Pneumocystosis

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Introduction

Pneumocystis is the classic opportunistic pathogen in that it does not produce any recognizable disease in an immunologically intact host, yet infection of the at-risk immunocompromised host results in a pneumonitis that is universally fatal if untreated. The organism was first identified in the early 1900s but was not appreciated to be a significant human pathogen until after World War II when outbreaks of *Pneumocystis* pneumonia (PCP) occurred in orphanages in Europe. These young infants who developed what was termed "interstitial plasma cell pneumonitis" were suspected to be immunosuppressed secondary to severe malnutrition. Two subsequent events firmly established *Pneumocystis* as a major opportunistic pathogen; the development of successful cancer chemotherapy in the late 1950s and 1960s and the start of the AIDS epidemic in the early 1980s. In fact, it was the recognition of a cluster of this "rare" pneumonia, PCP, in apparently healthy young gay men over a short period of time that led to the recognition that a new syndrome (AIDS) and infection (HIV) had emerged [1, 2].

Presently, the population of patients at risk to develop PCP is growing steadily as we develop new modalities of therapy and potent immunosuppressive drugs to treat malignancies, organ failure, autoimmune and inflammatory diseases. For example, in solid organ transplant recipients, as survival improves so does the recognition that these patients are at risk of developing PCP if not on specific prophylaxis. Most recently, the addition of antitumor necrosis factor (TNF) therapy to the management of patients with Crohn's disease, rheumatoid arthritis, and other inflammatory conditions has resulted in the occurrence of PCP in populations that previously had not been considered to be at risk for the development of PCP. The importance of PCP as an opportunistic pneumonia is likely to increase as the use of immunosuppressive biologic response modifiers increases.

Etiologic Agent

All strains of *Pneumocystis* are extracellular organisms found in the lungs of mammals. The taxonomic placement of these organisms has not been unequivocally established, largely due to the inability to adequately culture the organism. However, nucleic acid homologies indicate it is most closely related to the fungi, despite its morphologic features and susceptibility to drugs that are similar to those of protozoa. Both phenotypic and genotypic analysis demonstrates that each mammalian species is infected by a unique strain of *Pneumocystis* [3–5]. A biological correlate for these differences is evidenced by animal experiments that have shown organisms are not transmissible from one mammalian species to another [6]. This restricted host range is the one biologic characteristic of *Pneumocystis* that might achieve the level of uniqueness sufficient to define species of *Pneumocystis*.

Two forms of *Pneumocystis* are found in the alveolar spaces, thick-walled cysts (Fig. 14.1) that are 5–8 μm in diameter and may contain up to eight pleomorphic intracystic sporozoites, and trophozoites, which are 2–5 μm diameter cells with a more typical cell membrane, thought to be derived from excysted sporozoites. The terminologies sporozoites and trophozoites are based on the morphological similarities to protozoa, since there are not exact correlates for these forms of the organism among the fungi. Sporozoites are also called intracystic bodies and trophozoites are referred to as trophic forms.

As noted above, the host-species specificity of *Pneumocystis* has led some to propose the division of *Pneumocystis carinii* into multiple unique species, with the nomenclature *Pneumocystis jirovecii* being used to refer to human *P. carinii* [7]. The proposal for a change in nomenclature has been questioned because it also calls for species distinction

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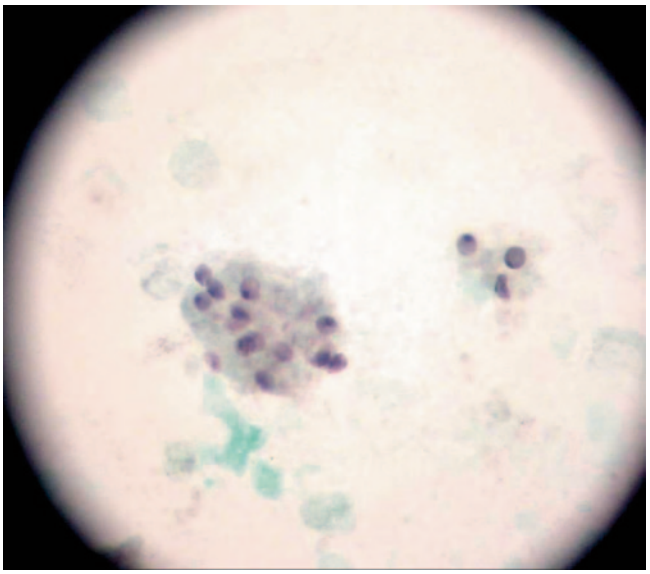

Fig. 14.1 Silver-stained bronchoalveolar lavage specimen showing characteristic clusters of *Pneumocystis* cysts

based on variation in gene sequences not known to result in a unique phenotype, so-called molecular phylogeny [8]. *Pneumocystis* that has not had a new name submitted for consideration can still be clearly defined using "special form" nomenclature (e.g., *P. carinii* f. sp. mustela for ferret *P. carinii*).

