regimens**

DRUG	DOSAGE (MG)†	COST ($)
Penicillin	500	6.62
Ampicillin	500	8.18
Amoxicillin	250	8.98
Tetracycline	500	5.73
Cephradine	500	28.38
Cephalexin	500	40.60
Cefadroxil	500	37.18
Co-trimoxazole	—†	6.82
Erythromycin stearate	500	10.42
Erythromycin ethylsuccinate	400	10.42

*Average cost from two pharmacies.

†All doses are given four times per day for 10 days except doses of co-trimoxazole (Bactrim DS or Septra DS), which is given twice daily for 10 days.

HISTORY AND PHYSICAL EXAMINATION

Current medical practice frequently involves extensive testing. Patients and physicians often place excessive confidence in test results and too little confidence in the history and physical examination. The history and physical examination may provide the most important information for the initial management of the patient with lower respiratory infection.

HISTORY

Symptoms

Most patients with lower respiratory infections have a cough. The duration of the cough may be helpful in suggesting the cause of the infection. A cough of a few days' duration is suggestive of a bacterial, viral, or mycoplasmal infection. Less common possibilities include Q fever, psittacosis, acute histoplasmosis, blastomycosis, or coccidioidomycosis. A cough of several weeks' duration is indicative of chronic bronchitis or another underlying disorder, with or without a superimposed acute infection, tuberculosis, or fungal infection. A nonproductive acute cough is suggestive of a viral or mycoplasmal infection or Legionnaires' disease. A cough associated with *Pneumocystis carinii* infection rarely produces sputum or produces a scant amount of nonpurulent sputum. A purulent, productive cough may be present in patients with such an infection, but it indicates a coexistent bacterial or fungal infection. A history of chronic productive cough is suggestive of chronic bronchitis or bronchiectasis.

Blood-streaked sputum develops as the result of a ruptured small vessel in the tracheobronchial tree, usually following vigorous coughing. Large quantities of blood in the sputum are suggestive of a bacterial, fungal, or tuberculous infection.

Fever is less common in mild viral respiratory infections, particularly

those caused by rhinovirus and coronavirus. Fever, a temperature of 100° F (37.8° C) or more orally, occurs more frequently in patients with influenza virus, adenovirus, bacterial, fungal, and tuberculous infections. Fever may be deceptively absent in immunosuppressed patients receiving corticosteroids. Noninfectious causes of fever and cough are listed in Table 2.

Retrosternal chest pain may be the result of almost any infection that produces a prominent cough. However, pleuritic pain is more common in patients with bacterial than in those with mycoplasmal or viral infections, unless the pain is the result of a fractured rib, which may be suspected during the physical examination. Chills may be present in almost any infection, but shaking chills (rigors) are suggestive of bacterial infection. A single shaking chill at the onset of illness is typical of pneumococcal pneumonia.

The onset of pneumococcal pneumonia frequently is sudden. Patients may be able to recall the hour of the day or, more likely, the portion of the day of onset. Most viral and mycoplasmal infections have a more gradual onset, developing over one to two days or longer.

Associated symptoms must be carefully interpreted. Viral and mycoplasmal infections usually are associated with upper respiratory symptoms, but upper respiratory symptoms frequently may precede pneumococcal pneumonia. Patients with chronic bronchitis resulting from smoking often have sinus and nasal symptoms. Headache, which is common in patients with Legionnaires' disease, may accompany fever due to any cause. Diarrhea and abdominal pain may be associated with pneumococcal and *Legionella* pneumonia.[2] Gastrointestinal symptoms are uncommonly observed in patients with influenza virus infections.

