Pneumocystis Pneumonia

Sergio L. Vargas
University of Chile School of Medicine, Santiago, Chile

Synonyms

P. carinii pneumonia; *P. jiroveci* pneumonia; *P. carinii* f. sp. *hominis* pneumonia; PcP; PCP

Definition and Characteristics

Pneumocystis pneumonia (PcP) is a life-threatening pulmonary infection that affects immunocompromised persons. Clinically, it is characterized by marked progressive hypoxemia and dyspnea with relative absence of auscultatory signs. Infiltrates are normally present in the chest radiography. Paradoxically, the clinical course is more abrupt and severe in less immunocompromised individuals, suggesting that the clinical presentation and outcome of the disease is more dependent on the type and extent of the immune response mounted by the patient than the pathogenic potential of *Pneumocystis* itself [1–5].

Prevalence

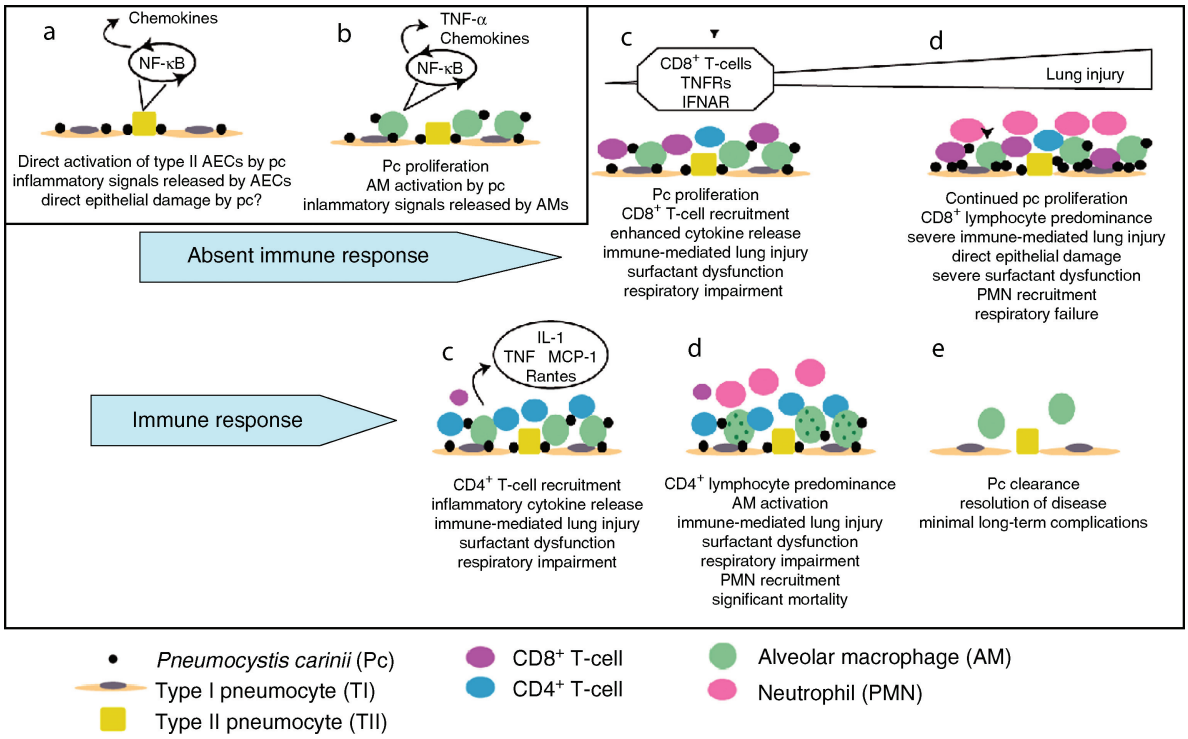
PcP occurs in direct proportion to the number of immunocompromised susceptible individuals not receiving anti-*Pneumocystis* prophylaxis. Without chemoprophylaxis, the risk of PcP is 5–25% in transplant patients, 2–6% in patients with collagen vascular disease, and 1–25% in oncology patients [2]. Historically, PcP remained as an occasional disease of undernourished infants since it was first reported, during World War II, to 1956 when reports on adults began to appear as a result of progressive implementation of anti-cancer chemotherapy. Numbers increased dramatically with the AIDS epidemic. HIV-infected persons are the highest risk group, as over half of AIDS patients developed PcP, before chemoprophylaxis and highly active antiretroviral agents (HAART) were adopted in 1989 and1996, respectively [3]. The prevalence in industrialized countries decreased after 1998 to 0.3 cases/100 person-years. Despite this achievement, PcP remains the most common severe opportunistic infection of AIDS. Available data on prevalence of PcP in non-industrialized countries is limited, and the number of reported cases may be low owing to shorter patient survival and/or difficulties in diagnosis [2].

Genes

PcP is an airborne-transmissible infectious disease. Phylogenetic analysis of the *Pneumocystis* 16S-like small-ribosomal RNA subunit indicates *Pneumocystis* is a fungus. The *Pneumocystis* genome is being sequenced and comprises ~8 million base pairs of DNA divided into 15 linear chromosomes. A few genes coding for important host–pathogen interaction processes have been cloned [1].

