Literature Review

Immunopathogenesis of Pneumocystis Pneumonia (PCP) and Its Clinical Implications

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Abstract

Pneumocystis pneumonia (PCP) is a serious lung infection caused by Pneumocystis jirovecii, primarily affecting immunocompromised individuals. It remains a major health concern, especially in HIV/AIDS patients and those undergoing immunosuppressive therapy. This review discusses how the immune system responds to P. jirovecii and why immunocompromised individuals are more vulnerable. In healthy individuals, CD4+ T cells, B cells, and macrophages help control the infection. However, in immunocompromised individuals, a weakened immune response allows fungal overgrowth, leading to severe lung damage. The review also covers symptoms, diagnosis, and treatment options. TMP-SMX is the preferred treatment, while alternative drugs are available for those who cannot tolerate it. Understanding the immune response to PCP can help improve treatment and patient care.

Keywords: immunocompromised, immunopathogenesis, pneumocystis pneumonia (PCP), T cells

INTRODUCTION

Pneumocystis pneumonia (PCP) is a fungal infection caused by *Pneumocystis jirovecii* that typically affects individuals with compromised immune systems. The global Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic that emerged in the 1980s led to a sharp rise in the incidence of PCP, making it a significant contributor to illness and death among immunosuppressed patients.[1] Initially, *P. jirovecii* was classified as a protozoan, but molecular studies later revealed that it is, in fact, a fungal organism.[2]

Despite advancements in antiretroviral therapy (ART) and the widespread use of TMP-SMX prophylaxis, PCP remains prevalent, particularly in non-HIV immunocompromised populations. The ongoing COVID-19 pandemic has further complicated PCP management, as severe SARS-CoV-2 infections induce lymphocytopenia and necessitate corticosteroid use, increasing susceptibility to opportunistic infections like PCP.[3]

The immunopathogenesis of PCP varies between immunocompetent and immunocompromised hosts. In the former, *P. jirovecii* infection is controlled with minimal lung damage, whereas in immunocompromised individuals, unchecked fungal proliferation leads to a severe inflammatory response, causing respiratory distress and lung tissue injury. This review explores the immune mechanisms underlying PCP, its clinical features, diagnostic methods, and current therapeutic strategies.[4]

PNEUMOCYSTIS PNEUMONIA (PCP)

Classification and Life Cycle

Previously classified as *Pneumocystis carinii*, the organism causing human infection was renamed *Pneumocystis jirovecii* to differentiate it from rodent-associated species. It exists in two life forms. The cystic form, which is the infectious stage, consists of thick-walled structures measuring 4 to 7 µm in diameter and contains eight ascospores that are released upon rupture. The trophozoite form is smaller, with an irregular shape ranging from 2 to 8 µm, and attaches to alveolar epithelial cells, initiating immune responses.[2–4]

Pneumocystis reproduces asexually via binary fission and sexually through meiotic division, forming infectious cysts that spread through airborne transmission. Although primarily affecting the lungs, disseminated infections involving the eyes, ears, thyroid, and bone marrow have been reported in severe cases. The Pneumocystis life cycle is depicted in Figure 1. Description of image detailing cyst and trophozoite forms, their interactions with alveolar epithelium, and modes of transmission.[2,5]

