



## **PNEUMONIA IN THE IMMUNOCOMPROMISED AND IN THE MALNOURISHED CHILD**

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### **I. INTRODUCTION**

The purpose of this chapter is to give an overview of the role of malnutrition and immunosuppression in children with pneumonia in light of the elevated morbidity and mortality in these patients.

The pulmonary defenses in children depend on a set of mechanical and immunological barriers. Malnourished children are at greater risk of developing respiratory infections, but there is little data that explain the complex association between malnutrition and the development of pneumonia.

Malnutrition is one of the major problems in children in developing countries, where millions die from infections every year (1). The interactions between infections and malnutrition are well recognized and have been extensively reviewed (2-5). These relations concern the effects of malnutrition on host defenses in children and the possible adverse effects of infection on the nutritional status of the host. In addition, the interactions between infections and malnutrition are influenced by many other factors such as living conditions, poor education, poverty, and poor sanitation.

With the appearance of the epidemic of acquired immunodeficiency syndrome (AIDS), many children began to be admitted to hospitals and clinics with unusual clinical pictures due to their

immunodeficiencies. This chapter will refer mainly to children with AIDS who present with pneumonia caused by different microorganisms.

Other reference works (6, 7) extensively cover most of the topics under review in this chapter. <sup>1</sup>

## II. LUNG DEFENSE MECHANISMS<sup>2</sup>

The lungs contain the largest surface area of the body exposed to environmental agents. Total pulmonary surface area is estimated to be about 200 m<sup>2</sup> (8). Given the density of bacteria, viruses, and fungi in the air and in light of an average person's inspiration of 10,000 to 20,000 liters of air every day (9), it is easy to see why patients with impaired resistance are prone to serious infections.

Lung defenses against infection have been reviewed by Murphy and Florman (10) and Quie (11). Under normal conditions they include mechanical movement, an intact epithelium, ciliary activity, oligopeptides, lymphoid tissues, and the alveolar macrophages. The many deficiencies in these mechanisms in association with malnutrition have been reviewed by Rochester and Esaun (12) and by Martin (13).

## III. PNEUMONIA IN MALNOURISHED CHILDREN

Deaths in children under 5 years of age in developing countries occur more frequently and with greater severity among those who are malnourished (14-17). The study conducted by Tupasi et al. (16) shows that the risk of death from acute lower respiratory infections (ALRI) is from 4.4 to 27 times greater in children suffering first, second, and third degree malnutrition than it is in normal children. The study conducted by Escobar et al. (15) in Colombia and other studies (14-17) coincide in their results.

Certain defects are found in the host defenses of children suffering from protein-energy malnutrition. These include abnormalities of epithelial surfaces, complement, phagocytosis, immunoglobulins, T and B lymphocytes, and natural killer cells (18-21). Many studies that have reviewed the microbiologic causes of pneumonia in children from developing countries (22) have found that *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacterial causes of pneumonia in these children.

Only one study, done in Chile by Mimica et al. (23), compared well- and malnourished children using lung puncture and microbiologic cultures for etiological diagnosis. It was found that opportunistic organisms represented a higher proportion of isolates from severely malnourished children than in less severely malnourished children or in normal children. Berkowitz

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1 As a complement to this chapter, consult the respiratory disorders part of the manual of clinical management *Pautas para la Atención Clínica del Niño Infectado por el VIH*, which was prepared by the PAHO Regional Programme on AIDS and STD based on the document Guidelines for the Clinical Management of HIV Infection in Children, 1993, of the WHO Global Programme on AIDS (WHO/GPA/IDS/HCS/93.3).

2 See Chapter 11, *Viral and bacterial pneumonias*, by R. Ruvinsky and A. M. C. Balanzat for amplification of the pulmonary defense mechanisms.

(24) underscored the difficulties in interpreting these data, pointing out that although the organisms were identified as opportunistic (mainly *Achromobacter*, *Corynebacterium* sp., and *Streptococcus faecalis*), extrapolation of these data in relation to other localities and populations in general would be problematic. In addition there were methodological questions; only 45% of the children were positive, and 60% of them had received antimicrobial therapy before their samples were taken for diagnosis.

There is little information to confirm whether malnourished children respond in the same way as immunocompromised children when they present pneumonia. Nevertheless, it can reasonably be assumed that one of the important findings of protein-energy malnutrition is a deterioration in host defenses. Therefore, malnourished children may be more easily affected by unusual microorganisms. It is also likely that malnourished children present greater incidence of infections from enteric bacilli, due to greater oropharyngeal colonization (25).

Some other studies (26-30) have consistently shown that the major bacterial causes of pneumonia in children in developing countries (with many malnourished children included) are *S. pneumoniae*, *H. influenzae*, and *Staphylococcus aureus*. The same microorganisms are responsible for pneumonia in well-nourished children in industrialized countries.

Recent studies (31) have shown that premature infants have specific risk factors that lead them to develop wheezing and probably pneumonia in the first three years of life. These children are born with smaller-gauge airways than those in normal children. This anatomical alteration occurs with particular frequency in the newborns of young mothers with little education. There is also a strong relationship between smoking and compromised lung function in the first few years of life.

The data make clear that children with narrower airways have a greater probability of presenting wheezing in their early years and of developing bacterial pneumonia more easily after viral episodes due to the blockage of smaller-gauge airways. A reasonable hypothesis, as yet unproven, is that malnourished children, as in the case of premature babies (or those who are small for their gestational age), present greater risk of developing severe pneumonia, often associated with wheezing, due to the smaller congenital gauge of their airways.

#### IV. PNEUMONIA IN THE IMMUNOSUPPRESSED HOST

A healthy individual can handle the many pathogens that penetrate the respiratory system. The term *immunocompromised host* has been used to designate patients in whom organisms that would normally present little virulence become life-threatening pathogens. Severe pneumonia may develop in patients with certain hereditary conditions (such as hypogammaglobulinemia, agammaglobulinemias, chronic granulomatous disease, and AIDS), or even in patients receiving immunosuppressive pharmacological therapy for underlying diseases.

There is an increased incidence of infection with common bacterial pathogens in these patients, but they can usually be identified in sputum or blood and treated with broad-spectrum

antibiotics. Immunocompromised patients are particularly susceptible to opportunistic organisms, which are difficult to isolate and often fail to respond to conventional antibiotic therapy.

The diagnosis and treatment of pulmonary infections in the immunocompromised host is different than in the normal patient. The clinical and radiographic signs may not be specific to a particular pathology, but there are some indications for diagnosis. Table 1 suggests an approach for differential diagnosis.

