Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Immune Responses to *Pneumocystis* in HIV-Infected and Non-HIV Immunocompromised Hosts

Yu Wang[1], Caopei Zheng[1], Yuqing Sun[1], Yulin Zhang[1–3]

[1]Department of Respiratory and Critical Care Medicine, Beijing Youan Hospital, Capital Medical University, Beijing, 100069, People's Republic of China; [2]Laboratory for Clinical Medicine, Capital Medical University, Beijing, 100069, People's Republic of China; [3]Beijing Research Center for Respiratory Infectious Diseases, Beijing, 100069, People's Republic of China

Correspondence: Yulin Zhang, Beijing Youan Hospital, Capital Medical University, No. 8, West Toutiao, Youanmenwai, Yulin West Road, Fengtai District, Beijing, People's Republic of China, Email yulinzhang@ccmu.edu.cn

Abstract: *Pneumocystis jirovecii* pneumonia (PJP) is a high-burden opportunistic infection with a significant risk of death among immunocompromised hosts. *Pneumocystis* spp. cycle between trophic forms and cysts within the host alveoli. The trophic form relies heavily on the folate biosynthesis pathway, whereas the cyst form, supported by a β-1,3-glucan-rich cell wall, is considered important for transmission. Immune evasion is mediated in part by major surface glycoprotein antigenic variation, and additional effects on host antigen-presentation pathways have been reported primarily in experimental rodent models and remain to be established in human disease. Innate recognition mediated by Dectin-1, with additional contributions from Toll-like receptor 2 (TLR2) signaling described in experimental models, may promote T helper 17 (Th17)- and Th1-biased immune responses. Distinct host immune contexts then shape divergent disease phenotypes. In HIV-infected hosts, CD4+ T-cell deficiency, high fungal burden, and impaired clearance predominate, and immune reconstitution inflammatory syndrome (IRIS) may occur early after initiation of antiretroviral therapy (ART). In non-HIV immunocompromised hosts, broader immune dysfunction, including impaired antibody responses and antigen presentation together with complement and neutrophil activation, more often leads to a low-burden but highly inflammatory pattern that can progress to acute respiratory distress syndrome (ARDS). This review summarizes the life cycle, adhesion and immune pathways, immune evasion mechanisms, and differences between HIV-infected hosts and non-HIV immunocompromised hosts, with the goal of supporting precision treatment for PJP and optimizing clinical strategies.

Keywords: *Pneumocystis jirovecii*, HIV-associated immunodeficiency, non-HIV immunocompromised hosts, innate immunity, adaptive immunity, immunopathogenesis

Introduction

Pneumocystis pneumonia is a common opportunistic infection in immunocompromised hosts, typically seen in human immunodeficiency virus (HIV)-infected hosts, people who have received solid organ transplants, and people receiving glucocorticoids or biologic agents.[1]

With the widespread use of ART, the incidence of PJP has declined markedly among HIV-infected hosts, particularly in high-income countries. However, PJP remains a substantial burden in many low- and middle-income regions, including parts of Africa, as well as among non-HIV immunocompromised populations. There are systematic differences in immunopathogenesis between HIV-associated and non-HIV-associated PJP, as demonstrated by human clinical and epidemiological studies: the former usually presents with subacute onset, higher alveolar fungal burden, and relatively mild inflammation, whereas the latter often shows acute fulminant disease with lower fungal burden but a stronger host inflammatory response, which more readily progresses to ARDS and carries higher mortality.[2–6]

https://doi.org/10.2147/JIR.S596115
Received: 14 January 2026
Accepted: 8 April 2026
Published: 17 April 2026

In recent years, anti-CD20 therapy represented by rituximab has been widely used, and the risk of PJP associated with B-cell depletion has increased significantly, further altering the epidemiology and phenotypic spectrum in non-HIV immunocompromised hosts.[7]

This review aims to explain why PJP presents with markedly different clinical and inflammatory phenotypes in HIV-infected hosts compared with non-HIV immunocompromised hosts. We focus on differences in fungal burden and host inflammatory responses, including CD4 T-cell deficiency in HIV and inflammation-driven lung injury in non-HIV PJP, to provide a framework for understanding disease severity and clinical outcomes. To further contextualize these distinct immunopathological patterns, we next turn to the biological features of *Pneumocystis* and the molecular mechanisms through which the organism interacts with the host immune system.

Pathogenic Mechanisms of Pneumocystis Spp

Pneumocystis jirovecii is an opportunistic fungal pathogen that readily causes lethal PJP in immunocompromised hosts.[8] A study in healthy children showed that environmental exposure often occurs in early childhood and infection is frequently asymptomatic, with anti-*Pneumocystis jirovecii* serum antibody titers increasing with age; about two thirds of children have a titer of ≥1:16 by 4 years of age.[9] Therefore, *Pneumocystis* may persist in the host as colonization, and disease can develop upon immune suppression either through reactivation of a pre-existing infection or through reinfection following renewed exposure.[10] Its pathogenic course generally proceeds as follows: initial adhesion to and colonization of the alveolar epithelium; subsequent evasion of immune recognition and clearance through multiple mechanisms while provoking an amplified inflammatory response; and ultimately disruption of alveolar structure and function, causing impaired gas exchange and hypoxemia.

Recent molecular epidemiological studies have increasingly challenged the universal applicability of the childhood latent infection reactivation hypothesis as the primary mechanism underlying *Pneumocystis* pneumonia. In recurrent cases, *Pneumocystis* strains detected during the first and subsequent episodes often exhibit different genotypes, and the genotype identified at recurrence is not detectable in bronchoalveolar lavage fluid from the initial episode, suggesting that disease may more commonly result from a new exogenous infection.[11] In addition, among solid organ transplant recipients, multilocus sequence typing has demonstrated that some patients share an identical and distinct genotype, and transmission mapping analyses further support the possibility of in-hospital transmission or a shared source of exposure.[12,13] Taken together, these findings indicate that recent reinfection may play an important role in the development of *Pneumocystis* pneumonia in immunocompromised populations.

Life Cycle and Metabolic Characteristics of Pneumocystis Spp

The life cycle of *Pneumocystis jirovecii* comprises two main forms: trophic forms and cysts. The cyst is the infectious stage that can be transmitted through the air to the host lung and then differentiates into trophic forms in the host. Trophic forms are the metabolically active stage that adhere, divide, and expand within the alveolar space, and ultimately convert back into cysts to continue the life cycle and enable transmission between hosts.[14] *Pneumocystis* shows strong dependence on folate biosynthesis. It cannot obtain exogenous folate from the host and must synthesize tetrahydrofolate (THF) de novo to sustain DNA replication and cell division. This pathway involves several key enzymes: aminodeoxychorismate synthase 1 (ABZ1) first converts chorismate to 4-amino-4-deoxychorismate (ADC), which is then cleaved to para-aminobenzoic acid (PABA) by ABZ2. Dihydropteroate synthase (DHPS) catalyzes the condensation of PABA with 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (DHPPP) to form dihydropteroate. Dihydrofolate synthase (DHFS) then catalyzes the ATP-dependent addition of L-glutamate to produce dihydrofolate (DHF), which is reduced to tetrahydrofolate (THF) by dihydrofolate reductase (DHFR).[15–17] Trimethoprim–sulfamethoxazole (TMP-SMX) inhibits DHFR and DHPS, respectively, thereby blocking this pathway and suppressing trophic proliferation and cyst formation.[16] Meanwhile, the cyst stage is crucial for transmission and persistence within the host. The cyst wall is enriched in β-1,3-glucan, which provides structural integrity, whereas trophic forms largely lack this component.[18] Although β-1,3-glucan is a potent immunostimulatory molecule, its spatial organization within the cyst wall and partial masking by major surface glycoproteins may modulate host recognition. In addition, a cyst-specific endo-β-1,3-glucanase (Eng) is expressed exclusively in cysts and is capable of releasing major surface glycoprotein in vitro, suggesting

a potential role in surface antigen remodeling.[18] Whether Eng-mediated glucan remodeling and major surface glycoprotein (Msg) release contribute to immune evasion or long-term persistence during *Pneumocystis* infection in vivo remains to be determined. Caspofungin inhibits β-1,3-glucan synthesis, selectively reduces cyst numbers, and may secondarily diminish Eng-dependent wall remodeling, offering a potential therapeutic strategy against *Pneumocystis*.[19] *Pneumocystis* also differs from other fungi in structural composition: its cell membrane lacks ergosterol and contains mainly cholesterol and phytosterols, with cholesterol believed to be scavenged from the host lung environment and incorporated into the fungal membrane, leading to intrinsic low susceptibility to azoles and polyenes.[20–22] This membrane specificity influences drug susceptibility and may relate to the functional requirements of different life cycle stages. Genomic and evolutionary studies indicate that *Pneumocystis jirovecii* has adopted a highly host-adapted, obligate biotrophic lifestyle, characterized by extensive loss of biosynthetic pathways and a strong dependence on host-derived nutrients within the lung environment. Such adaptations likely underlie its long-standing resistance to axenic in vitro cultivation, as many essential metabolic and signaling requirements cannot be readily reproduced outside the host. In addition, *Pneumocystis jirovecii* exhibits a reduced repertoire of lytic proteases and lacks many classical fungal virulence factors, further distinguishing its biology from that of typical pathogenic fungi.[23] Notably, because *Pneumocystis* cannot be maintained long term under routine culture conditions, studies of its metabolic features, drug targets, and resistance mechanisms still face substantial technical barriers.[20,21]

Adhesion of Pneumocystis to the Host

The trophic form of *Pneumocystis jirovecii* is the key mediator of adhesion, thereby initiating infection and pathogenesis.[24] The initial adhesion to alveolar epithelium presents as close apposition of cell surfaces, with membrane-free fusion and rearrangement of intramembranous particles; simple adhesion alone does not disrupt the epithelial barrier.[25] Msg is a central factor in this process.[26] Msg binds to host extracellular matrix components, such as fibronectin, vitronectin, and mannose residues, to mediate adherence to host cells.[27,28] Moreover, after contacting the epithelium, *Pneumocystis jirovecii* upregulates epithelial α5β1 integrin (a fibronectin-receptor subunit) through post-translational regulation, markedly increasing its surface expression and further stabilizing adhesion.[29] In addition, in a host-matched alveolar environment, adhesion and attachment are reinforced, with pseudopodia thought to participate.[25]

Host Phagocytosis of Pneumocystis

Phagocytosis is a prerequisite for the host's elimination of *Pneumocystis*, primarily mediated by macrophages. The β-glucan on the *Pneumocystis* surface is specifically recognized by Dectin-1, which triggers actin polymerization and internalization to form a phagosome. Within this compartment, a respiratory burst driven by NADPH oxidase generates hydrogen peroxide (H_2O_2), exerting the major microbicidal effect.[30,31] Meanwhile, oxidatively damaged fungal proteins are presumed to enter antigen-processing compartments. Based on canonical MHC class II pathways described in other fungal and inflammatory settings, antigenic peptides could be loaded onto MHC-II molecules following invariant chain (Ii) degradation and HLA-DM–mediated peptide exchange, ultimately enabling presentation to $CD4^+$ T cells.[32] However, the direct involvement of invariant chain and HLA-DM in *Pneumocystis*-specific antigen processing has not yet been experimentally demonstrated.