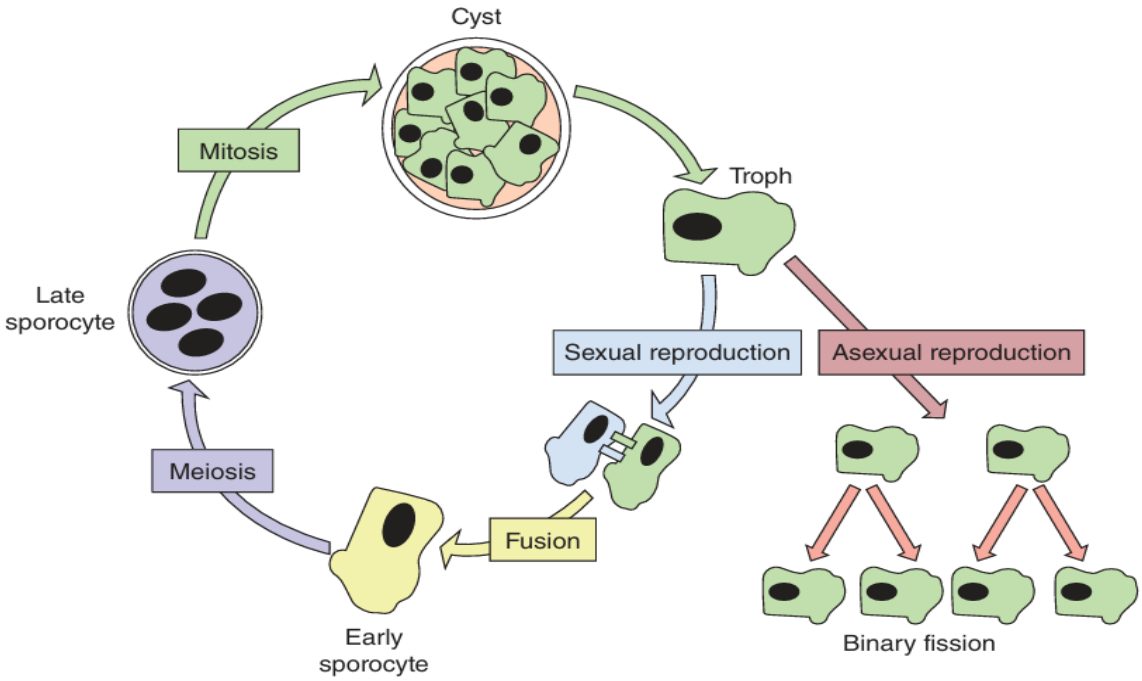

Figure 1. Life cycle of *Pneumocystis* [2]
(Adapted from Eddens et al with modifications by the authors)

RESPIRATORY IMMUNITY SYSTEM AGAINST INFECTION

The human immune system consists of two primary components: the innate and adaptive immune systems. The innate immune system includes various elements such as the skin epithelium, mucosal surfaces, dendritic cells, macrophages, and natural killer (NK) cells. It serves as the body's first defense against infections and is instrumental in activating the adaptive immune system.[6]

The adaptive immune system, which includes T and B cells, generates cytokines that trigger the activation of neutrophils and dendritic cells to help eliminate pathogens. In the lower respiratory tract, particularly in the alveoli, alveolar macrophages act as antigen-presenting cells (APCs). These cells present antigens to T and B cells in the adaptive immune system, which is crucial in clearing pathogens from the airways.[6]

IMMUNE RESPONSE TO *PNEUMOCYSTIS* INFECTION IN IMMUNOCOMPETENT INDIVIDUALS

People with a healthy immune system can clear *Pneumocystis* without symptoms. CD4+ T cells help B cells activate M2 macrophages, eliminating the fungus. In contrast, individuals with weakened immunity, such as those with HIV, lose CD4+ T cells, making them more vulnerable to infection. Studies show that mice with CD4+ T cells can clear *Pneumocystis*, while those lacking them develop severe pneumonia. CD4+ T cells and alveolar macrophages are essential for controlling the infection.[7]

Innate Immunity in Immunocompetent Individuals

When Pneumocystis infects the lungs, antigen-presenting cells (APCs), including macrophages and dendritic cells, identify Pneumocystis components such as the major surface glycoprotein (MSG) and beta-D-glucan (BDG). This recognition activates immune responses through pattern recognition receptors (PRRs), such as Toll-like receptors (TLR2 and TLR4) and C-type lectin receptors (Dectin-1 and Mincle). This interaction stimulates the production of immune signaling molecules, including interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). Afterward, the APCs migrate to lymphoid tissues to initiate the activation of the adaptive immune response.[6,7]