Epidemiology

PCP occurs only in patients who are significantly immunosuppressed, typically with abnormalities in $CD4^+$ T lymphocytes or B cells. Serologic studies have demonstrated that a high proportion of the population has evidence of infection and that seroconversion typically occurs during childhood. A recent prospective longitudinal study demonstrated that seroconversion began in the first few months of life and by 20 months of age, 85% of the infants in the study had seroconverted [9].

Aside from the serologic data, *Pneumocystis* was not known to actually infect the immunologically normal host. However, animal studies have proved that *Pneumocystis* produces a typical pattern of infection, transmission, and resolution in the normal host [10]. The other important biological feature of *Pneumocystis* infection is that the strain (or species) of *Pneumocystis* from any given mammalian host is transmissible only to members of the same host species. Cross-species transmission has never been convincingly demonstrated. Because of the finding of early seroconversion followed by disease later in life, PCP was postulated to be the result of reactivation of latent infection. However, no evidence for latency has ever been demonstrated, and mouse and rat models of PCP have shown that latency does not develop after infection. Considering all of these features, it would seem most likely that PCP is the result of new infection rather than reactivation of a latent infection. Person-to-person transmission is likely, based on the cumulative experience in animal models, but difficult to prove.

Without prophylaxis, PCP develops in approximately 70% of adults and 40% of infants and children with AIDS, and 10% of patients with organ transplants. It is often the sentinel event identifying infants with severe congenital immunodeficiencies such as severe combined immunodeficiency (SCID) syndrome. PCP also is a frequent occurrence in patients being treated for malignancies, occurring with an overall frequency of 10–15%. The actual incidence for any given malignancy depends on the treatment regimen and is positively correlated with the number of chemotherapeutic agents and the intensity of treatment.

Pathogenesis and Immunology

Control of infection is dependent on normally functioning $CD4^+$ T lymphocytes. Studies in patients with AIDS show an increase in the occurrence of *Pneumocystis* pneumonia as $CD4^+$ T lymphocytes drop. For adults and children over 6 years of age, a $CD4^+$ T cell count of 200 cells/μl or lower is a marker of very high risk for the development of PCP. Based on the occurrence of PCP in some patients and mouse strains with various immunologic defects which result in defective antibody production, a possible role for $CD4^+$ T lymphocytes could be to provide help for the production of specific antibody. Passively administered antibody has been shown to aid in the clearance of *Pneumocystis* in mouse models. Thus, antibody could be involved in the clearance of organisms through interaction with complement, phagocytes, and/or T lymphocytes.

The mechanism by which *Pneumocystis* damages the lung is not yet fully defined. Animal models have been valuable in helping us understand the immunopathogenesis of PCP [11]. Infection of SCID mice with *Pneumocystis* produces very little alteration in lung histology or function until very late in the course of the disease. However, if *Pneumocystis*-infected SCID mice are immunologically reconstituted with normal splenocytes, there is a rapid onset of an inflammatory response that results in an intense cellular infiltrate, markedly reduced lung compliance and significant hypoxia, all changes seen in humans with PCP. These inflammatory changes are associated with marked disruption of surfactant function. T cell subset analysis has shown that $CD4^+$ T lymphocytes produce an inflammatory response that not only clears the organisms but also results in lung injury. In contrast, $CD8^+$ T lymphocytes are ineffective in the eradication of *Pneumocystis,* but do produce a marked injurious inflammatory response, especially in the absence of $CD4^+$ T lymphocytes.