The initial approach to a child with this type of clinical picture is to take specimens of sputum, blood, and nasal mucus for routine bacterial and viral examination. The treatment is generally empirical and should cover *S. aureus* and Gram-positive and Gram-negative bacteria. The selection of antibiotics will change depending on the pattern of susceptibility of the cultured organisms. In general, vancomycin, a third-generation cephalosporin, and an aminoglycoside are good first choices. When these are unavailable or their cost is prohibitive, chloramphenicol is an excellent option. When *Pneumocystis carinii* is the possible etiological agent, high doses of trimethoprim-sulfamethoxazole (TMP-SMX) are used. When this approach fails

**Table 1.** Differential diagnosis of pulmonary infiltrates in the immunocompromised patient

Chest radiological course	Acute stage	Subacute/chronic
Consolidation	<ul style="list-style-type: none"> <li>Bacteria (including Gram-negative bacilli, <i>Staphylococcus aureus</i>, anaerobes, and <i>Legionella pneumophila</i>)</li> <li>Hemorrhagic thromboembolism</li> <li>Pulmonary edema</li> </ul>	<ul style="list-style-type: none"> <li>Fungi</li> <li><i>Nocardia asteroides</i></li> <li>Mycobacteria</li> <li>Tumors</li> <li>Virus</li> <li><i>Pneumocystis carinii</i></li> <li>Radiation</li> <li>Drugs</li> </ul>
Peribronchial infiltrates	<ul style="list-style-type: none"> <li>Pulmonary edema</li> <li>Leukocyte agglutinin reactions (Bacterial infections by <i>Staphylococcus aureus</i>, <i>Haemophilus influenzae</i>, <i>Streptococcus pneumoniae</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Virus</li> <li><i>Pneumocystis carinii</i></li> <li>Radiation</li> <li>Drugs</li> <li>Fungi</li> <li><i>Nocardia asteroides</i></li> <li>Mycobacteria</li> <li>Tumors</li> </ul>
Nodular infiltrates	<ul style="list-style-type: none"> <li>Bacteria</li> <li>Pulmonary edema</li> </ul>	<ul style="list-style-type: none"> <li>Tumors</li> <li>Fungi</li> <li><i>Nocardia asteroides</i></li> <li>Mycobacteria</li> <li><i>Pneumocystis carinii</i></li> </ul>

Source: Adapted from Respiratory Diseases in Children. Phelan PD, Landau LI, Olinsky A. p. 271.

invasive procedures are indicated to identify the offending organism (such as transtracheal aspiration, bronchoscopic aspiration and brushing, thoracoscopy with lung biopsy). Bronchoalveolar lavage has been very useful for the diagnosis of *P. carinii* pneumonia and pulmonary lymphoid hyperplasia in children with AIDS. Although open lung biopsy is the most invasive diagnostic procedure, it has the highest success rate in identifying the offending pathogen in other diseases in the immunodeficient child.

The following is more detailed view of some of the most common pathologies that affect the immunodeficient child.

## V. *PNEUMOCYSTIS CARINII* PNEUMONIA

It is generally believed that the majority of individuals throughout most of the world are infected early in life with *P. carinii* and that these infections are asymptomatic. Residual organisms persist in a latent state, unless the host experiences impairment of the immune system, and then, especially when there is a serious compromise in cell-mediated immunity, pneumonitis from *P. carinii* may occur. Some data suggest that about 50% of children with AIDS acquire *P. carinii* pneumonitis (32-34). Other studies have shown that 53% of infants with perinatally acquired AIDS develop *P. carinii* pneumonitis during the first year of life (35).

### a) Physiopathology

It has been presumed that *P. carinii* is acquired through the airborne route. It has been demonstrated that animal-to-animal transmission occurs, but whether animal-to-human or human-to-human transmission takes place is not known. Once in the alveolus, the organism adheres to the epithelial cell surface. Replication occurs in the alveolus. It is generally believed that normal competent hosts undergo an asymptomatic infection with no signs or symptoms of illness and that the organism persists indefinitely. If the immune system becomes compromised, the organism replicates and pneumonitis ensues.

This microorganism is found in the alveoli within a thick-walled cyst about 5 to 6 mm in diameter containing up to eight intracystic daughter cells termed *sporozoites*. Extracystic forms are also found in abundance in the alveoli of patients with pneumonitis. These are termed *trophozoites* and measure 4 to 5 mm in diameter. In vitro culture studies, using the epithelial lung cells of embryonic chicks, suggest that the trophozoite attaches to the alveolar cell surface and increases in size as the intracystic daughter cells develop, progressing to the cystic stage (36). The cyst detaches from the host cell, never having reached an intracytoplasmic stage. Breaks occur in the cyst wall, and the sporozoites are expelled. After excystation the sporozoite becomes a trophozoite. In the infantile form of *P. carinii* pneumonitis, the interstitial septa are thickened because of lymphocyte and plasma cell infiltration. The alveolar epithelium is hyperplastic. The alveolar lumen contains desquamated epithelial cells, *P. carinii* organisms, a few neutrophils, many alveolar macrophages, and edema fluid. *P. carinii* organisms may be found in both the alveolar lumen and the interstitial space (37).

In children and adults with immunodeficiency disorders, the interstitial component and plas-

ma cell infiltration may be absent or present only to a limited extent. The pattern in these patients is an extensive diffuse alveolitis. The extensive alveolar infiltrates and foamy exudate of the lumen interfere with oxygenation, resulting in severe hypoxemia. Carbon dioxide retention does not become significant until the patient reaches near-terminal status.

### **b) Clinical findings**

*P. carinii* pneumonia is characterized by a tetrad of signs: tachypnea, dyspnea, fever, and cough. These clinical manifestations occur with *P. carinii* pneumonitis in infants, children, and adults with AIDS and non-AIDS immunocompromising diseases. The magnitude of each of these signs changes from patient to patient. The patients may not be febrile, but all of them will present with tachypnea once pneumonitis is evident by radiograph.

The clinical findings of *P. carinii* pneumonitis have been classified into two clinical types. The infantile endemic interstitial plasma cell pneumonitis is seen in outbreaks in European nurseries; the adult-type occurs in immunocompromised hosts with cancer, organ transplants, congenital or acquired immunodeficiency disorders, and in those using immunosuppressive therapy. The infantile form is seen in debilitated infants 2 to 6 months of age. The onset of this type is subtle, with progression of tachypnea, cough, and intercostal retractions over a 1-week to 1-month interval. Rales are heard bilaterally and fever is usually absent. In the child-adult type of *P. carinii* pneumonitis, the onset is abrupt with fever, tachypnea, nasal flaring, and intercostal retractions. No rales are heard on auscultation. In some patients, especially those with AIDS, the clinical manifestations may vary between the child-adult type and the infantile types.