Adaptive Immunity in Immunocompetent Individuals

CD4+ T cells orchestrate the immune response, promoting M2 macrophage activation and fungal clearance without excessive inflammation. B-cell-mediated antibody responses also contribute to pathogen neutralization and macrophage stimulation.[7,8]

Figure 2 describes how adaptive immunity in immunocompetent individuals protects against *Pneumocystis.* APCs recognize *Pneumocystis* and activate CD4+ T cells, which stimulate B cells in Induced Bronchus Associated Lymphoid Tissue (iBALT) structures. Within iBALT, CD4+ T

cells become follicular T cells (Tfh) to support B cells. Activated macrophages undergo M2 polarization and engulf *Pneumocystis*. CD8+ T cells, polymorphonuclear (PMNs), and eosinophils also aid in clearing the infection. This immune response removes *Pneumocystis* without causing respiratory symptoms.[7,8]

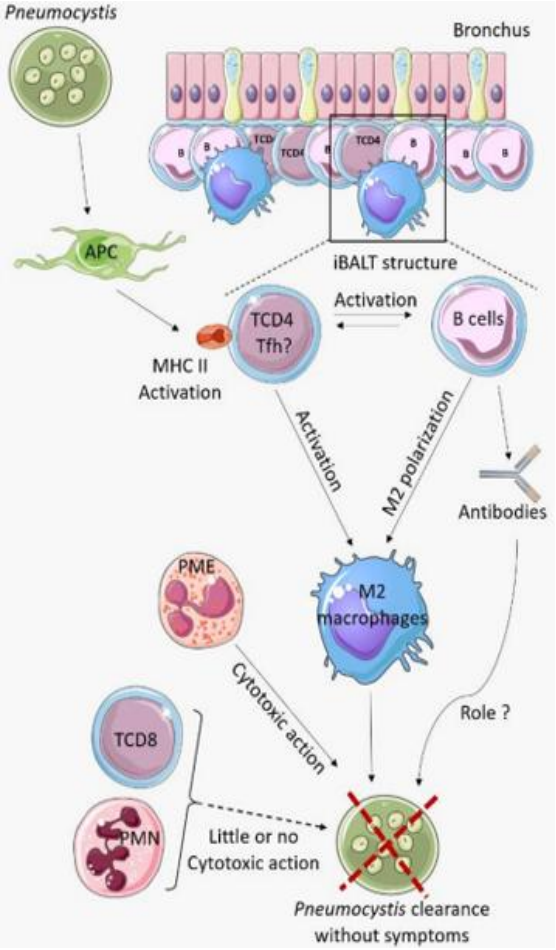

Figure 2. PCP Immunopathogenesis In Immunocompetent Individuals[7]
(Adapted from Charpentier et al with modifications by the authors)

IMMUNE RESPONSE TO *PNEUMOCYSTIS* INFECTION IN IMMUNOCOMPROMISED INDIVIDUALS

In immunocompromised individuals, the body loses its ability to eliminate *Pneumocystis* effectively, allowing the fungus to multiply in the alveoli. This leads to excessive and ineffective inflammation, causing lung damage and worsening respiratory symptoms.[7]

Innate Immunity in Immunocompromised Individuals

In HIV patients with PCP, eosinophilia in blood and bronchoalveolar lavage (BAL fluid) correlates with fungal growth two weeks post-infection, though the eosinophils' direct fungicidal role remains unclear.[9] Reduced macrophage numbers and NK cell deficiency impair fungal clearance, while increased TNF-α inhibition (due to immunosuppressive drugs such as glucocorticoids and anti-TNFα) elevates PCP risk. Macrophages and NK cell deficiency leads to increased fungal infections by the fourth week due to reduced IFNγ production.[8–10]