Immune reconstitution inflammatory syndrome (IRIS), also called immune restitution disease or immune reconstitu-

tion syndrome, is a recently described manifestation of pulmonary infection in AIDS patients with *Pneumocystis, Mycobacterium tuberculosis,* and other pulmonary pathogens who are experiencing rapid reconstitution of their immune system due to the administration of effective antiretroviral therapy [12]. In general, the severity of IRIS is directly related to the degree and rapidity of T cell recovery. Mouse models of PCP suggest that $CD8^+$ T lymphocytes help modulate the inflammation produced by $CD4^+$ T lymphocytes, but as mentioned above, their ineffectual inflammatory response can also contribute significantly to lung injury. These various T cell effects may be responsible for the variations in presentation and outcome of *Pneumocystis* pneumonia observed in different patient populations.

The inflammatory processes taking place during PCP do not appear to result in major long-term damage to the lung in those who recover. A long-term follow-up of 23 children with cancer and PCP showed a return to normal lung function by 6 months in all 18 survivors. Similar studies in adults are complicated by the fact that adult patients, especially those with AIDS, might have multiple pulmonary insults. While some studies, primarily of adult AIDS patients, suggest long-term pulmonary damage following PCP, other studies of renal transplant recipients have shown pulmonary function returned to nearly normal after recovery from PCP.

Clinical Manifestations

Pneumocystis Pneumonia

There are at least three distinct clinical presentations of PCP. In patients with profound immunodeficiency, such as young infants with congenital immunodeficiency, severe malnutrition, or in AIDS patients with very few $CD4^+$ T lymphocytes, the onset of hypoxia and symptoms is subtle with cough, dyspnea on exertion, or tachypnea, often without fever. Infants may show progression to nasal flaring, intercostal, suprasternal, and infrasternal retractions. As the disease progresses patients develop hypoxia, with cyanosis in severe cases. In the sporadic form of PCP, occurring in children and adults with underlying immunodeficiency, the onset of hypoxia and symptoms is usually more abrupt with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This latter type accounts for the majority of cases, although the severity of clinical expression may vary. Rales are usually not detected on physical examination. The third pattern of disease is that associated with rapid restoration of immune function referred to as IRIS. It has been best described in newly diagnosed AIDS patients who are severely immunocompromised and present with PCP as their initial manifestation of AIDS [12]. These patients appear to respond well to therapy for PCP but 3–6 weeks after beginning treatment they experience an unexpected recurrence of pulmonary symptoms and chest X-ray (CXR) abnormalities that coincide with return of immune function. IRIS may also occur in bone marrow transplant patients who engraft while infected with *Pneumocystis*.

Extrapulmonary Infections

Extrapulmonary infection with *Pneumocystis* is rare. The incidence is not well defined, but is estimated to be a 1000-fold less likely than PCP itself [13]. The most commonly reported sites of infection include the ear and eye. Why these two sites seem to predominate is unclear but may reflect the fact that infection at these sites may quickly produce readily apparent signs and symptoms. Other sites of involvement are the thyroid gland, liver, kidney, bone marrow, lymph nodes, spleen, muscles, and gastrointestinal (GI) tract. How the organism arrives at these sites is unknown. Response to treatment is usually good when extrapulmonary infections occur in the absence of pulmonary infection.

Diagnosis

Pulmonary symptoms in at-risk patients should always raise the suspicion of PCP. The classic chest radiograph reveals bilateral diffuse alveolar disease with a granular pattern (see Fig. 6.7, Chap. 6). The earliest densities are perihilar, and progression proceeds peripherally, typically sparing the apical areas until last. Less common chest radiograph appearances in PCP include cystic lesions, pneumothorax, or isolated focal infiltrates. In patients receiving aerosolized pentamidine for prophylaxis, there may be a predisposition for upper lobe infiltrates. The arterial oxygen tension (PaO_2) is invariably decreased.

A clinical pearl is that an elevated lactate dehydrogenase (LDH) may be a hint that one is dealing with PCP. This is due to the fact that LDH is a useful marker of alveolar and inflammatory cell damage. Because *Pneumocystis* is a diffuse alveolar infection, it tends to result in higher and more often elevated levels of LDH than some other more focal opportunistic pulmonary infections. For example, a recent analysis of LDH and pulmonary opportunistic infections in AIDS patients showed that about 90 % of those with definite PCP had elevated serum LDH [14]. Thus while not specific for PCP, very high LDH levels should raise one's suspicion for PCP and normal levels make the diagnosis of PCP much less likely.