Age

Mycoplasmal pneumonia is uncommon in persons older than 35 years and is very uncommon in those older than 45.[9] Acute bronchitis superimposed on chronic bronchitis resulting from smoking is much more frequent in persons 35 years of age or older. Pneumococcal and *Hemophilus* pneumonias are more common in the very young and older patients. Community-acquired *Klebsiella* pneumonia is more common in men between 40 and 60 years of age.[20]

Table 2. *Noninfectious Causes of Fever and Cough**

Atelectasis	Drug toxicity[10]
Congestive failure	Connective tissue disease[23]
Pulmonary embolism[5]	Lupus erythematosus
Aspiration	Scleroderma
Radiation	Polymyositis
Hypersensitivity pneumonitis[10]	Rheumatoid arthritis
Pancreatitis[34]	Vasculitis
Sarcoidosis	Periarteritis nodosa
Berylliosis (and other heavy metals)	Churg-Strauss syndrome
Lipoid pneumonia	Wegener's granulomatosis
Pulmonary infiltrate with eosinophilia syndromes[8]	Goodpasture's disease
	Pulmonary alveolar proteinosis

*Partial list only.

Occupation, Travel, Exposure, and Residence

Living in or traveling to the southwestern United States or certain Central and South American areas predisposes to coccidioidomycosis. Many patients with coccidioidal pneumonitis have lived their entire lives in the midwestern United States but have spent vacation or transient retirement periods in the southwestern United States. Endemic plague is present in the southwestern United States and may be transmitted by fleas, by direct contact with infected animals such as rodents, or by exposure to humans with plague pneumonia.[15, 29] Hunting and exposure to infected carcasses, particularly rabbits; ingestion of contaminated food; and exposure to ticks, deerflies, or other blood-sucking insects may predispose to tularemia. While tularemia may develop in residents of many states and has recently been reported in individuals living in Utah and New England, it is most common in the central southern United States.[6, 31, 47]

Melioidosis is most common in persons who have traveled to Southeast Asia, certain Pacific Islands, the Middle East, Australia, or South America.[22] Histoplasmosis is endemic in several regions of the world, particularly in the valleys of the Mississippi River and its tributaries, including the Ohio River.[13] Individuals in these areas are at greatest risk after the excavation or disturbance of soil or soil covering, particularly if it has been exposed to bird droppings. Army recruits have a relatively high incidence of adenovirus pneumonia, which otherwise is rather uncommon in adults.[24] Psittacosis (ornithosis) must be considered in persons who work with turkeys or other fowl and in those who have birds as pets.[38] Workers in microbiology laboratories may acquire various infections. Q fever is most likely in those who are exposed to farm animals (cattle, sheep, and goats).

Past History and Predisposing Disorder

Patients with hypogammaglobulinemia usually have monotonously recurrent sinopulmonary infections, most commonly produced by pneumococcus and *Hemophilus* organisms.[19]

Patients with illnesses or therapy that produces neutropenia (white blood cell counts less than 1500 per cu mm), particularly those with severe neutropenia (counts less than 500 per cu mm), usually have infections with *Staphylococcus aureus*, aerobic gram-negative bacilli, or both. After treatment for these bacterial infections, *Candida*, *Aspergillus*, and *Zygomycete (Mucor)* infections are common. Patients with other neutrophil-related defects, such as chronic granulomatous disease, also are predisposed to *S. aureus* and aerobic gram-negative bacterial infections.

Patients with T-lymphocyte defects, such as Hodgkin's disease, and those who have received a kidney transplant or who are receiving corticosteroids or azathioprine, are particularly susceptible to fungal infections, such as cryptococcosis and histoplasmosis; to tuberculosis and other mycobacterial infections; to nocardiosis, listeriosis, and infections caused by herpes group viruses (including cytomegalovirus, herpes simplex, and herpes zoster); to *Pneumocystis carinii*, *Toxoplasma*, and *Legionella* infections; and to infections caused by common bacterial pathogens. *Legionella*

infections are more common in patients with chronic obstructive pulmonary disease (COPD), immunosuppression, and diabetes. Patients who have undergone splenectomy may have rapidly fatal pneumococcal or *Hemophilus* bacteremia and intravascular coagulation with or without pneumonia. Patients with cystic fibrosis frequently have staphylococcal, *Pseudomonas*, and *Hemophilus* infections. Pulmonary alveolar proteinosis predisposes to *Nocardia* infections.