Adaptive Immunity in Immunocompromised Individuals

CD4+ T cell depletion impairs fungal clearance, shifting the immune response toward a CD8+ T cell and M1 macrophage-dominated reaction. Similarly, B cell deficiency hinders *Pneumocystis* elimination, increasing PCP risk. Monoclonal antibodies targeting B cells further elevate susceptibility. The absence of B cells disrupts antigen presentation and antibody production, particularly IgG, impairing CD4+ T cell activation. Lack of *Pneumocystis*-specific IgG facilitates fungal infections, while reduced IL-10 levels heighten inflammation by increasing Th1 and Th17 activity. This leads to excessive

inflammatory cytokine release, alveolar damage, and respiratory failure.[10,11]

Figure 3 describes how adaptive immunity in immunocompromised individuals against *Pneumocystis*. The lack of CD4+ T cells and B cells weakens the immune response. Th1 cells activate M1 macrophages with IFNγ to clear fungi, while CD8+ T cells and NK cells help by killing *Pneumocystis* directly. M1 macrophages also engulf the fungus, but excessive inflammation can damage lung tissue due to increased PMN infiltration.[7]

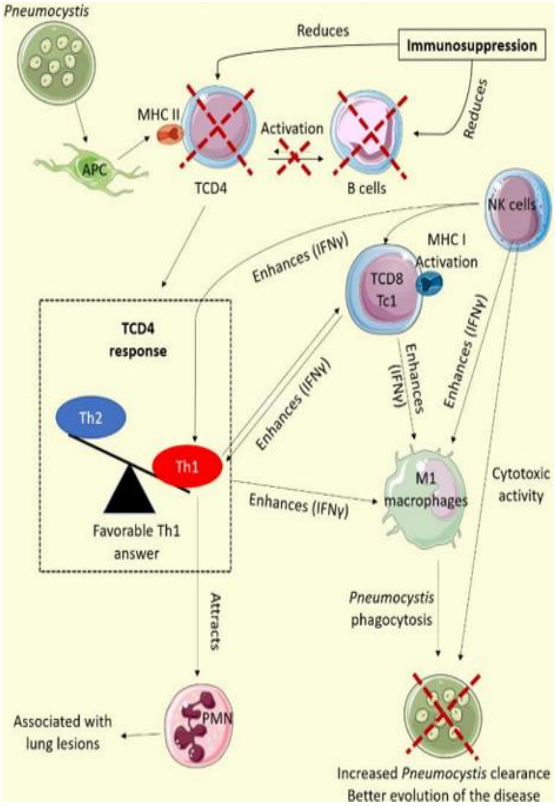

Figure 3. PCP Immunopathogenesis In Immunocompromised Individuals[7]
(Adapted from Charpentier et al with modifications by the authors)

CLINICAL MANIFESTATIONS

Pneumocystis pneumonia (PCP) presents with nonspecific respiratory symptoms that progressively worsen over days to weeks. The classic triad of PCP includes progressive exertional dyspnea, non-productive cough, and fever. Other symptoms include chest discomfort, fatigue, and weight loss, especially in immunocompromised patients. Patients with HIV-related PCP often exhibit an insidious onset with mild respiratory symptoms, while non-HIV immunocompromised patients experience a more aggressive course, frequently leading to acute respiratory failure requiring mechanical ventilation.[12,13]

In severe cases, PCP can progress to acute respiratory distress syndrome (ARDS), characterized by profound hypoxia, requiring intensive care support. On physical examination, patients may present with tachypnea, tachycardia, and diffuse bilateral crackles on auscultation. Hypoxemia, which worsens with disease progression, is a hallmark feature, often out of proportion to radiographic findings.[12,13]

DIAGNOSIS

Diagnosing Pneumocystis pneumonia (PCP) is challenging due to its non-specific clinical presentation, necessitating a high index of suspicion in patients with respiratory symptoms and immunosuppressive risk factors. Diagnostic approaches encompass clinical evaluation, radiologic imaging, and laboratory testing. Chest radiographs typically reveal bilateral interstitial infiltrates, which may progress to alveolar consolidation in advanced disease. High-resolution computed

tomography (HRCT) is more sensitive, often showing characteristic ground-glass opacities that can be diffuse or patchy.[13]