PCP can only be definitively diagnosed by demonstrating *Pneumocystis* in the lungs of a patient with compatible pulmonary signs and symptoms. Appropriate specimens for analysis include bronchoalveolar lavage, tracheal aspirate, transbronchial lung biopsy, bronchial brushings,

Table 14.1 Recommended treatment for *Pneumocystis* pneumonia

Drug	Adults	Children
Treatment of first choice		
Trimethoprim–sulfamethoxazole (TMP–SMX)	TMP 15–20 mg/kg/d with SMX 75–100 mg/kg/d IV divided into three or four doses; PO for mild disease	TMP 15–20 mg/kg/d with SMX 75–100 mg/kg/d IV divided into four doses; PO for mild disease
Alternate treatment regimens		
Pentamidine	4 mg/kg/d IV as single dose	4 mg/kg/d as single dose
Atovaquone	750 mg PO bid	3–24 mo of age: 45 mg/kg/d PO divided into two doses; 1–3 mo and more than 24 mo: 30 mg/kg/d in two divided doses (max. daily dose 1500 mg)
Dapsone plus trimethoprim	Dapsone 100 mg, PO once daily; TMP 15 mg/kg/d PO in three divided doses	Dapsone 2 mg/kg/d (100 mg max.) PO once daily; TMP 15 mg/kg/d PO in three divided doses
Primaquine plus clindamycin	Primaquine 15–30 mg, PO once daily; clindamycin 600 mg IV every 8 h	Primaquine 0.3 mg/kg (max. 30 mg) PO once daily; clindamycin 40 mg/kg/d IV in four divided doses (no pediatric data)
Trimetrexate plus leucovorin	Trimetrexate	
	50 kg: 1.5 mg/kg/d IV once daily 50–80 kg: 1.2 mg/kg/d IV once daily 80 kg: 1.0 mg/kg/d IV once daily	45 mg/m^2 IV once daily
	Leucovorin (continue 3 days beyond trimetrexate)	
	50 kg: 0.8 mg/kg/d IV or PO every 6 h 50 kg: 0.5 mg/kg/d IV or PO every 6 h	20 mg/m^2 IV or PO every 6 h

Duration of therapy is typically 3 weeks in patients with AIDS and 2 weeks in other immunosuppressed patients
IV intravenous, *PO* orally, *mg/kg* milligrams/kilogram, *mg/kg/d* milligrams/kilogram/day, *mo* months of age, *bid* twice daily

percutaneous transthoracic needle aspiration, and open lung biopsy. Induced sputum samples are gaining popularity, but are helpful only if positive; the absence of *Pneumocystis* in an induced sputum sample does not exclude infection. The open lung biopsy is the most reliable method, although bronchoalveolar lavage is generally more practical. Estimates of the diagnostic yield of the various specimens are as follows: induced sputum 20–40 %, tracheal aspirate 50–60 %, bronchoalveolar lavage 75–95 %, transbronchial biopsy 75–95 %, and open lung biopsy 90–100 %. Once obtained, the specimens are typically stained with one of the four commonly used stains: Gomori methenamine silver (GMS) and toluidine blue stains only stain cyst forms; polychrome stains, such as Giemsa, stain both trophozoites and sporozoites; and the fluorescein-labeled monoclonal antibody also stains both trophozoites and cysts. *Pneumocystis* can also be visualized by Papanicolaou stain. Polymerase chain reaction analysis of respiratory specimens offers promise as a rapid diagnostic method, but a standardized system for clinical use has not been established.

Treatment

The clear drug of choice for the treatment of PCP is trimethoprim–sulfamethoxazole (TMP–SMX; Table 14.1). Generally, TMP–SMX is administered intravenously, but it may be given orally if disease is mild and no malabsorption or diarrhea is present. The duration of treatment is generally 3 weeks for patients with AIDS and 2 weeks for other patients. Adverse reactions occur frequently, more so in adults than children, with TMP–SMX. These include rash, fever, and neutropenia in patients with AIDS. These side effects are less common in non-AIDS patients. For patients who cannot tolerate or fail to respond to trimethoprim–sulfamethoxazole after 5–7 days, pentamidine isethionate may be used. Adverse reactions are frequent with pentamidine and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone is an alternative treatment that has been used primarily in adults with mild-to-moderate disease. For adults and adolescents atovaquone is given twice a day with food. Less information is available for the treatment of younger children with this agent. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone and of clindamycin plus primaquine.