Perhaps the most common predisposing condition is COPD resulting from smoking, which is associated with recurrent acute bronchitis. Other examples of conditions predisposing to sinoplumonary infections are Kartagener's syndrome and other immotile cilia syndromes,[37, 41] $alpha_1$-antitrypsin deficiency, yellow nail syndrome,[4] and cystic fibrosis.[42]

Aspiration pneumonitis is more common in patients with alcoholism, disease of the central nervous system, gastroesophageal reflux, seizure disorders, or a history of vomiting.[46] Patients with nighttime reflux may have a history of awakening during sleep because of an episode of coughing. Chemical pneumonitis may quickly follow aspiration; secondary bacterial pneumonitis or abscess may require many days to develop. Thus, seizure or alcoholic semicoma may have occurred several days to weeks before the examination.

Recent illness, antibiotic treatment, hospitalization, or residence in a nursing home may result in a change in the oropharyngeal bacterial flora of a patient and thus a change in the etiology of bacterial pneumonia, usually aerobic gram-negative bacilli, in such patients.

The patient may, if questioned, reveal a history of tuberculosis or a positive tuberculin skin test without previous antimicrobial treatment.

Seasons

Many respiratory infections may occur at any time during the year, but some have a strong seasonal variation. Influenza occurs most frequently in the winter and is very unlikely in the summer, when *Legionella* infections have their peak incidence. Pneumococcal infections are more common in late winter and early spring. Mycoplasmal infections occur throughout the year but may be associated with a larger proportion of cases in the summer when cases caused by other organisms are less common. Adenovirus outbreaks in military recruits occur mainly between January and April.

Family

Multiple cases of mycoplasmal pneumonia may develop in families or other closed populations such as students in dormitories or military recruits; the incubation period of two to three weeks accounts for the slow spread of illness in families or close communities. A common exposure may lead to simultaneous infections with primary histoplasmosis, blastomycosis, or coccidioidomycosis in family members. A past family history of tuberculosis may be very important to ascertain. There may be a history of a hereditary disorder, such as $alpha_1$-antitrypsin deficiency, immotile cilia syndromes, or cystic fibrosis.

PHYSICAL EXAMINATION

Measurement of vital signs in the physician's office is very important. High fever, tachypnea, and hypotension or a toxic appearance signal the necessity for hospital admission. Substernal retraction, flaring of the nares, the use of accessory muscles, or cyanosis indicates respiratory distress.

Bullous myringitis may result from mycoplasmal infection. Otitis media may be observed in association with several respiratory infections. Very poor dentition may be a clue to an anaerobic aspiration pneumonia. Inspiratory stridor, fever with a history of a sore throat, and dysphagia are findings of acute epiglottitis, which is uncommon in adults but may be a medical emergency. Hoarseness with acute nasal congestion is suggestive of a viral or mycoplasmal infection.

A nonproductive or scarcely productive cough of nonpurulent sputum is suggestive of viral, mycoplasmal, or *Legionella* infection, while purulent sputum suggests bacterial infection. Foul-smelling sputum suggests anaerobic infection.

Nonfamilial or noncongenital clubbing is suggestive of underlying emphysema or a tumor. The yellow-brown fingers and fingernails of an individual who smokes should be distinguished from the widespread yellow discoloration of fingernails and toenails of the yellow nail syndrome. Buboes not only are suggestive of tularemia or plague but also serve as sources of material for Gram's stain and culture. Cutaneous abscesses may be present in patients with *S. aureus* bacteremia with pneumonia (with or without endocarditis). Such abscesses also are sources of material for Gram's stain and culture. Petechiae or hemorrhages in the conjunctiva, the optic fundus, or skin are suggestive of endocarditis. If they are present in association with respiratory disease, a diagnosis of right-sided endocarditis should be considered. Needle marks in a narcotic addict should lead the physician to consider the possibility of right-sided endocarditis with septic pulmonary emboli or pneumonia resulting from aspiration during a poorly responsive state. Petechiae, ecchymoses, or both may be seen in the splenectomized patient who has pneumococcal or *Hemophilus* pneumonia with bacteremia.