In terms of signal amplification and compensatory pathways, Dectin-1 signaling induces MIP-2 secretion, recruiting neutrophils. When Dectin-1 is blocked, opsonin-dependent FcγRII/III-mediated phagocytosis can partially compensate.[30] Cytokines such as IL-12, IL-6, IL-21, IL-23, and IL-27 regulate the differentiation of human $CD4^+$ T cells into T follicular helper (Tfh) cells-IL-12 acts via the tyrosine kinase 2-STAT3 axis, whereas the others depend on STAT3-to promote IL-21 secretion by Tfh cells, which in turn supports B-cell production of IgG and IgA.[33]

Complement activation generates iC3b, which covalently deposits on the pathogen surface as an opsonin. Complement receptor 3 (CR3), highly expressed on macrophages and neutrophils, recognizes iC3b and triggers phagocytic clearance, thereby markedly enhancing pathogen elimination.[34,35] In addition, CR3 contains a lectin-like site capable of directly binding fungal β-glucans, which primes the receptor and amplifies subsequent iC3b-mediated effector responses.[36] Activated neutrophils produce H_2O_2 via NADPH oxidase, and myeloperoxidase (MPO) uses H_2O_2 to oxidize chloride, bromide, and thiocyanate ions, generating potent oxidants, mainly hypochlorous acid, along with

hypothiocyanous acid. These oxidants attack methionine and cysteine residues in proteins, as well as lipids and DNA, leading to structural and functional destruction of the pathogen. MPO also serves as a key component of neutrophil extracellular traps (NETs), whose DNA–protein networks capture pathogens and sustain oxidative killing.[37] IFN-γ and GM-CSF enhance the phagocytic activity of alveolar macrophages. IFN-γ promotes macrophage production of reactive nitrogen intermediates (RNI) through a TNF-α–dependent L-arginine pathway, contributing to killing of rodent *Pneumocystis* in experimental models.[38] GM-CSF heightens macrophage responsiveness to stimuli and promotes TNF-α secretion, thereby improving clearance efficiency.[39] Conversely, pulmonary surfactant proteins facilitate immune evasion: SP-D promotes pathogen aggregation and suppresses macrophage phagocytosis, while SP-A interferes with recognition and uptake via its C-type lectin–like domain, both of which impair host clearance.[40,41] Surfactant protein D (SP-D) rapidly accumulates upon pathogen entry, binds the Msg through its carbohydrate recognition domain (CRD), and simultaneously engages macrophage surface molecules to form a pathogen–SP-D–macrophage triad that increases the probability of contact and adhesion; this process does not directly trigger phagocytosis and is independent of the mannose receptor.[42] Thus SP-D primarily provides low-threshold soluble recognition and adhesion enhancement, and conversion of adhesion into uptake and effector killing requires downstream signaling mediated by pattern-recognition receptors (Figure 1).[42]

Host Immune Activation Pathways Mediated by Pneumocystis

Innate Recognition and Signaling

In immunocompetent hosts, innate recognition first limits colonization and determines the direction of the response.[43] The host senses β-glucans exposed on the fungal cell wall to initiate innate immunity, and myeloid cells including macrophages and dendritic cells use C-type lectin receptors to detect pathogen and tissue damage signals, maintaining a dynamic balance between immune activation and pulmonary homeostasis.[43] Under homeostatic conditions, alveolar macrophages are predominantly M2-like, capable of clearing pathogens while avoiding excessive inflammation and thereby preserving barrier function.[44]

In mice, β-1,3-glucan recognition by Dectin-1 recruits and activates spleen tyrosine kinase (Syk) via the hem-immunoreceptor tyrosine-based activation motif, leading to robust ROS production by macrophages and dendritic cells; downstream activation of inflammasome components and Syk/CARD9/BCL10/MALT1/NF-κB-associated cytokine responses has been demonstrated in fungal and β-glucan-based models and is thought to contribute to IL-6, IL-12, IL-23, TNF-α, and IL-10 production in murine *Pneumocystis* infection models.[45,46] IL-23, together with IL-1β, can subsequently drive naïve $CD4^+$ T cells toward Th17 differentiation, indirectly increasing IL-17A levels.[45,46] In a human dendritic cell model, *Pneumocystis* cell wall β-glucan signals through Dectin-1 with activation of Syk and NF-κB and recruitment to lipid rafts, enhancing IL-23 and IL-6 in a dose-dependent manner and, in co-culture with T cells, promoting Th17 differentiation with release of IL-17 and IL-22, thereby validating and extending the above mechanisms.[47] *Pneumocystis* cell wall β-glucan also induces maturation of human dendritic cells and enhances their migratory capacity, upregulating surface CD80, CD86, CD40, and C-C chemokine receptor 7; it increases surface Fas and intracellular cellular FLICE inhibitory protein, improving resistance to Fas-mediated apoptosis.[48] In co-culture with activated T cells, dendritic cell Fas engages Fas ligand on the opposing T cells and partially regulates dendritic cell secretion of IL-1β and TNF-α.[48] Because IL-12 p35 is not induced, dendritic cells cannot produce IL-12 p70; however, with co-stimulation provided by IL-1β together with CD80 and CD86, dendritic cells can still drive naïve $CD4^+$ T cells toward Th1 differentiation under IL-12-independent conditions, and the resulting IFN-γ enhances the ability of alveolar macrophages to clear *Pneumocystis*.[48] Similarly, in murine models of pulmonary Cryptococcus neoformans infection, Notch signaling has been shown to support IFN-γ–producing Th1 responses; however, comparable evidence is currently lacking in *Pneumocystis* infection.[49] Dectin-2, another C-type lectin receptor, can recognize *Pneumocystis* surface components such as Msg and β-glucan, initiating FcRγ-Syk-associated innate signaling that promotes pro-inflammatory cytokine production by alveolar macrophages and participates in the initial host response to *Pneumocystis*, although Dectin-2 is not essential for clearance.[50] Although Msg can bind dendritic cell C-type lectin receptors, macrophage mannose receptor (MMR) and DC-SIGN, through its glycans, *Pneumocystis* lacks key genes for synthesis of high-mannose outer chains so Msg retains only the high-mannose core; this glycosylation defect prevents