Administration of corticosteroids in addition to anti-*Pneumocystis* drugs increases the chances for survival in moderate and severe cases of PCP [15]. The recommended regimen of corticosteroids for adolescents older than 13 years of age and for adults is oral prednisone, 80 mg/day divided in two doses on days 1–5, 40 mg/day once daily on days 6–10, and 20 mg/day once daily on days 11–21. While specific studies of adjunctive corticosteroid therapy in young children are not available, a reasonable regimen for children is oral prednisone, 2 mg/kg/day for the first 7–10 days, followed by a tapering regimen for the next 10–14 days.

Table 14.2 Recommended antibiotic prophylaxis for *Pneumocystis* pneumonia

Drug	Adults	Children
Trimethoprim–sulfamethoxazole (TMP–SMX)	One single or double strength tablet daily or 3 days/week	TMP 5 mg/kg/d with SMX 25 mg/kg/d given once daily or divided into two doses
Dapsone	100 mg daily or twice weekly	2 mg/kg/d as single dose (max. 100 mg/dose)
Atovaquone	1500 mg once daily	30 mg/kg/d as single dose for children aged 1–3 months and older than 24 mo; 45 mg/kg/d as single dose for children 4–23 mo
Aerosolized pentamidine	300 mg monthly given by Respirgard II nebulizer	For children ≥ 5 years—same as for adults

IV intravenous, *PO* orally, *mg/kg/d* milligrams/kilogram/day, *mo* months of age

Prevention

PCP is effectively prevented by the use of antimicrobial prophylaxis, thus all patients at high risk for PCP should be placed on chemoprophylaxis. As noted above, $CD4^+$ T cells are the key cells in determining susceptibility to PCP. However, defining the risk for PCP is not always clear. In AIDS patients, there is a clear-cut correlation between cell number and function so that firm cutoffs can be given. In adults with AIDS, prophylaxis is indicated at $CD4^+$ T cell counts of below 200 cells/μl. Because of the rapid changes in $CD4^+$ T cell counts in young infants, prophylaxis is recommended for all HIV-infected children during their first year of life. Thereafter, prophylaxis is started at $CD4^+$ T cell counts drop below 750 cells/μl for infants 12–23 months of age, 500 cells/μl for children from 2 to 6 years of age, and 200 cells/μl for those 6 and older. Prophylaxis is also recommended for all ages if $CD4^+$ T cell percentages drop below 15%. In other disease states where patients are placed at risk of PCP from being on immunosuppressive drugs, both lymphocyte number and function will be affected. Thus while a patient may have a lymphocyte count above the threshold for susceptibility to develop PCP, suppressed function of remaining lymphocytes may place them at risk for PCP. Because of the demonstrated increased risk of PCP with increasing intensity of chemotherapy in patients with cancer it would seem prudent, in our opinion, to consider prophylaxis for patients receiving prolonged (more than 6–8 weeks) therapy with two immunosuppressive agents and to give prophylaxis to all patients receiving three or more immunosuppressive agents.

TMP–SMX is the drug of choice for *Pneumocystis* prophylaxis and may be given for 3 days each week, or, alternatively, each day (Table 14.2). The original study testing less than daily administration of TMP–SMX used a schedule of three consecutive days on TMP–SMX and 4 days off with the idea of reducing potential bone marrow suppression from the TMP–SMX. Subsequent studies have used alternate day schedules such as dosing on Monday, Wednesday, and Friday. The double strength tablet is preferred for adults receiving 3 days a week dosing. Alternatives for prophylaxis, all of which are inferior to TMP–SMX, include dapsone, atovaquone, and aerosolized pentamidine. Prophylaxis must be continued as long as the patient remains immunocompromised. Studies in adult AIDS patients who reconstitute adequate immune response during antiretroviral therapy show that prophylaxis may be withdrawn without risk of developing PCP. Small studies in children have provided similar results. Patients who maintain their $CD4^+$ T cell count at or above the at-risk threshold for age, e.g., 200 cells/μl for older children and adults, for at least 3 months are candidates for discontinuation of both primary and secondary prophylaxis. Guidelines for the management of PCP in adults and children can be found at the National Institutes of Health (NIH) AIDS information web site [16, 17].

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Suggested Reading

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