Rhonchi or coarse rales may be heard in patients with bronchitis without pneumonia. Fine rales or crackles are suggestive of pneumonitis. Consolidative findings, such as dullness to percussion, egobronchophony, "E" to "A" change, bronchial breath sounds, and tactile fremitus, are suggestive of pneumococcal or other bacterial lobar pneumonia. Consolidative findings are uncommon in viral, mycoplasmal, or early *Legionella* pneumonia. The absence of wheezing is *not* a reliable indication that the asthmatic patient does not have a respiratory infection.

Posteroanterior and lateral roentgenographic views of the chest should be obtained in any patient suspected of pneumonia in order to establish the diagnosis, to determine the pattern of the infiltrate, and to ascertain the extent of pulmonary involvement. In patients with COPD, it may not be necessary to obtain a chest x-ray film with each episode of purulent sputum but only if fever or significant worsening of pulmonary symptoms occurs.

Although the appearance of the chest roentgenogram may not be pathognomonic, certain patterns indicate a likelihood of certain etiologies. Incomplete consolidations may be observed in pneumococcal pneumonia in patients with emphysema.[48] Mycoplasmal and viral pneumonias usually are manifest as focal or disseminated, lobular-bronchopneumonic infiltrates.[17] Lobar infiltrates, large pleural effusions, and cavitation are suggestive of bacterial infections. Bilateral diffuse infiltrates are most commonly observed in patients with viral or *Pneumocystis* infections. Multiple nodular infiltrates may be observed in patients with hematogenous *S. aureus* infections. Episodic infiltrates in various locations may be present in right-sided endocarditis, while recurring infiltrates at one location are suggestive of bronchiectasis or an obstructing tumor. Aspiration pneumonia usually is manifest as infiltrates in the superior or basilar segments of either lower lobe or the posterior segments of the upper lobes, depending on the position of the patient at the time of aspiration. *Legionella* infections frequently begin with patchy bronchopneumonia or poorly marginated nodular densities, but later this progresses to lobar or multilobar consolidation; cavitation is unlikely without superimposed bacterial infection. Newly diagnosed pulmonary tuberculosis in the adult may present various roentgenographic patterns other than upper lobe infiltrates with or without cavitation,[30] lower lobe infiltrates, pleural effusions, and hilar adenopathy.

The physician should make a vigorous attempt to collect a sample of expectorated sputum in a sterile container. Deep breathing by the patient, percussion over suspected areas of involvement, and encouragement by the physician often are helpful in obtaining a good sample of sputum.

A vigorous cough that produces no sputum or a slight amount of nonpurulent sputum is characteristic of viral, mycoplasmal, *Legionella*, and *Pneumocystis* infections. Patients with a vigorous nonproductive cough are unlikely to benefit from the performance of transtracheal aspiration or from other invasive procedures unless they have a significant underlying disorder. Patients with suspected lower respiratory infection and a poor cough may need to be hospitalized and may be candidates for transtracheal aspiration.

When a physician collects a specimen that appears to be purulent, it may be apparent that the sputum was "cleared from the throat" rather than "coughed up" from the lungs. A specimen "cleared from the throat" should not be sent to the laboratroy, regardless of its apparent purulence.

A sputum sample should be obtained for Gram's stain (to determine whether neutrophils, epithelial cells, and bacteria are present) and culture. The physician should perform the Gram's stain only if he or she is very experienced in the preparation and examination of Gram's stains and should compare the results of the Gram's stain with culture results. However, bacteremic pneumococcal pneumonia may be Gram's stain–positive and sputum culture–negative.[3] Some investigators believe that sputum samples in which there are more than 10 epithelial cells per 100× field should be rejected for culture because this indicates upper airway contamination.[36] Since the clinician uses information from many sources other than the sputum culture in making the diagnosis of pneumonia and in determining its cause, sputum samples generally are acceptable if they con-

tain 25 or more leukocytes per 100× field.[44] The most purulent portion of the specimens should be Gram's stained and cultured. The Gram's stain and culture of sputum are only two sources of information that are helpful in differential diagnosis and in planning treatment. For example, as many as 50 per cent of patients with pneumococcal pneumonia proven by positive blood cultures may have negative sputum cultures.[3] Sputum cultures may be positive only because of colonization, a condition that may be found in 5 to 60 per cent of the population.