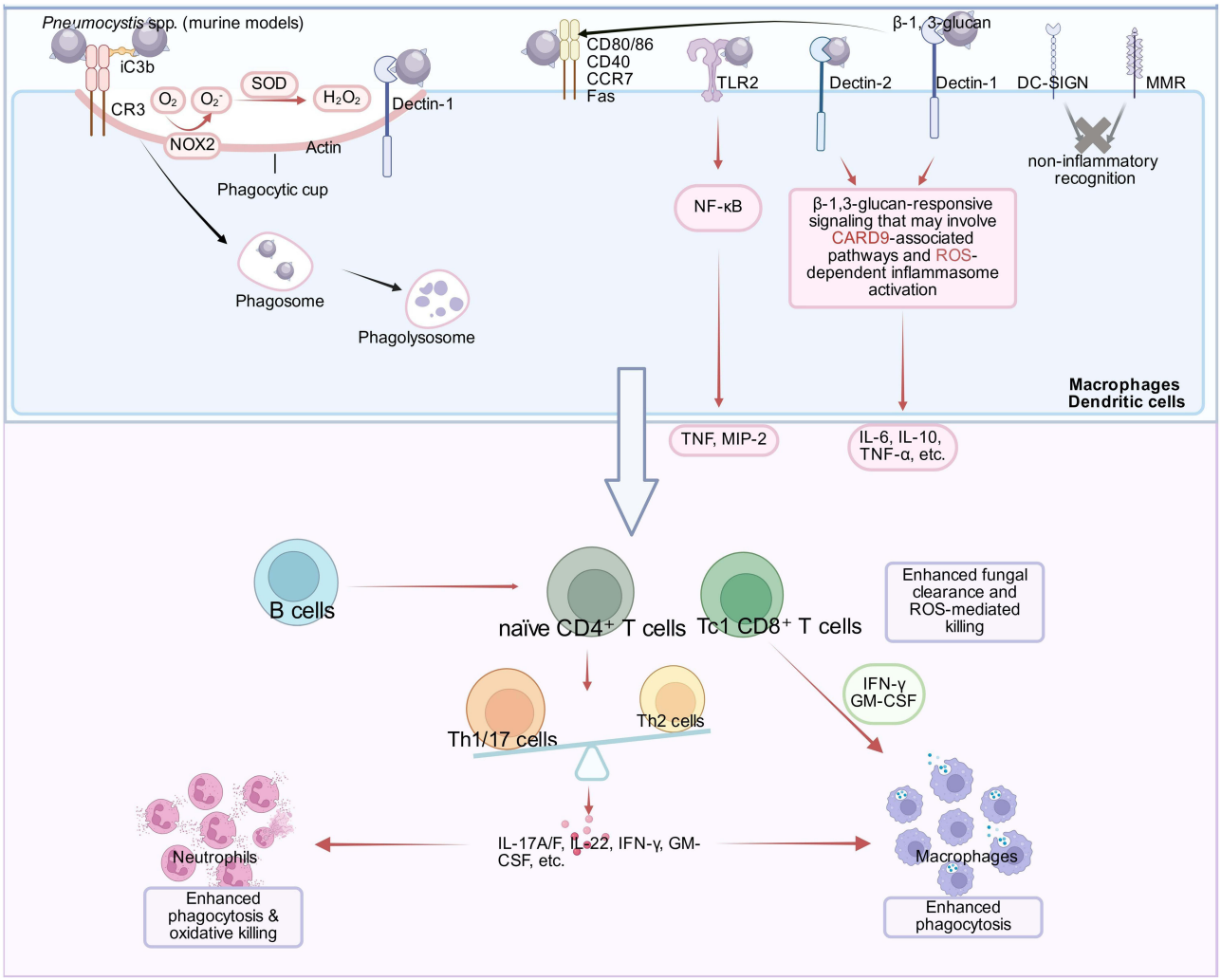

Figure 1 Recognition, phagocytosis, and host immune signaling pathways involved in responses to *Pneumocystis*. This figure was created using BioRender. Red arrows indicate pro-inflammatory or activating pathways; gray arrows represent non-inflammatory recognition pathways; black arrows indicate cellular processes or neutral transitions. β-1,3-glucan exposed on the *Pneumocystis* cell wall serves as a major pathogen associated molecular pattern and is recognized by multiple pattern recognition receptors expressed on macrophages and dendritic cells. Engagement of these receptors promotes actin remodeling during phagocytosis, generation of reactive oxygen species through NADPH oxidase activity, and opsonin dependent uptake mediated by complement receptor 3 following complement deposition. Dectin-2 participates in early innate recognition of *Pneumocystis*, whereas engagement of DC-SIGN or the macrophage mannose receptor is associated with non-inflammatory recognition. β-1,3-glucan can also activate Toll-like receptor 2, leading to induction of pro-inflammatory mediators through NF-κB signaling. Signaling events downstream of β-1,3-glucan recognition receptors involve pathways that include CARD9 and inflammasome activation driven by reactive oxygen species, contributing to the production of pro-inflammatory cytokines. Innate immune activation shapes downstream adaptive immune responses, including differentiation of $CD4^+$ T cells and enhancement of macrophage fungicidal activity by $CD8^+$ T cells. These coordinated innate and adaptive immune mechanisms ultimately contribute to effective clearance of *Pneumocystis*. Most mechanistic insights summarized in this figure are derived from rodent models of *Pneumocystis* species infection. Direct mechanistic validation in human *Pneumocystis jirovecii* infection remains limited because continuous in vitro culture of *Pneumocystis jirovecii* is not currently available.

Abbreviations: CARD9, caspase recruitment domain containing protein 9; CCR7, C-C motif chemokine receptor 7; CD40, cluster of differentiation 40; CR3, complement receptor 3; DC-SIGN, dendritic cell specific intercellular adhesion molecule 3 grabbing non-integrin; Fas, Fas cell surface death receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL-17, interleukin 17; iC3b, inactivated complement component 3b; MIP-2, macrophage inflammatory protein 2; MMR, macrophage mannose receptor; NF-κB, nuclear factor kappa B; NADPH, nicotinamide adenine dinucleotide phosphate; NOX2, NADPH oxidase 2; ROS, reactive oxygen species; SOD, superoxide dismutase; Th17, T helper 17; TLR2, Toll-like receptor 2.

receptor binding from triggering dendritic cell activation, maturation, cytokine secretion, or induction of immune-related genes.[51]

Innate recognition of *Pneumocystis* is not limited to the C-type lectin receptor network. During *Pneumocystis* infection, β-glucan has been shown to bind TLR2 on alveolar macrophages, inducing nuclear translocation of NF-κB p65 and driving the transcription and secretion of proinflammatory mediators such as TNF-α and macrophage inflammatory protein-2 (MIP-2).[52] Beyond this *Pneumocystis*-validated pathway, studies in other fungal and β-glucan-based systems have demonstrated that Dectin-1 and TLR2 can synergistically activate NF-κB to induce IL-10 production. IL-10

https://doi.org/10.2147/JIR.S596115

subsequently suppresses IL-12 and IL-23, restrains Th1 and Th17 polarization, and attenuates β-glucan-triggered ROS and TNF-α production in macrophages, thereby establishing a negative feedback loop on proinflammatory responses.[53] Whether such regulatory circuits operate during *Pneumocystis* infection remains to be directly demonstrated. Similarly, Dectin-1-dependent Ca^{2+}-CaMKII-Pyk2-ERK-CREB signaling has been shown to promote IL-10 production in zymosan-stimulated human macrophages and other fungal models; however, the involvement of this calcium-dependent pathway in *Pneumocystis* infection has not yet been experimentally validated.[54]

β-Glucan is also recognized by epithelial cells; binding of β-glucan to ephrin type-A receptor 2 on alveolar epithelial cells leads to phosphorylation and enhanced IL-6 expression, aggravating local inflammation.[55] In human airway epithelial cells, *Pneumocystis* cell wall β-glucan signals via glycosphingolipid receptors to activate calcium-dependent ERK/p38 mitogen-activated protein kinase (MAPK) pathways, induces NF-κB and activator protein-1 activation, promotes IL-8 secretion, and recruits neutrophils; in earlier studies of rat alveolar epithelial cells, *Pneumocystis* cell wall β-glucan activated NF-κB and induced MIP-2 through the lactosylceramide-protein kinase C axis, and in macrophages β-glucan induced TNF-α via the NF-κB pathway, all of which contribute to amplification of local inflammation.[56,57]

Adaptive Immune Activation and Effector Responses

In adaptive immunity, beyond the T-cell responses driven by the innate pathways above, B-cell–mediated antigen-specific responses provide protection: *Pneumocystis* can directly activate antigen-specific B cells through the B-cell receptor (BCR), enabling early antigen presentation via major histocompatibility complex class II (MHC II) and the delivery of co-stimulatory signals to $CD4^+$ T cells through CD80/CD86-CD28 or CD40-CD40L interactions, thereby promoting their activation and proliferation and helping to initiate effective clearance.[58,59] While naïve $CD4^+$ T cells receive co-stimulatory cues (such as CD80/CD86-CD28), the alarmin IL-33 released from epithelial and other tissue cells upon *Pneumocystis* stimulation first activates group 2 innate lymphoid cells (ILC2) by binding the ST2 receptor (IL1RL1) on ILC2, and activated ILC2 further helps establish a type 2 immune milieu; under these convergent signals, $CD4^+$ T cells differentiate toward Th2 and secrete IL-4, IL-5, and IL-13, which promote eosinophil recruitment, goblet-cell hyperplasia (for example Muc5ac and Clca3), and mucus secretion, ultimately causing airway hyperresponsiveness, reduced lung compliance, and increased airway resistance.[60] As key antigen-presenting cells, dendritic cells present antigen to $CD4^+$ T cells via MHC II and provide co-stimulation through CD80 or CD86 with CD28 and through CD40 with CD40L, driving in the lung a mixed response dominated by Th1 and Th17 with a Th2 component, which strengthens pathogen control yet requires counter-regulation to prevent excessive inflammation.[61]

In humoral immunity, T follicular helper T cells are key regulators of antibody quality and durability. Knowledge of the molecular programs that govern Tfh differentiation and function is largely derived from viral infection models, bacterial infection models, and immunization systems. In these settings, antigen-bearing dendritic cells prime naïve $CD4^+$ T cells in draining lymph nodes and, through co-stimulatory signals mediated by inducible T-cell co-stimulator and its ligand together with phosphoinositide 3-kinase and TANK-binding kinase 1 signaling, induce the expression of B-cell lymphoma 6 while upregulating C-X-C chemokine receptor 5, thereby promoting commitment to the Tfh lineage.[62] Mature Tfh cells, characterized by high CXCR5 expression, respond to C-X-C motif chemokine ligand 13 produced by follicular dendritic cells and localize to B-cell follicles and the light zone of germinal centers, where they provide help through CD40 ligand and inducible T-cell co-stimulator to support B-cell activation, immunoglobulin class switching, and the generation of high-affinity IgA and IgG.[63] Tfh cells are distinct from conventional Th1 and Th2 subsets and represent a specialized effector population dedicated to thymus-dependent antibody responses.[63] To limit excessive humoral activation, $Foxp3^+$ thymus-derived regulatory T-cell precursors can further differentiate into follicular regulatory T cells that co-express B-cell lymphoma 6 and Blimp-1. This population depends on CXCR5 and CXCL13-mediated trafficking to access germinal centers and, supported by CD28 signaling, signaling lymphocytic activation molecule-associated protein, and B-cell-derived differentiation cues, exerts suppressive activity to constrain Tfh cell numbers and restrict non-antigen-specific germinal center B-cell expansion, thereby fine-tuning response magnitude, B-cell selection, and humoral tolerance.[64]

In contrast to these broadly defined regulatory frameworks, *Pneumocystis*-specific $CD8^+$ T-cell effector functions have been directly demonstrated. In immunocompetent mice, in vitro polarized Tc1 $CD8^+$ T cells recognize *Pneumocystis* antigens presented by dendritic cells through major histocompatibility complex class I and release granulocyte-macrophage colony-stimulating factor, which enhances macrophage-mediated fungicidal activity, whereas Tc2 cells lack this protective effect and instead suppress macrophage function (Figure 1).[65]

Immune Evasion by Pneumocystis

Pneumocystis evades immune clearance through multiple mechanisms. The trophic form of *Pneumocystis murina* suppresses dendritic cell proinflammatory responses by downregulating MHC-II, CIITA, and CD40, key molecules involved in antigen presentation and costimulation, thereby weakening the activation of $CD4^+$ T-cell proliferation and the induction of Th1/Th17 responses. Through both soluble factors and direct cell–cell contact, it shapes an immunosuppressive microenvironment that favors pulmonary colonization and immune evasion. In contrast, the cystic form can, to some extent, counteract this inhibitory effect.[66] Although the suppressive phenotype of trophic forms is well documented, the precise molecular mediators responsible for MHC-II and CD40 downregulation remain incompletely defined. Available evidence suggests that this effect is independent of trophic form viability and may involve shed or secreted glycoproteins, such as Msg, rather than a classical protease-driven degradation mechanism. This layered suppression of dendritic cell maturation likely delays effective adaptive immune activation during early infection.[66] By leveraging the diversity of the Msg gene family together with a monoallelic expression strategy, it dynamically switches the Msg variants expressed in the host, thereby escaping T-cell recognition; because $CD4^+$ T cells recognize Msg antigens with high specificity and the amino-acid identity between variants is only 86%-91%, preexisting T cells recognize only portions of variant peptides and cannot effectively respond to substantially altered antigens, resulting in escape from cellular immunity.[67] Studies in rodent *Pneumocystis* models indicate that the pathogen can persist in the host by forming biofilms that hinder macrophage phagocytosis and mask β-glucan and other moieties, thereby reducing host immune recognition.[68] However, whether similar biofilm-like structures exist in human *Pneumocystis jirovecii* infection, and how they are structurally organized in vivo, remain to be fully characterized.