Molecular and Systemic Pathophysiology

An underlying T-lymphocyte defect is the main factor predisposing to PcP. Adult patients are at risk when their T cell CD4+ lymphocyte count falls below 300–200 cells per mm. This generally occurs as a result of HIV infection or administration of immunosuppressive agents including corticosteroids that affect T-lymphocyte number or function. In addition, a variety of genetic immune defects like Severe Combined Immunodeficiency Syndrome (SCIDS) T-B− and T-B+, hyper-immunoglobulin E syndrome or X-linked hyper-IgM syndrome may predispose to PcP [3]. Molecularly, *Pneumocystis* attaches to alveolar pneumocyte type I cells inducing cellular immune responses with participation of innate and adaptive immune mechanisms [4,5]. Contact with alveolar macrophages and pneumocyte type II cells activate complex and expanding, CD 4+ T cells, CD8+ T cells, neutrophils, host proteins, and other interactions that lead to cytokine and chemokine expression and inflammation. Balanced CD4 + and CD8+ T-cell responses and B-cell lymphocytes are required to clear the infection (Fig. 1) [4].



***Pneumocystis* Pneumonia. Figure 1** Schematic representation of the progression of immune-mediated lung injury during PcP. Direct activation of Pneumocyte type II in the alveolar epithelium by *Pneumocystis* leads to NF-κB activation and the release of proinflamatory signals. PcP progresses differently in the absence of CD4+ lymphocyte immune response (as in AIDS), than when residual immune response is present, as may be the case in chemotherapy-mediated immunodeficient cancer patients (adapted from [4] with permission).

Diagnostic Principles

Clinical diagnosis of PcP is difficult due to non-specific signs and symptoms. Therefore, the diagnosis necessarily relies on the demonstration of *Pneumocystis* cyst or trophozoite forms in respiratory specimens by microscopy. Molecular tools like the polymerase chain reaction (PCR; real-time PCR) detect nucleic acids of *Pneumocystis*, and their use for diagnosis needs better definition. More immunocompromised individuals may harbor larger numbers of *Pneumocystis* organisms per diagnostic specimen than less immunocompromised individuals, implying that the sensitivity and specificity of the diagnostic tests is highly dependent on the type and quality of the diagnostic specimen and on the patient's underlying immunodeficiency condition. This way, the sampling procedure and the diagnostic specimen volume and processing in the laboratory are critical, especially when specimens are from non-AIDS patients. The most frequently used stains for microscopy are Gomori Grocott methenamine silver and Toluidine Blue O that stain the cyst form, Wright-Giemsa that stains trophozoites, and fluorescein-conjugated monoclonal antibodies may stain both forms depending on the monoclonal antibody that is used. Other stains used for diagnosis are calcofluor white, cresyl echt violet, Gram-Weigert, and Papanicolaou.

Therapeutic Principles

PcP is uniformly fatal if untreated. Anti-PcP drugs in chemoprophylaxis schemes aiming to prevent the disease should be indicated to susceptible immunocompromised patients at risk and can be discontinued in AIDS patients with sustained response to HAART, and in other patients, if predisposing factors are resolved. Treatment of PcP aims to decrease the *Pneumocystis* burden with therapeutic doses of an anti-*Pneumocystis* agent for 2–3 weeks, to control hypoxemia with supportive oxygen, and to modulate the host immune response with steroids when more severe disease is present. The preferred prophylactic and therapeutic drug scheme is the combination of Trimethoprim and Sulfamethoxazole. These drugs target enzymes that participate in the folic acid cycle pathway and produce a *Pneumocystis*-"static" effect. Anti-*Pneumocystis* drug alternatives are few, and no "cydal" drugs are available

***Pneumocystis* Pneumonia. Table 1** Anti-*Pneumocystis* drugs and their metabolic targets

Agent	Therapeutic use	Prophylactic use	Primary molecular target
Trimethoprim sulfamethoxazole	First choice	First choice	DHPS/DHFR
Primaquin clindamycin	Second choice	Not used	Uncertain/protein synthesis inhibition
Pentamidine	Alternative choice	Aerosolized/rarely used	DNA synthesis
Atovaquone	Alternative choice[a] (for mild to moderate infection)	Alternative choice	Cytochrome b complex
Dapsone trimethoprim	Alternative choice[b]	Dapsone alone or dapsone with pyrimethamine and leucovorin	DHPS/DHFR

Adapted from [1] with permission.
[a]Administer with high-fat meals to maximize absorption.
[b]Hemolysis can occur with G6PD deficiency.

(Table 1). Given access to standard of care, the outcome is better in AIDS patients than in patients with immunosuppression resulting from chemotherapy or other disorders [1,4].

References

1. Thomas C, Limper A (2007) Nature Rev Microbiol 5:298–308
2. Morris A, Lundgren JD, Masur H, Walzer PD, Hanson DL, Frederick T, Huang L, Beard CB, Kaplan JE (2004) Emerg Infect Dis 10:1713–1720
3. Hughes WT (2005) In: Walzer PD, Cushion MT (eds) *Pneumocystis* pneumonia, 3rd edn. Marcel Dekker, New York, pp 1–37
4. Gigliotti F, Wright TW (2005) Expert Rev Mol Med 7:1–16
5. Steele C, Shellito JE, Kolls JK (2005) Med Mycol 43:1–19