In patients with acute respiratory infections, transtracheal aspiration, bronchoscopy with cultures carefully collected through catheters protected from upper airway contamination, and pleural fluid aspiration usually are best performed in the hospital rather than the office.

Two blood cultures should be obtained prior to the administration of antibiotics to febrile patients, particularly in those with an underlying disorder, in those with evidence suggestive of pneumonia or a heart murmur, or in those who have findings consistent with bacteremia. If possible, the cultures should be obtained immediately after the patient has been hospitalized.

TREATMENT

Patients suspected of having bacterial pneumonia generally should be hospitalized for treatment and observation. One possible exception is the young, otherwise healthy person suspected of having a mycoplasmal infection, who has no underlying disorder, has not undergone splenectomy, and who is reliable and lives with reliable relatives. Such a patient can be treated with erythromycin stearate, 500 mg four times per day, or erythromycin ethylsuccinate, 400 mg four times per day orally, and the physician should receive a daily status report by telephone. Otherwise healthy, middle-aged adults with typical findings of pneumococcal pneumonia, who do not appear to be ill, have no evidence of endocarditis or meningitis, and live with reliable relatives can also be treated outside the hospital. Procaine penicillin G, 600,000 units intramuscularly, can be administered in the office, then penicillin V, 500 mg four times per day, can be taken by the patient orally at home; duration of therapy depends on the rapidity of clinical response but generally requires at least one week. The physician should inquire about the patient's progress daily by telephone. Repeat chest x-rays should be obtained when indicated. In patients who are allergic to penicillin, alternative drugs will be required. When it is known that the patient who is allergic to penicillin can tolerate cephalosporins, a 1 gm intramuscular dose of cefazolin, followed by 500 mg of cephradine or cephalexin four times per day orally, may suffice.

The classic presentation of pneumococcal pneumonia includes the sudden onset of fever, a single shaking chill with or without pleuritic pain, and the production of bloody sputum, with localized consolidative findings on physical examination and chest roentgenogram and lancet-shaped, gram-positive displococci among neutrophils on Gram's stained smear of

the sputum. Such patients should receive their first dose of intramuscular penicillin in the office *after* blood and sputum cultures have been obtained. This may save hours of delay in treatment.

One controversial area in the management of lower respiratory infections is the treatment or prevention (or both) of exacerbations of acute bronchitis in patients with COPD.[14, 16, 18, 26, 27, 43, 45] The general management of such patients includes cessation of smoking, pneumococcal and influenza immunizations, avoidance of respiratory irritants, regular exercise, the use of bronchodilators, low flow oxygen for the hypoxemic patient, and adjustment of life-style.

Gump et al. have found that acute exacerbations of chronic bronchitis were associated with evidence of viral or mycoplasmal infection in 32 per cent of patients.[18] Other studies have shown much lower or much higher incidences. Very few of the patients have clinical evidence of mycoplasmal infection. *Streptococcus pneumoniae* and *Hemophilus influenzae* are the two bacterial species most commonly isolated during acute exacerbations. Sputum cultures obtained during acute exacerbations demonstrated new strains of pneumococci in 76 per cent of patients, while those taken during remission revealed new strains in 8 per cent. The therapy of acute exacerbations of chronic bronchitis has diminished the symptoms and the duration of purulent sputum but has not been demonstrated to reduce the progression of pulmonary dysfunction.

In a 5-year study, Johnston et al. compared a group of patients treated prophylactically through the winter with tetracycline to a placebo group.[26] Tetracycline also was given to all patients in the treatment group who experienced acute exacerbations. There was a significant reduction in the number of acute exacerbations among patients who usually had more than one exacerbation through the winter. The average decline in forced expiratory volume during a 5-year period was less in the treated group than in the placebo group, although the difference was not statistically significant. Diarrhea was observed only in the treatment group. In reviewing multiple studies of antibiotic treatment in patients with chronic bronchitis, Tager and Speizer found no evidence that antibiotics prevented long-term deterioration in pulmonary function.[43]

My choice is to give antibiotics for 7 to 10 days to patients who have COPD and nonfebrile episodes of increased cough with production of purulent sputum but who have no symptoms or signs of pneumonia. Suggested regimens include tetracycline, 500 mg four times per day on an empty stomach; ampicillin, 500 mg (or amoxicillin 250 mg) four times per day; or co-trimoxazole, 160 mg trimethoprim and 800 mg sulfamethoxazole (Bactrim DS or Septra DS) two or three times each day.