Pathogenesis in HIV-Associated Hosts

Immune Suppression and Impaired Clearance Before ART

In HIV-infected hosts, alveolar macrophages exhibit markedly reduced expression of mannose receptors and impaired phagocytic function.[69] Under immunodeficient conditions, elevated pulmonary SP-A levels may further diminish the clearance capacity of alveolar macrophages through this mechanism, thereby increasing susceptibility to PJP.[41] In HIV-infected hosts, both the number and function of $CD4^+$ T cells decline markedly, local IFN-γ levels fall, alveolar macrophages fail to achieve full activation, and antigen presentation is limited, together weakening immune clearance of *Pneumocystis*. The immune response exhibits a Th2-dominant pattern. In HIV-infected hosts who have not received ART, who have *Pneumocystis* pneumonia, $CD4^+$ T cells are markedly reduced, and the IL-4 rs2243250 TT/TC genotype is associated with an increased risk of infection, suggesting that elevated IL-4 expression and Th2 polarization may suppress IFN-γ- and TNF-α–mediated Th1 responses and impair pathogen clearance. Similar changes have been observed in SHIV-infected nonhuman primate models, where *Pneumocystis* colonization leads to increased levels of IL-4, IL-5, IL-13, IL-6, and GM-CSF, while IFN-γ shows only a transient increase.[70,71]

At the same time, the reduction of $CD4^+$ T cells expressing CD40L deprives B cells of effective help, thereby exacerbating both quantitative B-cell depletion and functional impairment in antigen presentation, further constraining T-cell activation and expansion and creating multiple bottlenecks along the clearance pathway.[72,73] Early in infection, some individuals may exhibit asymptomatic colonization. As CD4+ T-cell counts decline below 200 cells per microliter, the risk of *Pneumocystis* pneumonia increases and clinical disease may develop. In more advanced immunodeficiency, particularly when CD4+ T-cell counts fall below 50 cells per microliter, pathogen burden may rise sharply, accompanied by dysregulated inflammatory responses, including neutrophil infiltration and cytokine imbalance. These processes damage the alveolar epithelium, lead to foamy exudate accumulation and interstitial inflammation, and ultimately disrupt

the air–blood barrier, resulting in hypoxemia and respiratory distress.[74] In HIV-infected hosts who have not received ART, although dendritic cells and macrophages are reduced in number or function, they still detect pathogen-associated molecular patterns and signal through Dectin-1 with Syk and CARD9 to engage NF-κB and mechanistic target of rapamycin complex 1 pathways, inducing a proinflammatory program dominated by IL-12, TNF-α, and IFN-α, together with activation of type I and type II interferon pathways and the complement and coagulation cascades, creating a distinctive state of persistent inflammation with dysregulated metabolism.[75]

Despite $CD4^+$ T-cell impairment, the host can mobilize compensatory clearance pathways. IFN-γ-induced type 1 cytotoxic T cells (Tc1) upregulate C-X-C chemokine receptor 3 (CXCR3) and are recruited via its ligands monokine induced by IFN-γ (Mig; CXCL9), IFN-γ–inducible protein-10 (IP-10; CXCL10), and IFN-inducible T-cell alpha chemoattractant (I-TAC; CXCL11), sustaining IFN-γ release in the lung to enhance macrophage phagocytosis and Dectin-1-linked intracellular killing; in adoptive-transfer models of murine *Pneumocystis* infection, such $CD8^+$ T cells can clear the pathogen independently, partially compensating for CD4 deficiency.[76] Tc1-type $CD8^+$ T cells also secrete granulocyte–macrophage colony-stimulating factor, promote macrophage oxidative burst and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, and upregulate phagocytic receptors such as Dectin-1 and the mannose receptor, further improving microbicidal activity and clearance.[65] In PJP, the CXCR3 axis recruits $CXCR3^+$ Tc1 cells through IP-10, Mig, and I-TAC and drives IFN-γ release; even in the absence of CD4 cells, IP-10 can augment CD8 effector function and accelerate pathogen clearance.[77] However, under conditions of high pathogen burden and profound CD4 deficiency, this compensatory axis often cannot sustain full control on its own, and imbalance between clearance and inflammation progressively emerges (Figure 2).

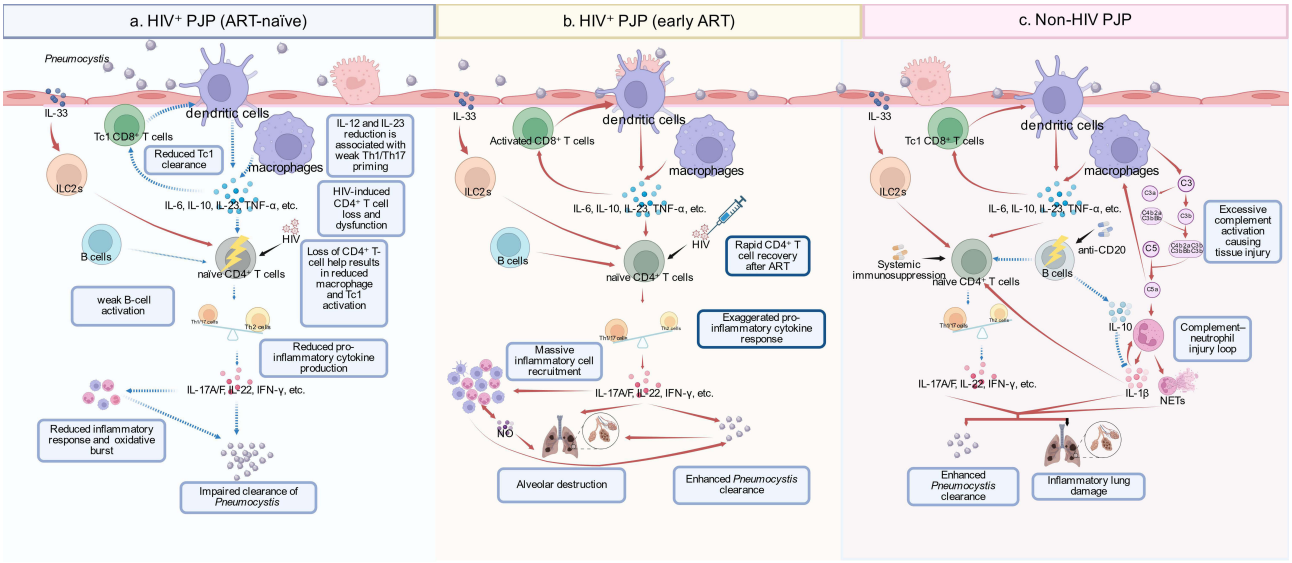

Figure 2 Comparative immunopathogenesis of Pneumocystis pneumonia under different immune conditions. This figure was created using BioRender. Red arrows indicate pro-inflammatory or activating pathways; blue dashed arrows denote reduced, impaired, or suppressive signaling; black arrows indicate cellular processes or neutral transitions. The pathways depicted reflect a synthesis of clinical observations in human PJP and mechanistic insights derived primarily from murine models. The panels schematically summarize distinct immune-response patterns observed in different host contexts: HIV-positive individuals before antiretroviral therapy (ART), HIV-positive individuals during early ART, and immunocompromised individuals without HIV. Left panel: a. HIV^+ PJP (ART-naïve): In untreated HIV infection, profound $CD4^+$ T-cell depletion and dysfunction impair downstream adaptive immune responses. Reduced Th1/Th17-associated cytokine production leads to weakened activation of macrophages and neutrophils, resulting in diminished inflammatory responses and oxidative killing. Consequently, fungal clearance is inefficient, and pathogen burden remains high despite limited tissue inflammation. Middle panel: b. HIV^+ PJP (early ART). Following ART initiation, rapid $CD4^+$ T-cell recovery restores Th1/Th17 responses and enhances proinflammatory cytokine production. During this phase, enhanced fungal clearance is observed and may be accompanied by marked inflammatory-cell recruitment, increased production of nitric oxide and related mediators, and substantial alveolar injury, potentially giving rise to features of immune reconstitution inflammatory syndrome. Right panel: c. Non-HIV PJP. In non-HIV hosts with iatrogenic immunosuppression, particularly those receiving systemic immunosuppressive therapy, susceptibility to PJP reflects heterogeneous defects in adaptive immunity. B-cell, directed therapies, including anti-CD20 antibodies, impair humoral responses, whereas broader immunosuppressive regimens predominantly compromise $CD4^+$ T-cell, mediated immunity. In parallel, heightened complement activation and neutrophil responses may amplify pulmonary inflammation and contribute to lung injury. Although fungal burden is often lower than in HIV-associated PJP, excessive inflammatory responses can lead to diffuse alveolar damage and severe respiratory dysfunction.