### **c) Diagnosis**

The chest radiograph reveals bilateral diffuse alveolar infiltrate without hilar adenopathy. The earliest abnormality is increased haziness in the hilar regions with clear peripheral zones. A variety of atypical lesions caused by *P. carinii* have been described, but are uncommon. These include lobar, miliary, nummular, cavitary, and nodular lesions. Pleural effusion may be seen but is usually small. With treatment, the radiographs may show gradual clearing of the infiltrates, but this often does not commence for 2 to 3 weeks and during this time the disease may progress.

During the early days of treatment clinical response is best judged by blood gas studies (PaO<sub>2</sub>, alveolar-arterial gradients, PaCO<sub>2</sub>, and pH). The chest radiograph is less precise in revealing improvement or worsening in the pneumonitis.

Identification of the organism is essential for diagnosis, but isolation is difficult. It is rarely possible to identify it in the sputum. It can be collected from secretions or tissue of the lower respiratory tract. Lung specimens obtained by open lung or transbronchial biopsy provide the most sensitive and specific findings. However, specimens obtained by bronchoscopy and bronchoalveolar lavage (BAL) or by procedures to induce sputum are often diagnostic for *P. carinii* pneumonitis. Failure to establish a diagnosis by these relatively simple and safe procedures may lead to use of open-lung biopsy. Specimens should be stained with Gomori-Grocott methenamine-silver nitrate, Giemsa stain, or toluidine O stain.

#### d) Treatment

Once *P. carinii* has been established by chest radiography and clinical signs, the outcome is fatal in approximately 100% of cases, if untreated. Trimethoprim-sulfamethoxazole (TMP-SMX or cotrimoxazole) is the drug of choice for the treatment of *P. carinii* pneumonitis. The dosage is 15-20 mg/kg/day of trimethoprim and 75-100 mg/kg/day of sulfamethoxazole intravenously divided into three or four doses. In all but the mildest cases the initial doses of the drugs should be given intravenously. Once the pneumonitis is resolving, TMP-SMX may be administered orally (20-100 mg/kg/day) in three or four doses for two to three weeks. At the completion of therapy the drugs are reduced to prophylactic doses, which are continued indefinitely.

Bernstein et al. (38) report that of 18 children with AIDS and *P. carinii* pneumonitis, 60% (11) required intubation; 7 died during the initial hospitalization, and of the 11 surviving the episode of pneumonitis, 5 were dead within a year of recovery, the other 6 (55%) recovered from the first episode of *P. carinii* pneumonitis within 15 months of the initial illness. This remarkably high rate of recurrence emphasizes the need for chemoprophylaxis.

Patients who have adverse reactions to TMP-SMX or who do not respond to this drug should be given pentamidine isethionate intravenously in a single daily dose of 4.0 mg/kg. The duration of the treatment is the same as for TMP-SMX. For unknown reasons, the adverse reaction rates to TMP-SMX and pentamidine are higher in patients with AIDS. For patients that cannot tolerate either drug, experimental drugs are available through investigation centers.

*P. carinii* pneumonitis can be prevented in high-risk patients by regular administration of TMP-SMX in the dosage of 5.0 mg of trimethoprim and 25 mg/kg/day of sulfamethoxazole orally in two divided doses. The prophylaxis is effective when given daily or only three consecutive days per week. Pentamidine aerosol has been used successfully in adults, but no studies have been reported in children.

## VI. TUBERCULOSIS AND HIV INFECTION

Tuberculosis is the main infectious cause of death worldwide (39-42). Between 20 and 33% of the world population is infected and approximately 3 million people die annually from the disease. The increase in tuberculosis in many areas of the world is superimposed on the emergency of the AIDS epidemic. This spread occurs in Africa, regions of Asia, Central and South America, and the United States. It is estimated that 100,000 individuals are currently co-infected with HIV and the tubercle bacillus.

#### a) Pathogenesis

Immunity plays a central role in controlling the course of tuberculosis in immunocompetent individuals. Several *Mycobacterium tuberculosis* antigens have been detected and cloned. There are still questions about which antigens and immune responses are essential for protecting the host. Nevertheless, immunodeficiency resulting from HIV clearly increases susceptibility to tuberculosis.

The development of tuberculosis in patients with HIV may follow three separate patterns:

1. reactivation of a latent infection acquired months or years before either prior to or after HIV infection took place;
2. immediate progression of the disease due to *M. tuberculosis* acquired after HIV infection;
3. superinfection with a new strain of the bacillus in patients with prior infection or disease caused by *M. tuberculosis*.

### **b) Clinical findings**

The most notable clinical findings in patients with HIV infection are among a vast spectrum of clinical manifestations and the considerable frequency of extrapulmonary effects. There is such a variety of atypical manifestations that *M. tuberculosis* should be part of the differential diagnosis of almost any febrile process and an essential consideration when the lung condition of these patients is evaluated.

### **c) Diagnosis**

Patients may be asymptomatic with normal chest X-rays even when their sputum and bronchoscopy samples reveal the presence of *M. tuberculosis*. Computerized axial tomography (CAT scan) and magnetic resonance imaging (MRI) may demonstrate lesions that are not always visible through routine chest X-rays. There is no clear distinction between the clinical and radiological manifestations in relation to the typical presentations of other common processes of *P. carinii* pneumonia (43, 44). Radiological manifestations may appear as atypical primary tuberculosis or typical reactivation or there may be no manifestations at all.

The most distinctive findings of tuberculosis are cavitations, hilar adenopathy, or pleural effusions. *P. carinii* pneumonia, lymphoma, and Kaposi's sarcoma may also present with these manifestations, as may cryptococcosis, coccidioidomycosis, or histoplasmosis.

The sputum stains remain the best initial tests for investigating tuberculosis. Fluorescence microscopy increases the sensitivity of the sputum stains by 15 to 20% as compared to conventional stains; specificity is close to 100%. If no sputum is available or there remains doubt about the diagnosis, other options are still at hand: gastric aspirates, bronchoalveolar washings, but in children biopsies are generally not recommended.

*M. tuberculosis* may also grow in blood cultures. Between three and six weeks are normally needed to detect any growth. Two new techniques may hasten the process. One is based on detection of radioactively labeled CO<sub>2</sub> by using precursor marked with special media (BACTEC®). The other technique is a system of lysis by centrifugation that disintegrates the erythrocytes in the blood sample, allowing the cultivation of the sediment they leave in the liquid media. The detection of various antigens or of tuberculostearic acid is done in many laboratories. Polymerase chain reactions are also studied.

Reactions above 5 mm to the purified protein derivative test (PPD) are considered as evidence of tuberculosis infection in the HIV-positive population, and the U.S. Centers for Disease

Control (CDC) and the American Lung Association recommend that these patients receive isoniazid prophylaxis regardless of whether they have received the BCG vaccine. Many studies have shown that HIV-positive patients have possibly had depressed reactions to tuberculosis tests prior to the development of HIV-related symptoms. Anergy tests (such as for mumps, tetanus toxoid, or candidiasis) should be performed in the patients with higher risk of tuberculosis exposure but whose tuberculin tests are negative.