In patients with bronchiectasis who have significant and increasing loss of pulmonary function that does not respond to trials of other antibiotic regimens, chloramphenicol (500 mg four times per day orally) has decreased the dyspnea, improved the patient's well-being, and decreased the amount of purulent secretions. It should be emphasized that this represents an unusual clinical situation, and that chloramphenicol is rarely indicated in patients who are not hospitalized.[40]

OFFICE MANAGEMENT TO REPLACE HOSPITAL MANAGEMENT

Office management may partially or completely replace the hospital management of lower respiratory infections. Several principles are important to consider. The patient must be well enough to be cared for at home, help at home must be reliable and adequate for the patient's needs, appropriate antimicrobial agents must be available by an acceptable route, and adequate follow-up mechanisms must be practical for the patient and the physician.

It was noted earlier that a reasonably healthy, mildly or moderately ill, middle-aged adult with typical pneumococcal pneumonia, with reliable relatives, without an underlying disorder (including splenectomy), and without evidence of endocarditis and meningitis probably can be treated at home. Similarly, a patient with uncomplicated pneumococcal pneumonia whose condition definitely has improved with treatment in the hospital may have treatment completed at home, with outpatient follow-up and a chest roentgenogram in 6 weeks. The patient should telephone the physician daily during the remainder of the first week of treatment.

The patient with anaerobic aspiration pneumonia, particularly with lung abscess, may require weeks of antimicrobial therapy. Initial hospitalization is required but, once the patient's condition has stabilized, office management with an oral antibiotic such as penicillin V may be possible. Patients with mixed anaerobic and aerobic aspiration pneumonia may have therapy completed as outpatients, if a suitable antibiotic regimen is available. Recently, a number of oral anaerobic isolates, particularly *Bacteroides melaninogenicus,* have been found to be resistant to penicillin G. In such cases, other agents, such as tetracycline, clindamycin, or chloramphenicol, may be administered.

Fungal respiratory infections usually must be managed entirely in the hospital, with months of intravenous amphotericin B therapy. Several centers experienced in the treatment of fungal infections have successfully used amphotericin B in an office practice setting, usually daily or three times weekly. The patient usually has been hospitalized for initial diagnosis and the institution of therapy. Amphotericin B therapy is then completed on an outpatient basis, permitting the patient to remain at home and possibly to continue working. The cost savings are significant. Details of management may be coordinated by a telephone conversation between the primary physician and a specialist with experience in the use of amphotericin B. The hemoglobin level, leukocyte count, platelet count, potassium and magnesium levels, and liver function tests are monitored weekly or more frequently, if necessary.

Many patients tolerate amphotericin B administered during a 1- to 2-hour period, while others do not. Tolerance may be determined during hospital treatment by gradually decreasing the length of administration of maintenance doses. This "rapid" administration, over 1 to 2 hours, may be accomplished conveniently in the office.

The role of ketoconazole, an oral antifungal agent with activity against many pathogenic fungi, remains to be determined. In some cases, the drug

has been effective, permitting office management of some deep-seated fungal infections that previously were treated in the hospital.

Perhaps the most remarkable advance in the office management of lower respiratory infections is in pulmonary tuberculosis. Several factors permit patients to be treated without hospitalization. First, powerful oral antituberculous treatment regimens, particularly those including isoniazid and rifampin, have been demonstrated to produce high cure rates when the patient faithfully takes the medication. Second, it has been demonstrated that there is no significant increase in the incidence of infection in contacts when patients remain at home or are dismissed from the hospital on specific therapy shortly after diagnosis. Third, newer therapeutic regimens allow for effective short-course (6 to 9 months), and intermittent (thrice weekly) therapy.