Abbreviations: ART, antiretroviral therapy; C3, complement component 3; CD20, cluster of differentiation 20; HIV, human immunodeficiency virus; IFN-γ, interferon gamma; IL-33, interleukin 33; ILC2, group 2 innate lymphoid cells; NETs, neutrophil extracellular traps; NO, nitric oxide; PJP, *Pneumocystis jirovecii* pneumonia; Tc1, type 1 cytotoxic T cells; Th17, T helper 17; TNF-α, tumor necrosis factor alpha.

Immune Reconstitution and Inflammatory Injury After ART

In the setting of immunosuppression, impaired clearance and amplified inflammation progress in parallel, whereas rapid CD4 reconstitution after initiation of ART can precipitate immune reconstitution inflammatory syndrome (IRIS).[44] The syndrome may occur during initial initiation of ART, following re-initiation of ART, or after switching to a more effective regimen in patients who previously failed to achieve adequate viral suppression.[78–80] After ART initiation, IRIS may manifest in two distinct clinical forms: first, as worsening inflammatory responses of a previously diagnosed and treated opportunistic infection, termed paradoxical IRIS; and second, as the emergence of a previously subclinical and unrecognized infection following immune recovery, often accompanied by a pronounced inflammatory phenotype, termed unmasking IRIS.[81] Characterized by the reactivation of Th1 and Th17 responses, this phase features excessive release of proinflammatory cytokines, leading to concomitant alveolar injury and fungal clearance.[82] Animal studies show that after transfer of $CD4^+$ T cells into severely immunodeficient hosts, these cells become pathogen antigen specific in the lung, produce IFN-γ, and strongly activate alveolar macrophages, with concurrent worsening of macrophage hyperactivation and alveolar edema and marked increases in mediators such as TNF-α and IL-2.[83] TNF-α induces endothelial intercellular adhesion molecule-1 (ICAM-1) expression, promotes recruitment of neutrophils and monocytes into the lung interstitium, and exerts direct toxicity on alveolar epithelium, disrupting the air–blood barrier and fluid homeostasis and thereby aggravating edema.[84] IL-2 drives clonal expansion of T cells and increases microvascular permeability, which amplifies exudation and impairs diffusion.[85,86] In murine models, IFN-γ enhances the microbicidal capacity of alveolar macrophages and, via activation of the Janus kinase–signal transducer and activator of transcription pathway, induces inducible nitric oxide (NO) synthase transcription to catalyze L-arginine into excess NO.[87] Excess NO promotes nonenzymatic S-nitrosylation of SP-D at Cys15 and Cys20 to generate SNO-SP-D, which disrupts the dodecameric structure and causes depolymerization into monomers or trimers; depolymerized SNO-SP-D engages the calreticulin (CRT)/low-density lipoprotein receptor-related protein 1 receptor complex to activate the macrophage p38 MAPK pathway, thereby promoting macrophage chemotaxis and recruitment of inflammatory cells.[87] However, its applicability in humans remains uncertain, as human alveolar macrophages do not consistently generate high output nitric oxide.[88] Therefore, in human *Pneumocystis* pneumonia, host defense may rely less on nitric oxide mediated antimicrobial pathways and more on reactive oxygen species and downstream reactive nitrogen intermediates generated through oxidative burst mechanisms potentially driven by NADPH oxidase, although their specific roles in *Pneumocystis* infection remain to be further elucidated.[89] For $CD8^+$ T cells, if a non-Tc1 phenotype predominates, adoptive transfer can trigger Fas ligand-mediated apoptosis that perturbs alveolar surfactant homeostasis and increases capillary permeability, leading to elevated lactate dehydrogenase and total protein in bronchoalveolar lavage fluid, greater exudates and fibrinous material histologically, and further impairment of lung function.[76] *Pneumocystis* infection and inflammation also reduce SP-B, weakening regulation of alveolar surface tension. Experimental SP-B deficiency models demonstrate that increased minimal surface tension directly impairs lung compliance and promotes alveolar collapse, providing a mechanistic basis for the stiff lung physiology observed in PJP-related ARDS. Meanwhile, the proinflammatory effect of SNO-SP-D further exacerbates alveolar edema, forming a vicious cycle of SP-B loss, inflammatory surfactant dysfunction, and escalating lung injury (Figure 2).[87,90]

Impairment of the B-Cell Axis and Mechanisms of Susceptibility in Non-HIV Immunocompromised Hosts

Non-HIV immunocompromised hosts often have underlying conditions and receive immune-targeted therapies that reduce B-cell number and function, thereby diminishing humoral immunity and B-cell–dependent antigen presentation. B-cell defects markedly increase susceptibility to *Pneumocystis carinii* infection in mouse models, indicating that B cells and humoral immunity are essential components of defense against this pathogen.[91] The widely used anti-CD20 monoclonal antibody rituximab targets pre-B, mature B, and memory B cells without affecting hematopoietic stem cells or terminally differentiated plasma cells; after administration, near-complete depletion of peripheral B cells occurs by about 72 hours, the depleted state usually persists for 2 to 6 months, and peripheral B-cell reconstitution typically appears at approximately 12 months after monotherapy and gradually returns toward baseline.[92,93] The resulting decline

in humoral immunity is associated with secondary immunodeficiency and increased susceptibility to this pathogen, so in populations with hematologic malignancies and autoimmune diseases, the relationship between use of rituximab and infection risk remains a continuing concern.[94] Corticosteroids are often given concurrently with or alternated with these therapies, and they significantly downregulate B-cell–related genes such as CD19, CD20, and Tnfrsf13c in lung tissue and peripheral blood in mice and patient samples, reduce B-cell numbers including CD79b-positive and BAFF-R–positive subsets, simultaneously suppress innate and adaptive immunity, further weaken B-cell–mediated antimicrobial responses, and increase susceptibility.[95]

Impairment of the B-cell axis not only weakens antibody- and complement-mediated opsonization but also disrupts key conduits linking innate and adaptive immunity.[59] Through CD40-CD40L interactions, B cells contribute to control of murine *Pneumocystis* infection and, as professional antigen-presenting cells, support CD4 T-cell proliferation via MHC II–dependent antigen presentation.[59] This process depends on B-cell expression of MHC II to drive effector CD4 T-cell trafficking to the lung and the establishment of protective memory, culminating in clearance; when B cells are absent or lack MHC II, CD4 T cells can be primed but fail to undergo effective pulmonary recruitment and memory formation, resulting in loss of infection control.[96] Therapeutic B-cell depletion also reshapes the magnitude and quality of CD4 responses; with dendritic-cell involvement, anti-CD20 treatment selectively suppresses antigen-specific CD4 T-cell activation, clonal expansion, and effector differentiation, reflected by reduced IL-2 and IFN-γ secretion, while exerting relatively limited effects on CD8 T-cell function.[97] Notably, in some primary B-cell disorders such as X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID), reported rates of *Pneumocystis jirovecii* pneumonia are low, suggesting the existence of B-cell–independent pathways for CD4 activation under specific host and exposure contexts, which delineates the bounds and references for mechanistic interpretation.[98]

In HIV-negative immunocompromised hosts with PJP, an increased proportion of Th1 cells has been observed in the lungs.[99] In the context of amplified inflammation, hosts pretreated with corticosteroids or with impaired immune axes are more prone to a complement- and granulocyte-driven injury loop: during infection, alveolar macrophages synthesize large amounts of C3, whose cleavage generates C3b to promote formation of C5 convertase and subsequent C5a, thereby increasing endothelial permeability, stimulating macrophages and epithelial cells to release proinflammatory cytokines, and upregulating endothelial ICAM-1 to facilitate neutrophil adhesion and transmigration, which aggravates alveolitis and tissue damage.[100] Pathogen-associated stimuli can also activate the NLRP3 inflammasome in neutrophils, driving caspase-1–dependent maturation of IL-1β, while peptidylarginine deiminase 4 (PAD4)–mediated chromatin decondensation triggers NET-mediated cell death (NETosis) with release of extracellular traps enriched in elastase and myeloperoxidase; PAD4 forms a positive feedback with NLRP3 to sustain IL-1β production and amplify inflammation.[101] Conversely, B cells provide important immunoregulation and hematopoietic support: in type I interferon–deficient mouse models, B cells help maintain hematopoietic progenitor activity partly via their own IL-10 and by inducing IL-10 from other cells, and IL-10 modulates the number and differentiation of mature neutrophils, indicating that B-cell populations, including regulatory B cells, can participate in post-infection hematopoietic protection and immune regulation through IL-10.[102] In tumor settings, adoptively transferred regulatory B cells can suppress macrophage activation via IL-10, thereby weakening the antitumor effect of anti-CD20 antibodies, underscoring the strong anti-inflammatory capacity of regulatory B cells and their impact when B-cell depletion coincides with heightened infection risk.[103] Clinical and basic studies further show that regulatory B cells often decline in frequency or function in systemic lupus erythematosus and rheumatoid arthritis, whereas in cancer and chronic infection their suppressive phenotype may be remodeled and linked to immune evasion.[104] In PJP, IL-10–producing regulatory B cells can suppress the proinflammatory cytokine IL-1β, thereby limiting excessive activation and proliferation of Th1 and Th17 cells, reducing tissue injury, and maintaining an immune balance favorable for pathogen clearance; when B-cell maturation is impaired—such as with BAFF-R deficiency leading to reduced regulatory B cells—this regulatory mechanism is compromised and pathology worsens.[105] Together, these factors in non-HIV PJP yield a pattern of low pathogen burden but reduced clearance efficiency, exacerbated lung injury, a potential for fulminant course, and high mortality (Figure 2).[106–108]

Future Perspectives

Despite significant advances in understanding the immunopathogenesis of *Pneumocystis* pneumonia, several critical knowledge gaps remain. Future studies should prioritize defining the molecular mechanisms by which distinct *Pneumocystis* life cycle stages modulate antigen-presenting cell function and host immune responses, particularly in human-relevant systems. Improved experimental models and access to human lung-derived samples will be essential to clarify species-specific differences in macrophage effector pathways, immune reconstitution dynamics, and surfactant dysfunction.