#### **d) Treatment**

The same drugs used to treat HIV-positive adults who have tuberculosis appear to be the most appropriate ones for children. Every person infected by HIV and exposed to tuberculosis should be considered a candidate for receiving prophylaxis with isoniazid. Housemates and hospital roommates of tuberculosis patients as well as other persons with prolonged exposure to infected persons in enclosed areas are at greater risk of infection than persons briefly exposed to these patients.

The most common drug therapy for normally immunocompetent individuals consists of isoniazid, rifampicin, and pyrazinamide over a two-month period. In HIV-positive patients, the isoniazid and rifampicin should be administered for seven months (for a total of nine months) and at least six months after the negative conversion of the cultures (42, 43). When resistance to these drugs is suspected, an additional two drugs, to which the microorganisms are susceptible, should also be indicated. Extrapulmonary tuberculosis should be treated with the same chemotherapy and for the same time as the pulmonary tuberculosis.

Figure 1 should be used for decision-making in relation to treatment. Table 2 shows the recommended drug dosage for treating tuberculosis in HIV-positive patients under 12 years of age.

## **VII. LYMPHOID INTERSTITIAL PNEUMONITIS (LIP)**

A severe parenchymal disease, referred to as LIP, has been associated with human immunodeficiency virus (HIV) infection in infants and children. It is the most frequent form of diffuse pneumonitis in pediatric patients with AIDS (45).

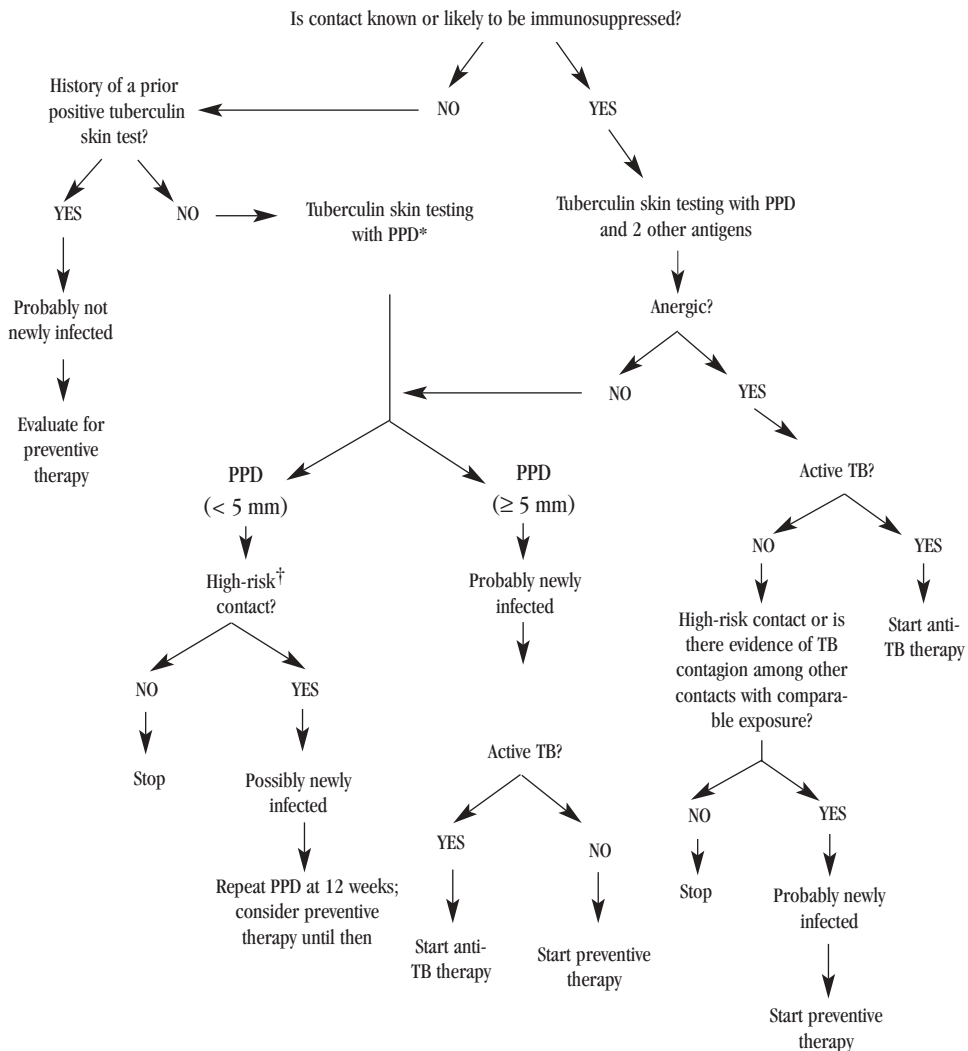
#### **a) Physiopathology**

The cause of LIP is not known, and there is no conclusion that it is an infectious process. There is evidence that links LIP to HIV and Epstein-Barr virus (EBV), or other opportunistic organisms. In a study by Rubinstein (46), four of five children with AIDS and LIP were found to have EBV-specific DNA in lung specimens, as compared to a group of children with AIDS and *P. carinii* pneumonitis, in which no EBV-specific DNA was found. The usual histopathologic appearance is of nodules formed by clusters of mononuclear cells, including lymphocytes and plasma cells. These lesions are located around the bronchial epithelium and in the adjacent intra-alveolar septa. In addition, a diffuse lymphocytic interstitial infiltrate is present.

**b) Clinical findings**

The onset is often subtle with a slow progressive course and mild hypoxemia. The patients are usually afebrile and have generalized lymphadenopathy and enlargement of the salivary glands. Digital clubbing may be evident. Tachypnea, cough, and chest retractions may or may not be present. Table 3 compares the clinical findings of *P. carinii* pneumonitis and LIP.

**Figure 1.** Estimating the likelihood of new infection with *M. tuberculosis* and preventive therapy decision-making for contacts of infectious TB cases



Source: CDC: MMWR 41 (RR-11): 63, 1992

\* PPD = purified protein derivative

† Members of the immediate family, close social contacts, or others who shared the same indoor environment with an infectious TB patient for substantial periods

<b>Table 2.</b> Drug therapy and dosages for children with tuberculosis infected by HIV			
<b>Frequency of administration</b>	<b>Daily</b>	<b>2 times/week</b>	<b>3 times/week</b>
<b>Medications</b>	<b>Dose per kg of weight and maximal quantity per dose</b>		
• Isoniazid	10 to 20 mg Max. 300 mg	20 to 40 mg Max. 99 mg	20 to 40 mg Max. 900 mg
• Rifampicin	10 to 20 mg Max. 600 mg	10 to 20 mg Max. 600 mg	10 to 20 mg Max. 600 mg
• Pyrazinamide	15 to 30 mg Max. 2 g	50 to 70 mg Max. 4 g	50 to 70 mg Max. 3 g
• Ethambutol*	15 to 25 mg Max. 2.5 g	50 mg Max. 2.5 g	25 to 30 mg Max. 2.5 g
• Streptomycin	20 to 30 mg Max. 1 g	25 to 30 mg Max. 1.5 g	25 to 30 mg Max. 1 g

Source: Adapted from CDC: Morb Mortal Wkly Rep 42(RR-7):1, 1993.