Laboratory tests play a crucial role in PCP diagnosis. Serum biomarkers, such as elevated β-D-glucan levels, suggest fungal infection, though specificity is limited. Arterial blood gas analysis often demonstrates hypoxemia with an increased alveolar-arterial gradient. Microbiological testing includes microscopy, where staining methods such as Giemsa and silver stain detect cysts or trophozoites in bronchoalveolar lavage (BAL) or induced sputum samples. Polymerase chain reaction (PCR) assays are highly sensitive for detecting *P. jirovecii* DNA and are particularly useful in cases with a low organism burden.[14,15]

TREATMENT AND ALTERNATIVE THERAPIES

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the gold standard for treating Pneumocystis pneumonia (PCP). The recommended dosage is 15–20 mg/kg/day of the trimethoprim component, divided into three or four doses, administered either orally or intravenously over a 21-day course.[16,17]

Alternative therapies for TMP-SMX intolerance include pentamidine, atovaquone, and clindamycin plus primaquine. Pentamidine is administered intravenously at 4 mg/kg once daily over 21 days. Atovaquone is administered orally at 750 mg twice daily for 21 days. Clindamycin is administered at 600 mg intravenously or orally every 6 hours, combined with primaquine at 30 mg orally once daily for 21 days.[17,18]

For moderate to severe cases of PCP, characterized by a partial pressure of oxygen (PaO_2) below 70 mmHg or an alveolar-arterial (A-a) gradient exceeding 35 mmHg, the use of adjunctive corticosteroids is advised. The standard treatment protocol includes prednisone at 40 mg twice daily for the first five days, followed by 40 mg once daily for the next five days, and then 20 mg once daily for 11 days, completing a 21-day treatment course. This method helps reduce inflammation and has been shown to enhance survival outcomes.[18]

Immunotherapy has shown promise as an adjunctive treatment for PCP, especially in individuals with compromised immune systems. One emerging strategy involves the use of monoclonal antibodies targeting immune checkpoint inhibitors, such as pembrolizumab and nivolumab. These medications, primarily used in cancer treatment, work by blocking the programmed cell death-1/programmed cell death ligan-1 (PD-1/PD-L1) pathway, which typically dampens T-cell activity.[19,20]

By inhibiting this pathway, the immune system may be better equipped to fight infections like PCP in cancer patients, particularly in patients with significantly low T-cell counts. While clinical studies on the application of immune checkpoint inhibitors for PCP are still limited, preliminary results indicate that these drugs might enhance immune responses and reduce the occurrence of recurrent infections in high-

risk populations, including those with HIV or transplant recipients.[19,20]

Another potential immunotherapeutic approach is the use of intravenous immunoglobulin (IVIG), which contains antibodies against various pathogens, including *Pneumocystis jirovecii*. IVIG has been studied as a potential therapy for individuals with recurrent or treatment-resistant PCP, particularly in cases of B-cell deficiencies or impaired antibody production. IVIG provides passive immunity by supplying exogenous antibodies, which can aid in neutralizing and eliminating the pathogen.[21]

Some clinical studies have suggested that IVIG therapy can improve clinical outcomes and decrease mortality in immunocompromised patients with PCP by boosting the immune response. However, more research, including randomized controlled trials, is needed to determine its optimal use and effectiveness in managing PCP.[21]

CONCLUSION

Pneumocystis pneumonia is a life-threatening infection, especially for people with weak immune systems. CD4+ T cells play a crucial role in fighting *P. jirovecii*, and their absence leads to severe disease. Early diagnosis using imaging and lab tests is essential for proper treatment. TMP-SMX is the most effective drug, but other options like pentamidine and atovaquone are available. Severe cases may require corticosteroids to reduce lung inflammation.

Understanding the immunopathogenesis of PCP is crucial for developing targeted therapies, immunotherapies, and improved diagnostic strategies. Future research should focus on novel antifungal agents with fewer side effects, host-directed therapies to modulate inflammatory responses, and improved prophylactic strategies for high-risk populations.

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