Conclusion

In recent years, *Pneumocystis* pneumonia has become increasingly recognized among non-HIV immunocompromised hosts, particularly in immunocompromised populations. Host immune context strongly shapes disease phenotype. In HIV-infected hosts, profound CD4 T-cell deficiency is associated with high fungal burden and impaired clearance, and IRIS may occur after initiation of ART, especially in those with advanced immunodeficiency. In contrast, in non-HIV immunocompromised hosts, *Pneumocystis* pneumonia arises in the setting of multiple forms of immunosuppression, including but not limited to anti-CD20 antibody therapy, high-dose corticosteroid use, and other immunomodulatory or cytotoxic treatments. Depending on the underlying cause, these conditions may involve impaired B-cell function and antigen presentation in some patients, together with exaggerated complement and neutrophil responses, and more often lead to a low-burden but highly inflammatory pattern that can progress to acute respiratory distress syndrome. These differences highlight the need for risk-stratified monitoring, appropriate prophylaxis, and immune-informed clinical strategies to improve outcomes in vulnerable populations.

Data Sharing Statement

No new data were generated or analyzed in this study.

Author Contributions

Yu Wang: Conceptualization; Methodology; Investigation; Writing-Original Draft; Visualization; Caopei Zheng: Investigation; Writing-Original Draft; Yuqing Sun: Investigation; Writing-Original Draft; Yulin Zhang: Supervision; Project Administration; Funding Acquisition; Conceptualization; Writing-Review & Editing. All authors have agreed on the final version of the article for publication, have agreed on the journal to which the paper is submitted, and have agreed to be accountable for the work published.

Funding

This review is supported by Beijing Research Ward Excellence Program (BRWEP2024W042180101).

Disclosure

The authors report no conflicts of interest in this work.

References

1. White PL, Backx M, Barnes RA. Diagnosis and management of *Pneumocystis jirovecii* infection. *Expert Rev Anti Infect Ther*. 2017;15(5):435–447. doi:10.1080/14787210.2017.1305887
2. Pulsipher AM, Vikram HR, Gotway MB, et al. An observational analysis of a large cohort of *Pneumocystis jirovecii* pneumonia. *Open Forum Infect Dis*. 2025;12(7):ofaf390. doi:10.1093/ofid/ofaf390
3. Kao TW, Ruan SY, Huang YT, et al. Evolving risk factors and predisposing conditions of Pneumocystis pneumonia in non-HIV patients: a seven-year multicenter study. *J Infect*. 2025;91(3):106592. doi:10.1016/j.jinf.2025.106592
4. Fujioka H, Matsui H, Homma Y, et al. Association of time-to-treatment with prognosis in pneumocystis pneumonia among immunocompromised patients without HIV infection: a multi-center, retrospective observational cohort study. *BMC Infect Dis*. 2025;25(1):531. doi:10.1186/s12879-025-10933-3
5. Wang D, Guan L, Li X, Tong Z. A combined immune and inflammatory indicator predict the prognosis of severe *Pneumocystis jirovecii* pneumonia patients: a 12-year, retrospective, observational cohort. *BMC Pulm Med*. 2024;24(1):285. doi:10.1186/s12890-024-03093-8

6. Li X, Guan L, Wang D, et al. Comparative dosing of adjunctive corticosteroids therapy for pneumocystis pneumonia with ARDS in non-HIV immunocompromised patients. *Infect Drug Resist*. 2024;17:5545–5555. doi:10.2147/idr.S493298
7. Park JW, Curtis JR, Jun KI, et al. Primary prophylaxis for *Pneumocystis jirovecii* pneumonia in patients receiving rituximab. *Chest*. 2022;161 (5):1201–1210. doi:10.1016/j.chest.2021.11.007
8. Xue T, Ma Z, Liu F, et al. *Pneumocystis jirovecii* colonization and its association with pulmonary diseases: a multicenter study based on a modified loop-mediated isothermal amplification assay. *BMC Pulm Med*. 2020;20(1):70. doi:10.1186/s12890-020-1111-4
9. Pifer LL, Hughes WT, Stagno S, Woods D. Pneumocystis carinii infection: evidence for high prevalence in normal and immunosuppressed children. *Pediatrics*. 1978;61(1):35–41. doi:10.1542/peds.61.1.35
10. Morris A, Norris KA. Colonization by *Pneumocystis jirovecii* and its role in disease. *Clin Microbiol Rev*. 2012;25(2):297–317. doi:10.1128/cmr.00013-12
11. Keely SP, Baughman RP, Smulian AG, Dohn MN, Stringer JR. Source of Pneumocystis carinii in recurrent episodes of pneumonia in AIDS patients. *Aids*. 1996;10(8):881–888. doi:10.1097/00002030-199607000-00011
12. Schmoldt S, Schuhegger R, Wendler T, et al. Molecular evidence of nosocomial *Pneumocystis jirovecii* transmission among 16 patients after kidney transplantation. *J Clin Microbiol*. 2008;46(3):966–971. doi:10.1128/jcm.02016-07
13. Charpentier E, Garnaud C, Wintenberger C, et al. Added value of next-generation sequencing for multilocus sequence typing analysis of a *Pneumocystis jirovecii* pneumonia outbreak1. *Emerg Infect Dis*. 2017;23(8):1237–1245. doi:10.3201/eid2308.161295
14. Martinez A, Halliez MC, Aliouat M, et al. Growth and airborne transmission of cell-sorted life cycle stages of Pneumocystis carinii. *PLoS One*. 2013;8(11):e79958. doi:10.1371/journal.pone.0079958
15. Nahimana A, Rabodonirina M, Bille J, Francioli P, Hauser PM. Mutations of *Pneumocystis jirovecii* dihydrofolate reductase associated with failure of prophylaxis. *Antimicrob Agents Chemother*. 2004;48(11):4301–4305. doi:10.1128/aac.48.11.4301-4305.2004
16. Luraschi A, Cissé OH, Monod M, Pagni M, Hauser PM. Functional characterization of the *Pneumocystis jirovecii* potential drug targets dhfs and abz2 involved in folate biosynthesis. *Antimicrob Agents Chemother*. 2015;59(5):2560–2566. doi:10.1128/aac.05092-14
17. Nev OA, Zamaraeva E, De Oliveira R, et al. Metabolic modelling as a powerful tool to identify critical components of Pneumocystis growth medium. *PLoS Comput Biol*. 2024;20(10):e1012545. doi:10.1371/journal.pcbi.1012545
18. Kutty G, Davis AS, Ma L, Taubenberger JK, Kovacs JA. Pneumocystis encodes a functional endo-β-1,3-glucanase that is expressed exclusively in cysts. *J Infect Dis*. 2015;211(5):719–728. doi:10.1093/infdis/jiu517
19. Li J, Liu H, Li J, et al. Cryo-EM structure of the β-1,3-glucan synthase FKS1-Rho1 complex. *Nat Commun*. 2025;16(1):2054. doi:10.1038/s41467-025-57152-7
20. Kaneshiro ES. Sterol biosynthesis in Pneumocystis: unique steps that define unique targets. *Drug Resist Updat*. 2002;5(6):259–268. doi:10.1016/s1368-7646(02)00122-x
21. Thomas CF, Limper AH. Pneumocystis pneumonia. *N Engl J Med*. 2004;350(24):2487–2498. doi:10.1056/NEJMra032588
22. Kaneshiro ES, Amit Z, Chandra J, Baughman RP, Contini C, Lundgren B. Sterols of Pneumocystis carinii hominis organisms isolated from human lungs. *Clin Diagn Lab Immunol*. 1999;6(6):970–976. doi:10.1128/cdli.6.6.970-976.1999
23. Cissé OH, Pagni M, Hauser PM. Comparative genomics suggests that the human pathogenic fungus *Pneumocystis jirovecii* acquired obligate biotrophy through gene loss. *Genome Biol Evol*. 2014;6(8):1938–1948. doi:10.1093/gbe/evu155
24. Catherinot E, Lanternier F, Bougnoux ME, Lecuit M, Couderc LJ, Lortholary O. *Pneumocystis jirovecii* Pneumonia. *Infect Dis Clin North Am*. 2010;24(1):107–138. doi:10.1016/j.idc.2009.10.010
25. Aliouat-Denis CM, Chabé M, Demanche C, et al. Pneumocystis species, co-evolution and pathogenic power. *Infect Genet Evol*. 2008;8 (5):708–726. doi:10.1016/j.meegid.2008.05.001
26. Kutty G, England KJ, Kovacs JA. Expression of *Pneumocystis jirovecii* major surface glycoprotein in Saccharomyces cerevisiae. *J Infect Dis*. 2013;208(1):170–179. doi:10.1093/infdis/jit131
27. Pottratz ST, Paulsrud J, Smith JS, Martin WJ. Pneumocystis carinii attachment to cultured lung cells by pneumocystis gp 120, a fibronectin binding protein. *J Clin Invest*. 1991;88(2):403–407. doi:10.1172/jci115318
28. Limper AH, Pottratz ST, Martin WJ. Modulation of Pneumocystis carinii adherence to cultured lung cells by a mannose-dependent mechanism. *J Lab Clin Med*. 1991;118(5):492–499.
29. Pottratz ST, Weir AL, Wisniowski PE. Pneumocystis carinii attachment increases expression of fibronectin-binding integrins on cultured lung cells. *Infect Immun*. 1994;62(12):5464–5469. doi:10.1128/iai.62.12.5464-5469.1994
30. Steele C, Marrero L, Swain S, et al. Alveolar macrophage-mediated killing of Pneumocystis carinii f. sp. muris involves molecular recognition by the Dectin-1 beta-glucan receptor. *J Exp Med*. 2003;198(11):1677–1688. doi:10.1084/jem.20030932
31. Brown GD, Taylor PR, Reid DM, et al. Dectin-1 is a major beta-glucan receptor on macrophages. *J Exp Med*. 2002;196(3):407–412. doi:10.1084/jem.20020470
32. Roche PA, Furuta K. The ins and outs of MHC class II-mediated antigen processing and presentation. *Nat Rev Immunol*. 2015;15(4):203–216. doi:10.1038/nri3818
33. Ma CS, Avery DT, Chan A, et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. *Blood*. 2012;119 (17):3997–4008. doi:10.1182/blood-2011-11-392985
34. Fernández FJ, Santos-López J, Martínez-Barricarte R, et al. The crystal structure of iC3b-CR3 αI reveals a modular recognition of the main opsonin iC3b by the CR3 integrin receptor. *Nat Commun*. 2022;13(1):1955. doi:10.1038/s41467-022-29580-2
35. Wells J, Haidaris CG, Wright TW, Gigliotti F. Complement and Fc function are required for optimal antibody prophylaxis against Pneumocystis carinii pneumonia. *Infect Immun*. 2006;74(1):390–393. doi:10.1128/iai.74.1.390-393.2006
36. Vetvicka V, Thornton BP, Ross GD. Soluble beta-glucan polysaccharide binding to the lectin site of neutrophil or natural killer cell complement receptor type 3 (CD11b/CD18) generates a primed state of the receptor capable of mediating cytotoxicity of iC3b-opsonized target cells. *J Clin Invest*. 1996;98(1):50–61. doi:10.1172/jci118777
37. Lin W, Chen H, Chen X, Guo C. The roles of neutrophil-derived myeloperoxidase (MPO) in diseases: the new progress. *Antioxidants*. 2024;13 (1):132. doi:10.3390/antiox13010132
38. Downing JF, Kachel DL, Pasula R, Martin WJ. Gamma interferon stimulates rat alveolar macrophages to kill Pneumocystis carinii by L-arginine- and tumor necrosis factor-dependent mechanisms. *Infect Immun*. 1999;67(3):1347–1352. doi:10.1128/iai.67.3.1347-1352.1999