\* Ethambutol generally is not recommended for children whose visual acuity cannot be monitored (younger than 6 years). Nevertheless, it should be considered for all children with microorganisms resistant to other drugs when sensitivity to ethambutol has been proven or is possible.

### c) Diagnosis

The chest radiograph shows bilateral, diffuse, fine nodular infiltrates, and hilar nodes may be enlarged. A definitive diagnosis requires histologic examination of a biopsy specimen.

### d) Treatment

There is no specific therapy for LIP. The treatment of AIDS patients with azidothymidine has been associated with improvement of LIP. Some non-controlled studies suggest that corticotherapy may lead to resolution of LIP (47).

## VIII. TOXOPLASMOSIS

Immunocompromised hosts are susceptible to severe, life-threatening infections caused by the protozoan *Toxoplasma gondii*. In most of these infections the disease appears as a necrotizing encephalopathy (48).

### a) Physiopathology

The appearance of clinical disease appears to be a recrudescence of a latent infection. The primary infection follows the ingestion of cysts from improperly cooked meats. Once the organisms are released they invade the intestinal epithelium and are spread in the arterial or lymph system to many organs, where cysts are formed (49).

**b) Clinical findings**

The symptoms are not specific. Cough, fever, and shortness of breath may be noticed as symptoms of pulmonary toxoplasmosis. Generalized lymphadenopathy, skin rash, and neurological signs of encephalitis may coexist with pulmonary lesions.

**c) Diagnosis**

The chest radiograph may show diffuse bilateral infiltrates, but lesions may be limited to one lobe (50). The demonstration of specific immunoglobulin M (IgM) antibodies is useful for diagnosis of acute infection. A single high titer or a serial two-tube rise in IgM antibody titer is diagnostic of acute infection. The absence of IgM antibody does not rule out active infection. The microorganism, taken from tissues or secretions (by bronchoalveolar lavage or open-lung biopsy), can be stained with hematoxylin/eosin augmented by Giemsa stain.

**d) Treatment**

Once *T. gondii* is found in an immunocompromised patient, it must be searched out in other organs, especially the brain. The drug combination of pyrimethamine and a sulfonamide is the treatment of choice. The combination of clindamycin and pyrimethamine has shown some promise, but needs further study. Unfortunately, the outcome is usually fatal.

**IX. VIRAL PNEUMONIA**

Many viruses that cause little harm to a normal host can lead to devastating pneumonia in the immunocompromised patient. The most common ones are: measles, cytomegalovirus, rubella, herpes simplex, and respiratory syncytial viruses.

**a) Giant cell pneumonia**

This pneumonia occurs mainly in patients with immunodeficiencies or in children using cytotoxic drugs because of neoplastic disorders. Debilitating conditions such as cystic fibrosis may occasionally be a predisposing factor for giant cell pneumonia.

Although it is considered to be a complication following an initial measles virus infection, not all patients develop a classic measles clinical picture. There may be no rash and if present, it is usually atypical. Some other causes have been suggested, such as parainfluenza viral infection (51).

**a.1) Pathophysiology**

The characteristic changes in the lung include very little air-containing lung tissue. Microscopically, the alveolar spaces are filled with inflammatory exudate and the alveolar walls are thickened and infiltrated with inflammatory cells. The most typical feature is giant cell transformation of the alveolar lining cells. The giant cells contain both intranuclear and intracytoplasmic inclusions, composed of viral filaments. A common but less constant feature is squamous metaplasia of the bronchial and bronchial epithelium.

**Table 3.** Comparison of clinical findings between lymphoid interstitial pneumonitis (LIP) and that caused by *P. carinii* (in %)

Clinical findings	<i>P. carinii</i> (N = 8)	LIP (N = 11)
Cough	38	100
Tachypnea	100	9
Fever	100	9
Digital clubbing	0	100
Salivary gland enlargement	0	100
Generalized lymphadenopathy	0	100
Nodular pattern on radiograph	0	100

Source: Modified from Rubinstein et al. (46).

### a.2) Clinical findings

The disease begins with cough, high fever, and tachycardia, three to four weeks after exposure to measles. An atypical rash may appear a week before the respiratory symptoms develop. Most patients have a high fever that can last two to ten weeks and is unaffected by any therapy. Tachypnea develops very early and becomes very marked prior to death. Fine crackles can initially be heard over the lung bases, and as the disease progresses through the thorax the crackles disseminate. The progression of the disease leads to cyanosis even with oxygenation.

### a.3) Diagnosis

Chest radiographs show widespread coarse nodular pulmonary infiltrates quite different from the uniform opacity seen in pneumocystis pneumonia. In the early stages the radiological changes are more pronounced than the findings from clinical examination.

Culture of measles virus, especially if accompanied by poor antibody response, confirms the diagnosis. In most patients the diagnosis is made at autopsy and confirmation must rely on histology, immunofluorescence, and virus culture from the lung.

### a.4) Treatment

Most patients with giant cell pneumonia die, although many patients diagnosed with post-measles pneumonia survive. Susceptible patients should be given a high dose of measles-immune globulin soon after exposure. Convalescent serum and cellular infusions may also be useful. The role of steroids and antiviral agents is still uncertain.

## b) Cytomegalovirus (CMV) pneumonia

CMV pneumonia can occur in almost any disease or therapy causing immunosuppression, but it occurs more commonly in patients receiving allogeneic bone marrow transplants for

leukemia or other malignancies; the incidence rate is 15%. Once CMV is clinically evident, lethality is 85%.

### **b.1) Physiopathology**

CMV pneumonia occurs as part of a systemic infection from the virus. Studies on the molecular epidemiologic characteristics of CMV infection suggest that at least some of the infections that occur after bone marrow transplantation may be caused by strains that had previously been present (52). The virus can also be transmitted through transfusion of blood products to seronegative transplant recipients. CMV often causes enlargement of infected cells with intranuclear inclusions similar to those of other herpesvirus infections.

### **b.2) Clinical findings**

Systemic CMV infection often presents with an infection syndrome similar to mononucleosis with fever, subclinical hepatitis, splenomegaly, and lymphocytosis, with atypical lymphocytes. Tachypnea and signs of respiratory distress emerge as pneumonitis occurs. In some cases, the clinical findings of pneumonitis can be the sole evidence of CMV infection.