One recent study compared the efficacy of four thrice-weekly regimens given for 6 months with that of one daily regimen given for 6 months (Table 3).[21] There were no bacteriologic failures during treatment among the patients whose organisms were sensitive at the initiation of therapy. The thrice-weekly regimens containing pyrazinamide (PZA) were superior to the regimen without PZA (Table 3). Furthermore, the thrice-weekly regimens containing PZA appeared to be as effective as the daily regimen. The incidence of side effects was higher in the regimens containing PZA (25 to 35 per cent) than in the regimen without PZA (18 per cent). However, the incidence of hepatotoxicity was 5 per cent in the daily regimen

Table 3. *Total Relapses of Patients with Tuberculosis During 12-Month Follow-Up after Chemotherapy**

REGIMEN†	NUMBER OF PATIENTS ASSESSED	BACTERIOLOGIC RELAPSES	
		Number	*Per cent*
	Sensitive Organisms		
$HRSZE_3$	150	1	0.7
$HRSZ_3$	150	2	1.3
$HRSE_3$	160	12	7.5
$HRZE_3$	164	4	2.4
$HRZE_7$	161	1	0.7
	Resistant Organisms		
$HRSZE_3$	32	2	6.3
$HRSZ_3$	19	0	0.0
$HRSE_3$	27	7	25.9
$HRZE_3$	22	1	4.5
$HRZE_7$	31	0	0.0

*Data from Hong Kong Chest Service/British Medical Research Council: Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet, *1*:171–174, 1981.

†H = isoniazid, 15 mg per kg thrice weekly or 300 mg daily; R = rifampin, 600 mg thrice weekly or 450 to 600 mg daily; S = streptomycin, 1 gm thrice weekly; Z = pyrazinamide, 2 to 2.5 gm thrice weekly or 1.5 to 2 gm daily; E = ethambutol, 30 mg per kg thrice weekly or 25 mg per kg for 2 months, then 15 mg per kg daily; subscript 3 = thrice weekly; subscript 7 = daily.

and 0 to 1 per cent in the thrice-weekly regimens. Others have noted a lower incidence of hepatotoxicity in intermittent therapy.

While the total dose of isoniazid was larger in the intermittent group, the total doses of rifampin and PZA, both potentially hepatotoxic, were higher in the daily regimen. Age is an important variable in isoniazid hepatotoxicity. Of patients with hepatotoxicity, 32 per cent were older than 45 years, 33 per cent were 25 to 45 years old, and 35 per cent were less than 25 years old. Use of alcohol and underlying liver disease may be two other important factors in the production of hepatotoxicity.

Outpatient therapy is not more likely to result in increased risk to contacts than is hospital therapy, even though positive smears or cultures for *M. tuberculosis* may still be present.[7, 12, 28] While some patients may require hospitalization for diagnosis and institution of therapy, in many the entire illness has been handled on an outpatient basis. With the closing of tuberculosis sanatoriums, responsibility for the diagnosis and management of patients with tuberculosis has been transferred from specialists to physicians in general hospitals and in office practice.

Because brief general hospital admission and extended ambulatory management have replaced sanatorium care for tuberculosis, MacGregor reviewed experiences during a one-year period of management of patients with tuberculosis at a private urban hospital to assess problems created by the closing of sanatoria.[33] Almost one half of the patients with tuberculosis were misdiagnosed, exposing large numbers of unsuspecting hospital personnel to nonisolated patients with tubercle bacilli in sputa. Transfer to ambulatory care for half the patients was complicated by having different physicians manage their hospital and outpatient care. There was poor communication between hospital and outpatient physicians and poor identification and investigation of contacts. Efficient communication and cooperation by telephone and mail among the specialist, the primary care physician, and public health services are essential for optimal care. Special "custom" programs may be necessary for the difficult alcoholic patient.[1] Intermittent short-course therapy may be ideal for recalcitrant patients, with public health personnel actively involved in monitoring and/or administering the medication.

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