39. Mandujano JF, D'Souza NB, Nelson S, Summer WR, Beckerman RC, Shellito JE. Granulocyte-macrophage colony stimulating factor and Pneumocystis carinii pneumonia in mice. *Am J Respir Crit Care Med*. 1995;151(4):1233–1238. doi:10.1164/ajrccm/151.4.1233
40. Yong SJ, Vuk-Pavlovic Z, Standing JE, Crouch EC, Limper AH. Surfactant protein D-mediated aggregation of Pneumocystis carinii impairs phagocytosis by alveolar macrophages. *Infect Immun*. 2003;71(4):1662–1671. doi:10.1128/iai.71.4.1662-1671.2003
41. Koziel H, Phelps DS, Fishman JA, Armstrong MY, Richards FF, Rose RM. Surfactant protein-A reduces binding and phagocytosis of pneumocystis carinii by human alveolar macrophages in vitro. *Am J Respir Cell Mol Biol*. 1998;18(6):834–843. doi:10.1165/ajrcmb.18.6.3059
42. O'Riordan DM, Standing JE, Kwon KY, Chang D, Crouch EC, Limper AH. Surfactant protein D interacts with Pneumocystis carinii and mediates organism adherence to alveolar macrophages. *J Clin Invest*. 1995;95(6):2699–2710. doi:10.1172/jci117972
43. Sancho D, Reis e Sousa C. Signaling by myeloid C-type lectin receptors in immunity and homeostasis. *Annu Rev Immunol*. 2012;30 (1):491–529. doi:10.1146/annurev-immunol-031210-101352
44. Charpentier E, Ménard S, Marques C, Berry A, Iriart X. Immune response in pneumocystis infections according to the host immune system status. *J Fungi*. 2021;7(8):625. doi:10.3390/jof7080625
45. Saijo S, Fujikado N, Furuta T, et al. Dectin-1 is required for host defense against Pneumocystis carinii but not against Candida albicans. *Nat Immunol*. 2007;8(1):39–46. doi:10.1038/ni1425
46. Saijo S, Iwakura Y. Dectin-1 and Dectin-2 in innate immunity against fungi. *Int Immunol*. 2011;23(8):467–472. doi:10.1093/intimm/dxr046
47. Carmona EM, Kottom TJ, Hebrink DM, et al. Glycosphingolipids mediate pneumocystis cell wall β-glucan activation of the IL-23/IL-17 axis in human dendritic cells. *Am J Respir Cell Mol Biol*. 2012;47(1):50–59. doi:10.1165/rcmb.2011-0159OC
48. Carmona EM, Vassallo R, Vuk-Pavlovic Z, Standing JE, Kottom TJ, Limper AH. Pneumocystis cell wall beta-glucans induce dendritic cell costimulatory molecule expression and inflammatory activation through a Fas-Fas ligand mechanism. *J Immunol*. 2006;177(1):459–467. doi:10.4049/jimmunol.177.1.459
49. Neal LM, Qiu Y, Chung J, et al. T cell-restricted notch signaling contributes to pulmonary Th1 and Th2 immunity during cryptococcus neoformans infection. *J Immunol*. 2017;199(2):643–655. doi:10.4049/jimmunol.1601715
50. Kottom TJ, Hebrink DM, Jenson PE, et al. Dectin-2 is a C-type lectin receptor that recognizes pneumocystis and participates in innate immune responses. *Am J Respir Cell Mol Biol*. 2018;58(2):232–240. doi:10.1165/rcmb.2016-0335OC
51. Sassi M, Kutty G, Ferreyra GA, et al. The major surface glycoprotein of *Pneumocystis murina* does not activate dendritic cells. *J Infect Dis*. 2018;218(10):1631–1640. doi:10.1093/infdis/jiy342
52. Zhang C, Wang SH, Lasbury ME, et al. Toll-like receptor 2 mediates alveolar macrophage response to *Pneumocystis murina*. *Infect Immun*. 2006;74(3):1857–1864. doi:10.1128/iai.74.3.1857-1864.2006
53. Desamero MJM, Chung SH, Kakuta S. Insights on the functional role of beta-glucans in fungal immunity using receptor-deficient mouse models. *Int J Mol Sci*. 2021;22(9):4778. doi:10.3390/ijms22094778
54. Kelly EK, Wang L, Ivashkiv LB. Calcium-activated pathways and oxidative burst mediate zymosan-induced signaling and IL-10 production in human macrophages. *J Immunol*. 2010;184(10):5545–5552. doi:10.4049/jimmunol.0901293
55. Kottom TJ, Schaefbauer K, Carmona EM, Limper AH. EphA2 is a lung epithelial cell receptor for Pneumocystis β-glucans. *J Infect Dis*. 2022;225(3):525–530. doi:10.1093/infdis/jiab384
56. Carmona EM, Lamont JD, Xue A, Wylam M, Limper AH. Pneumocystis cell wall beta-glucan stimulates calcium-dependent signaling of IL-8 secretion by human airway epithelial cells. *Respir Res*. 2010;11(1):95. doi:10.1186/1465-9921-11-95
57. Evans SE, Hahn PY, McCann F, Kottom TJ, Pavlovic ZV, Limper AH. Pneumocystis cell wall beta-glucans stimulate alveolar epithelial cell chemokine generation through nuclear factor-kappaB-dependent mechanisms. *Am J Respir Cell Mol Biol*. 2005;32(6):490–497. doi:10.1165/rcmb.2004-0300OC
58. Opata MM, Hollifield ML, Lund FE, et al. B lymphocytes are required during the early priming of CD4+ T cells for clearance of pneumocystis infection in mice. *J Immunol*. 2015;195(2):611–620. doi:10.4049/jimmunol.1500112
59. Sassi M, Curran SJ, Bishop LR, Liu Y, Kovacs JA. CD40 expression by B cells is required for optimal immunity to murine pneumocystis infection. *J Infect Dis*. 2024;230(4):1033–1041. doi:10.1093/infdis/jiae133
60. Eddens T, Campfield BT, Serody K, et al. A novel CD4(+) T cell-dependent murine model of pneumocystis-driven asthma-like pathology. *Am J Respir Crit Care Med*. 2016;194(7):807–820. doi:10.1164/rccm.201511-2205OC
61. Swain SD, Meissner N, Han S, Harmsen A. Pneumocystis infection in an immunocompetent host can promote collateral sensitization to respiratory antigens. *Infect Immun*. 2011;79(5):1905–1914. doi:10.1128/iai.01273-10
62. Wikenheiser DJ, Stumhofer JS. ICOS Co-stimulation: friend or foe? *Front Immunol*. 2016;7:304. doi:10.3389/fimmu.2016.00304
63. Breitfeld D, Ohl L, Kremmer E, et al. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J Exp Med*. 2000;192(11):1545–1552. doi:10.1084/jem.192.11.1545
64. Linterman MA, Pierson W, Lee SK, et al. Foxp3+ follicular regulatory T cells control the germinal center response. *Nat Med*. 2011;17 (8):975–982. doi:10.1038/nm.2425
65. McAllister F, Steele C, Zheng M, Shellito JE, Kolls JK. In vitro effector activity of *Pneumocystis murina*-specific T-cytotoxic-1 CD8+ T cells: role of granulocyte-macrophage colony-stimulating factor. *Infect Immun*. 2005;73(11):7450–7457. doi:10.1128/iai.73.11.7450-7457.2005
66. Evans HM, Simpson A, Shen S, Stromberg AJ, Pickett CL, Garvy BA. The trophic life cycle stage of the opportunistic fungal pathogen *Pneumocystis murina* hinders the ability of dendritic cells to stimulate CD4(+) T cell responses. *Infect Immun*. 2017;85(10). doi:10.1128/iai.00396-17
67. Bishop LR, Helman D, Kovacs JA. Discordant antibody and cellular responses to Pneumocystis major surface glycoprotein variants in mice. *BMC Immunol*. 2012;13(1):39. doi:10.1186/1471-2172-13-39
68. Cushion MT, Collins MS, Linke MJ. Biofilm formation by *Pneumocystis spp*. *Eukaryot Cell*. 2009;8(2):197–206. doi:10.1128/ec.00202-08
69. Koziel H, Eichbaum Q, Kruskal BA, et al. Reduced binding and phagocytosis of Pneumocystis carinii by alveolar macrophages from persons infected with HIV-1 correlates with mannose receptor downregulation. *J Clin Invest*. 1998;102(7):1332–1344. doi:10.1172/jci560
70. Wójtowicz A, Bibert S, Taffé P, et al. IL-4 polymorphism influences susceptibility to *Pneumocystis jirovecii* pneumonia in HIV-positive patients. *Aids*. 2019;33(11):1719–1727. doi:10.1097/qad.0000000000002283
71. Shipley TW, Kling HM, Morris A, et al. Persistent pneumocystis colonization leads to the development of chronic obstructive pulmonary disease in a nonhuman primate model of AIDS. *J Infect Dis*. 2010;202(2):302–312. doi:10.1086/653485