### **b.3) Diagnosis**

Chest radiographs show bilateral diffuse interstitial infiltrates without specific signs differentiating CMV pneumonitis from other types of pneumonia in the immunocompromised host. The positive finding of CMV antibody serology establishes the diagnosis of CMV infection, but does not prove that a concomitant pneumonitis is caused by CMV. The diagnosis is difficult because subclinical CMV infection is present in most immunocompromised patients. The definitive diagnosis is usually made from a biopsy of the lung parenchyma.

### **b.4) Treatment**

No drug has shown great efficacy against CMV infection. However, ganciclovir, an acyclovir analog, presents activity against CMV (53). The drug has been effective in preventing CMV pneumonitis in bone marrow transplant recipients under controlled conditions. When transfusions of blood or blood products are needed for transplant recipients, CMV antibody-negative blood or freezing and thawing of deglycerolized red blood cells may aid in the prevention of transmission.

## **c) Varicella-zoster virus pneumonitis**

The dissemination of varicella-zoster and consequent pneumonitis is the most feared complication of this infection in immunosuppressed patients. For example, of children with cancer

who acquire varicella, approximately one-third will progress to disseminated systemic varicella, with an overall mortality rate of 7%. Feldman et al. (54) found that all deaths in their study were related to varicella pneumonitis.

### **c.1) Physiopathology**

Lung pathology ranges from focal necrosis to diffuse consolidation. Pneumonitis is accompanied by cellular infiltrates, fibrin and hyaline membranes in alveolar spaces, as well as focal areas of interstitial necrosis. Intranuclear inclusions are present in alveolar lining cells. Pulmonary lesions resemble the pox-like lesions seen on the skin. There is usually extensive involvement of the trachea and larger bronchi.

### **c.2) Clinical findings**

Usually the pneumonitis occurs while the varicella or zoster rash is erupting. Rarely, if ever, does the pneumonitis occur before or in the absence of the cutaneous rash. Cough and tachypnea are early signs, but respiratory distress becomes more pronounced as the disease progresses. Varicella in the immunosuppressed host is often complicated with secondary bacterial infection, the most common pathogen being *Staphylococcus aureus*.

### **c.3) Diagnosis**

Chest radiographs may range from the bilateral nodular infiltrates with apical sparing to widespread consolidation. These findings plus the typical skin lesions of varicella are enough to establish the diagnosis.

### **c.4) Treatment**

Acyclovir is the drug of choice for treatment of varicella and zoster. The treatment should be started as soon as possible in immunosuppressed patients. It is uncommon for patients to develop pneumonitis when treatment is started before the lungs are affected. The dosage for acyclovir administration is 30 mg/kg/day, every 8 hours for seven days or for two days after the last appearance of new skin lesions, whichever is longer. Immunosuppressed patients who are susceptible to varicella-zoster infection should be given specific immunoglobulin within three days of exposure. Live, attenuated varicella-zoster virus vaccine (54) was approved by the U.S. Food and Drug Administration in March 1995 and has been marketed since May 1995 by Merck, Sharpe & Dohme under the brand name Varivax.<sup>3</sup>

## **d) Respiratory syncytial virus (RSV)**

Immunocompromised children have more severe RSV disease, with pneumonia occurring at all ages and a high mortality rate. These children have more severe lung disease and more prolonged virus excretion. Patients with T lymphocyte deficiencies seem to be especially susceptible.

3 Morbid Mortal Wkly Rep, April 7/95, 44:13-264.

**d.1) Physiopathology**

In reports of severe RSV infections authors have described extensive pulmonary involvement or giant cell pneumonia with prolonged virus shedding for as long as 100 days. Underlying diseases include AIDS resulting from HIV-1, severe combined immunodeficiency syndromes, malignancy, and host-versus-graft reaction.

**d.2) Clinical findings**

There is no definitive clinical picture for RSV disease. Fever, dyspnea, wheezing, cough, and tachypnea may occur during its course.

**d.3) Diagnosis**

The virus can be isolated from nasal washings. An early diagnosis may be made using immunofluorescence to identify the viral antigen. ELISA and RIA (radioimmunoassay) methods are also useful.

**d.4) Treatment**

Ribavirin is the only available drug to be used in RSV infection in these patients. It is used in aerosol form in the same manner as for RSV bronchiolitis (55). Immunocompromised children should be protected from possible nosocomial infection when hospitalized; infected patients should be placed in isolation during the infectious period.

**X. FUNGAL PNEUMONIAS****a) Pulmonary candidiasis**

This is the most common fungal infection in immunocompromised patients. *Candida albicans* is found in the mouth and gastrointestinal tract and may become invasive with impairment of host defenses.

**a.1) Physiopathology**

Pulmonary infection may result from hematogenous or direct invasion of the bronchopulmonary tree. The patients are often neutropenic or receiving broad-spectrum antibiotics. Bacterial and viral infections are often concomitant. Histologically, pseudohyphae forms of *Candida* species invade alveoli and capillaries and may progress by direct invasion.

**a.2) Clinical findings**

Fever may be the only sign to present in an immunocompromised host with or with-

out respiratory symptoms. Cough and tachypnea may occur in patients with extensive pneumonitis.

### **a.3) Diagnosis**

Clinical and radiological changes may be minimal, they are nonspecific, and the nature of the disease is usually not recognized until autopsy. Chest radiographs in patients with widespread pneumonia show generalized patchy soft infiltrates. The culture of *C. albicans* from blood is very suggestive of generalized candidiasis, but culture from the throat swab or sputum does not establish a diagnosis of pulmonary disease, and a negative blood culture does not exclude the diagnosis. Lung biopsy or needle aspiration of alveolar fluid are better diagnostic methods. Serologic tests for antigen and antibody are not sufficiently sensitive and specific for solid diagnosis confirmation.

### **a.4) Treatment**

A combination of amphotericin B and flucytosine is the best choice for effective treatment of pulmonary candidiasis. Amphotericin on its own is the essential component of therapy. Daily intravenous doses of 0.5 mg/kg of amphotericin B and 150 mg/kg/day daily oral doses of flucytosine are usual. Ketoconazole is a less effective alternative. Fluconazole is a new drug that has been successful in some patients with systemic candidiasis (56) but has not been evaluated in pulmonary disease.

## **b) Pulmonary aspergillosis**

*Aspergillus* species such as *Aspergillus fumigatus*, *A. flavus*, and *A. niger* are common pathogens in the hospital environment and other sites and cause pulmonary mycotic infection.

### **b.1) Physiopathology**

*Aspergillus* spores are inhaled and cause pulmonary infection in immunocompromised patients. Infections can be associated with direct invasion from the respiratory airway or from hematogenous dissemination to alveolar capillaries. The septate hyphae invade the alveolus and initiate a necrotizing or hemorrhagic pneumonic infiltrate.

### **b.2) Clinical findings**

Fever may be the only sign presented. Cough, tachypnea, chest pain, and hemoptysis may also occur but with no characteristic pattern. Severe neutropenia is often a predisposing factor.

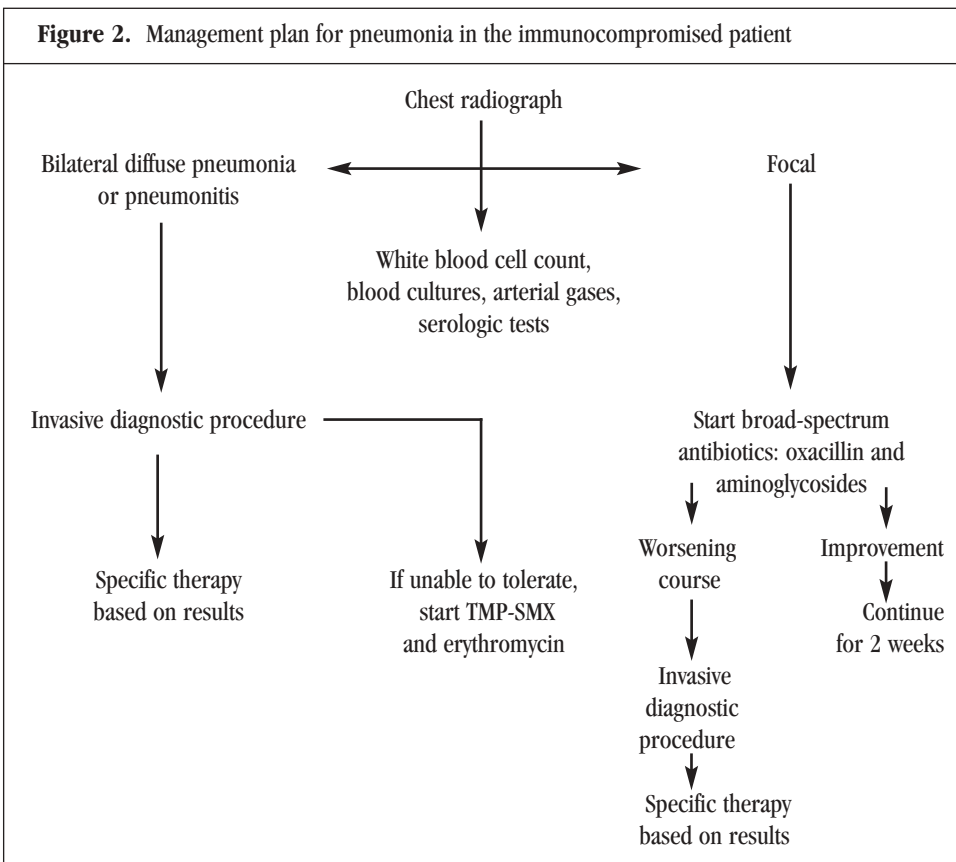
### **b.3) Diagnosis**

Chest radiographs may reveal a fairly typical aspergilloma, which represents an area of consolidation with a central clearing. More common, however, is the typical nonspecific nodular or lobar lesion. The open-lung biopsy is the most sensitive method for diagnosis. Isolation of *Aspergillus* species from the tracheobronchial airway or the

nares provides strong evidence for diagnosis if the clinical picture is suggestive of aspergillosis.

#### b.4) Treatment

Amphotericin B is the drug of choice. Starting intravenous dose at 0.25 mg/kg/day, increasing to a maintenance dose of 1.0 mg/kg/day for four to six weeks.



Source: Modified from Hughes WT. Pneumonia in the immunosuppressive host. In: Hilman V. Pediatric respiratory disease: Diagnosis and treatment. 1992;303.

## XI. REFERENCES

1. Haaya J, Kendrick C, Test K, Mason J. *An estimate of the prevalence of child malnutrition in developing countries*. World Health Stat Q 1985;38:331-347.
2. Scrimshaw NS, Taylor CE, Gordon JE. *Interactions of nutrition and infection*. World Health Organization Monograph Series no. 57. Geneva: World Health Organization, 1968.
3. Gordon JE, Scrimshaw NS. *Infectious disease in the malnourished*. Med Clin North Am 1970;54:1495-1508.
4. Scrimshaw NS. *Interactions of malnutrition and infection: Advances in understanding*. In: Olson RE, ed. Protein-calorie malnutrition. The Nutrition Foundation. Monograph series. New York, NY: Academic; 1975:353-357.
5. Mata LJ. *Malnutrition-infection interactions in the tropics*. Am J Trop Med Hyg 1975;24:564-574.
6. Blinkhorn Jr. RJ. *Pulmonary infections in the acquired immunodeficiency syndrome*. In: Braun GL, Wolinski E, eds. Textbook of pulmonary disease. 5th ed. Boston, MA: Little, Brown; 1994.
7. Stansell J, Murray. *Pulmonary complications of human immunodeficiency virus infection*. In: Murray JE, Nadel JA, eds. Textbook of respiratory medicine. 2nd ed. Philadelphia, PA: Saunders; 1994.
8. Huer GL, First MW. *Perspectives: Pulmonary host defense. The host and the development of lung disease*. Semin Respir Med 1980;1:87.
9. Hinds WC. *The drug and the environment*. Semin Respir Med 1980;1:197.
10. Murphy S, Florman AL. *Lung defenses against infection: A clinical correlation*. Pediatrics 1983;72:1-15.
11. Quie PG. *Lung defense against infection*. J Pediatr 1986;108:813-816.
12. Rochester DF, Esau SA. *Malnutrition and the respiratory system*. Chest 1984;85:411-415.
13. Martin TR. *The relationship between malnutrition and lung infections*. Clin Chest Med 1987;8:359-372.
14. James JW. *Longitudinal study of the morbidity of diarrheal and respiratory infections in malnourished children*. Am J Clin Nutr 1972;25:690-694.
15. Escobar JA, Dover AS, Dueñas A, et al. *Etiology of respiratory tract infections in children in Cali, Colombia*. Pediatrics 1976;57:123-130.
16. Tupasi TE, Velmonte MA, Sanvictors MEG, et al. *Determinants of morbidity and mortality due to acute respiratory infections: Implications for intervention*. J Infect Dis 1988;157:615-623.
17. Spooner V, Barker J, Tullock S, et al. *Clinical signs and risk factors associated with pneumonia in children admitted to Goroka Hospital, Papua New Guinea*. J Trop Pediatr 1989;35:295-300.
18. Suskind RM, ed. *Malnutrition and the immune response*. Kroc Foundation Series. Vol. 7. New York, NY: Raven Press; 1977.
19. Chandra RK. *Nutrition, immunity and infection: Present knowledge and future directions*. Lancet 1983;i:688-691.