72. Swain SD, Siemsen DW, Pullen RR, Han S. CD4+ T cells and IFN-γ are required for the development of Pneumocystis-associated pulmonary hypertension. *Am J Pathol*. 2014;184(2):483–493. doi:10.1016/j.ajpath.2013.10.027
73. Kornbluth RS. The emerging role of CD40 ligand in HIV infection. *J Leukoc Biol*. 2000;68(3):373–382. doi:10.1189/jlb.68.3.373
74. Siegel M, Masur H, Kovacs J. *Pneumocystis jirovecii* pneumonia in human immunodeficiency virus infection. *Semin Respir Crit Care Med*. 2016;37(2):243–256. doi:10.1055/s-0036-1579556
75. Kumar A, Wang J, Esterly A, et al. Dectin-1 stimulation promotes a distinct inflammatory signature in the setting of HIV-infection and aging. *Aging*. 2023;15(16):7866–7908. doi:10.18632/aging.204927
76. McAllister F, Steele C, Zheng M, et al. T cytotoxic-1 CD8+ T cells are effector cells against pneumocystis in mice. *J Immunol*. 2004;172 (2):1132–1138. doi:10.4049/jimmunol.172.2.1132
77. McAllister F, Ruan S, Steele C, et al. CXCR3 and IFN protein-10 in Pneumocystis pneumonia. *J Immunol*. 2006;177(3):1846–1854. doi:10.4049/jimmunol.177.3.1846
78. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. 2004;39(11):1709–1712. doi:10.1086/425742
79. Shelburne SA, Darcourt J, White AC, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40(7):1049–1052. doi:10.1086/428618
80. Brust JCM, McGowan JP, Fine SM, et al. Management of IRIS. New York State department of health AIDS institute clinical guidelines program. 2024. Available from: https://www.hivguidelines.org. Accessed March 8, 2026.
81. Schregenberger S, Graup V, Schibli A, et al. Immune reconstitution inflammatory syndrome (IRIS): case series and review of the literature. *Respiratory Med Case Reports*. 2025;55:102213. doi:10.1016/j.rmcr.2025.102213
82. Dellière S, Guery R, Candon S, et al. Understanding pathogenesis and care challenges of immune reconstitution inflammatory syndrome in fungal infections. *J Fungi*. 2018;4(4). doi:10.3390/jof4040139
83. Roths JB, Sidman CL. Both immunity and hyperresponsiveness to Pneumocystis carinii result from transfer of CD4+ but not CD8+ T cells into severe combined immunodeficiency mice. *J Clin Invest*. 1992;90(2):673–678. doi:10.1172/jci115910
84. Javaid K, Rahman A, Anwar KN, Frey RS, Minshall RD, Malik AB. Tumor necrosis factor-alpha induces early-onset endothelial adhesivity by protein kinase Czeta-dependent activation of intercellular adhesion molecule-1. *Circ Res*. 2003;92(10):1089–1097. doi:10.1161/01.Res.0000072971.88704.Cb
85. Huh D, Leslie DC, Matthews BD, et al. A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. *Sci Transl Med*. 2012;4(159):159ra147. doi:10.1126/scitranslmed.3004249
86. Cantrell DA, Smith KA. The interleukin-2 T-cell system: a new cell growth model. *Science*. 1984;224(4655):1312–1316. doi:10.1126/science.6427923
87. Atochina-Vasserman EN, Gow AJ, Abramova H, et al. Immune reconstitution during Pneumocystis lung infection: disruption of surfactant component expression and function by S-nitrosylation. *J Immunol*. 2009;182(4):2277–2287. doi:10.4049/jimmunol.0802775
88. Schneemann M, Schoedon G, Hofer S, Blau N, Guerrero L, Schaffner A. Nitric oxide synthase is not a constituent of the antimicrobial armature of human mononuclear phagocytes. *J Infect Dis*. 1993;167(6):1358–1363. doi:10.1093/infdis/167.6.1358
89. Prolo C, Alvarez MN, Radi R. Peroxynitrite, a potent macrophage-derived oxidizing cytotoxin to combat invading pathogens. *Biofactors*. 2014;40(2):215–225. doi:10.1002/biof.1150
90. Ikegami M, Whitsett JA, Martis PC, Weaver TE. Reversibility of lung inflammation caused by SP-B deficiency. *Am J Physiol Lung Cell Mol Physiol*. 2005;289(6):L962–70. doi:10.1152/ajplung.00214.2005
91. Marcotte H, Levesque D, Delanay K, et al. Pneumocystis carinii infection in transgenic B cell-deficient mice. *J Infect Dis*. 1996;173 (4):1034–1037. doi:10.1093/infdis/173.4.1034
92. Athni TS, Barmettler S. Hypogammaglobulinemia, late-onset neutropenia, and infections following rituximab. *Ann Allergy Asthma Immunol*. 2023;130(6):699–712. doi:10.1016/j.anai.2023.01.018
93. Barreto JN, Ice LL, Thompson CA, et al. Low incidence of pneumocystis pneumonia utilizing PCR-based diagnosis in patients with B-cell lymphoma receiving rituximab-containing combination chemotherapy. *Am J Hematol*. 2016;91(11):1113–1117. doi:10.1002/ajh.24499
94. Martin-Garrido I, Carmona EM, Specks U, Limper AH. Pneumocystis pneumonia in patients treated with rituximab. *Chest*. 2013;144 (1):258–265. doi:10.1378/chest.12-0477
95. Hu Y, Wang D, Zhai K, Tong Z. Transcriptomic analysis reveals significant B lymphocyte suppression in corticosteroid-treated hosts with pneumocystis pneumonia. *Am J Respir Cell Mol Biol*. 2017;56(3):322–331. doi:10.1165/rcmb.2015-0356OC
96. Lund FE, Hollifield M, Schuer K, Lines JL, Randall TD, Garvy BA. B cells are required for generation of protective effector and memory CD4 cells in response to Pneumocystis lung infection. *J Immunol*. 2006;176(10):6147–6154. doi:10.4049/jimmunol.176.10.6147
97. Bouaziz JD, Yanaba K, Venturi GM, et al. Therapeutic B cell depletion impairs adaptive and autoreactive CD4+ T cell activation in mice. *Proc Natl Acad Sci U S A*. 2007;104(52):20878–20883. doi:10.1073/pnas.0709205105
98. Sirianni MC, Atzori C, De Santis W, et al. A case of Pneumocystis jiroveci pneumonia in X-linked agammaglobulinaemia treated with immunosuppressive therapy: a lesson for immunologists. *Int Arch Allergy Immunol*. 2006;140(1):82–88. doi:10.1159/000092139
99. Zhang NN, Huang X, Feng HY, et al. Circulating and pulmonary T-cell populations driving the immune response in non-HIV immunocompromised patients with *Pneumocystis jirovecii* pneumonia. *Int J Med Sci*. 2019;16(9):1221–1230. doi:10.7150/ijms.34512
100. Lasbury ME, Durant PJ, Tschang D, et al. Expression and activation of complement protein and alveolar damage during Pneumocystis pneumonia. *J Eukaryot Microbiol*. 2006;53 Suppl 1:S136–7. doi:10.1111/j.1550-7408.2006.00204.x
101. Sayson SG, Ashbaugh A, Porollo A, Smulian G, Cushion MT. *Pneumocystis murina* promotes inflammasome formation and NETosis during Pneumocystis pneumonia. *mBio*. 2024;15(8):e0140924. doi:10.1128/mbio.01409-24
102. Hoyt TR, Dobrinen E, Kochetkova I, Meissner N. B cells modulate systemic responses to *Pneumocystis murina* lung infection and protect on-demand hematopoiesis via T cell-independent innate mechanisms when type I interferon signaling is absent. *Infect Immun*. 2015;83 (2):743–758. doi:10.1128/iai.02639-14
103. Horikawa M, Minard-Colin V, Matsushita T, Tedder TF. Regulatory B cell production of IL-10 inhibits lymphoma depletion during CD20 immunotherapy in mice. *J Clin Invest*. 2011;121(11):4268–4280. doi:10.1172/jci59266

104. Catalán D, Mansilla MA, Ferrier A, et al. Immunosuppressive mechanisms of regulatory B cells. *Front Immunol*. 2021;12:611795. doi:10.3389/fimmu.2021.611795
105. Rong HM, Li T, Zhang C, et al. IL-10-producing B cells regulate Th1/Th17-cell immune responses in Pneumocystis pneumonia. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(1):L291–l301. doi:10.1152/ajplung.00210.2018
106. Matsumura Y, Shindo Y, Iinuma Y, et al. Clinical characteristics of Pneumocystis pneumonia in non-HIV patients and prognostic factors including microbiological genotypes. *BMC Infect Dis*. 2011;11(1):76. doi:10.1186/1471-2334-11-76
107. Otieno-Odhiambo P, Wasserman S, Hoving JC. The contribution of host cells to pneumocystis immunity: an update. *Pathogens*. 2019;8(2):52. doi:10.3390/pathogens8020052
108. Grønseth S, Rogne T, Heggelund L, Åsvold BO, Afset JE, Damås JK. Role of fungal burden in risk stratification of HIV-negative patients with Pneumocystis pneumonia: a 12-year, retrospective, observational, multicenter cohort. *Int J Infect Dis*. 2023;134:177–186. doi:10.1016/j.ijid.2023.06.013