20. Chandra RK. *Nutritional regulation of immunity and infection: From epidemiology to phenomenology to clinical practice*. J Pediatr Gastroenterol Nutr 1986;5:844-852.
21. Salimanu LS, Ojo-amaize E, Williams A, et al. *Depressed natural killer cell activity in children with protein-calorie malnutrition*. Clin Immunol Immunopathol 1982;24:1-7.
22. Berman S. *Epidemiology of acute respiratory infections in children of developing countries*. Rev Infect Dis 1991;13(Suppl 6):S454-S462.
23. Mimica I, Donoso E, Howard JE, Lederman GW. *Lung puncture in the etiological diagnosis of pneumonia: A study of 543 infants and children*. Am J Dis Child 1971;122:278-282.
24. Berkowitz FE. *Infections in children with severe protein-energy malnutrition*. Pediatr Infect Dis J 1992;11:750-759.
25. Gilman RH, Brown KH, Gilman JB, et al. *Colonization of the oropharynx with Gram negative bacilli in children with severe protein-calorie malnutrition*. Am J Clin Nutr 1982;36:284-289.
26. Morehead CD, Morehead M, Allen DM, Olson RE. *Bacterial infections in malnourished children*. J Trop Pediatr 1974;20:141-147.
27. Diallo AA, Silverman M, Egler LJ. *Bacteriology of lung puncture aspirates in malnourished children in Zaire*. Nigerian Med J 1979;9:421-423.
28. Silverman M, Stratton D, Diallo AA, Egler LJ. *Diagnosis of acute bacterial pneumonia in Nigerian children: Value of needle aspiration of the lung and countercurrent immunoelectrophoresis*. Arch Dis Child 1977;52:925-931.
29. Shann F, Gratten M, Germer S, Linneman V, Hazlett D, Payne R. *Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea*. Lancet 1984;ii:537-541.
30. Berkowitz FE. *Infections in children with severe protein-energy malnutrition*. Ann Trop Paediatr 1983;3:79-83.
31. Martínez F, Morgan W, et al. *Diminished lung function as a predisposing factor for wheezing respiratory illness in infants*. New Engl J Med 1988;319:1112-1117.
32. Rodgers ME, Thomas PA, Starcher ET, Noa MC, Bush TJ, Jafee HW. *Acquired immunodeficiency syndrome in children: Report of the Centers for Diseases Control National Surveillance, 1982-1985*. Pediatrics 1987;79:1008-1014.
33. Vernon DD, Holzman BH, Lewis P, Scott GB, Birriel JA, Scott MB. *Respiratory failure in children with acquired immunodeficiency syndrome and acquired immunodeficiency syndrome-related complex*. Pediatrics 1988;82:223-228.
34. Bye MR, Bernstein L, Shah K, Ellawie M, Rubinstein A. *Diagnostic bronchoalveolar lavage in children with AIDS*. Pediatr Pulmonol 1987;3:425-428.
35. Oxtoby MJ. *Perinatally acquired human immunodeficiency virus infection*. Pediatr Infect Dis J 1990;9:609-619.
36. Piffer LL, Hughes WT, Murphy MJ. *Propagation of P. carinii in vitro*. Pediatr Res 1977;11:305-313.

37. Sheldon WH. *Pulmonary P. carinii infection*. J Pediatr 1962;61:780-789.
38. Bernstein LJ, Bye MR, Rubinstein A. *Prognostic factors and life expectancy in children with acquired immunodeficiency syndrome and Pneumocystis carinii*. Am J Dis Child 143:775-778.
39. Bloom BR, Murray JL. *Tuberculosis: Commentary on a reemergent killer*. Nature 1992;257:1055.
40. Ellner JH, Hinman AR, Dooley SW, et al. *Tuberculosis symposium: Emerging problems and promises*. J Infect Dis 1993;168:537.
41. World Health Organization. *Tuberculosis Control Program: Program evaluation report*. EB 8714, Nov 1990.
42. Centers for Disease Control. *Tuberculosis morbidity: United States*. Morbid Mortal Wkly Rep 1992;42:699.
43. Barnes PF, Bloch AB, Davidson PT, et al. *Tuberculosis in patients with human immunodeficiency virus*. N Engl J Med 1991;324:1644.
44. Edlin BR, Tokars JI, Grieco MH, et al. *An outbreak of multi-drug resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome*. N Engl J Med 1992;326:1514.
45. Pitt J. *Lymphocytic interstitial pneumonia*. Pediatr Clin North Am 1991;38:89-95.
46. Rubinstein A, Moeckis R, Silverman B, Charytan M, Krieger BZ, Andiman W, et al. *Pulmonary disease in children with acquired immunodeficiency syndrome and AIDS-related complex*. J Pediatr 1986;108:498-503.
47. Solal-Celigny P, Couderc L, Herman D, et al. *Lymphoid interstitial pneumonitis in acquired immunodeficiency syndrome-related complex*. Am Rev Respir Dis 1985;131:956-960.
48. Luft B, Remington J. *Toxoplasmic encephalitis in AIDS*. Clin Infect Dis 1992;15:211-222.
49. Schnapp L, Geaghan S, Campagna A, et al. *Toxoplasma gondii pneumonitis in patients infected with the human immunodeficiency virus*. Arch Intern Med 1992;152:1073-1077.
50. Goodman P, Schnapp L. *Pulmonary toxoplasmosis in AIDS*. Radiology 1992;184:791-793.
51. Delage G, Bronchu P, Petteitier M, Jasmin G, Lapointe M. *Giant-cell pneumonia caused by parainfluenza virus*. J Pediatr 1979;94:426-429.
52. Winston DU, Huang ES, Miller MJ, et al. *Molecular epidemiology of cytomegalovirus infections associated with bone marrow transplantation*. Ann Intern Med 1985;102:16-20.
53. Cheng YC, Huang ES, Lin JC, Mar EC, Pagano JS, Dutschman GE, Grill SP. *Unique spectrum of activity of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine against herpesviruses in vitro and its mode of action against herpes simplex virus type 1*. Proc Natl Acad Sci USA 1983;80:2767-2770.
54. Gershon AA, Steinberg SP, Gelb L. *Live attenuated varicella vaccine use in immunocompromised children and adults*. Pediatrics 1986;78(Suppl):757-763.
55. Hall CB, McBride JT, Walsh EE, et al. *Aerosolized ribavirin treatment of infants with respiratory syncytial virus infection: A randomized double-blind study*. N Engl J Med 1986;314:20-26.
56. Kaufmann CA, Bradley SF, Ross SC, Weber DR. *Successful treatment of hepatic candidiasis with fluconazole*. (Abstract 577) presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, 1990.

