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PNEUMOCYSTIS JIROVECII PNEUMONIA IN TRANSPLANT RECIPIENTS: TIME-DEPENDENT RISK AND CLINICAL IMPLICATIONS – A LITERATURE REVIEW

Karolina Baran *(Corresponding Author, Email: karolina.ba01@gmail.com)*
John Paul II Western Hospital in Grodzisk Mazowiecki, Daleka 11, 05-825 Grodzisk Mazowiecki, Poland
ORCID ID: 0009-0006-3076-2892

Aleksandra Serafin
Czerniakowski Hospital Sp. z o.o., Stępińska 19/25, 00-739 Warsaw, Poland
ORCID ID: 0009-0002-2573-0811

Maja Podolak
Mazovian Bródnowski Hospital Sp. z o.o., ul. Kondratowicza 8, 03-242 Warsaw, Poland
ORCID ID: 0009-0005-5409-8511

Aleksandra Suchołbiak
Infant Jesus Clinical Hospital, Williama Heerleina Lindleya 4, 02-005 Warsaw, Poland
ORCID ID: 0009-0001-2931-157X

Oskar Mikołajczyk
Infant Jesus Clinical Hospital, Williama Heerleina Lindleya 4, 02-005 Warsaw, Poland
ORCID ID: 0009-0006-8470-6845

Klaudia Pachulska
Medical University of Warsaw, ul. Żwirki i Wigury 61, 02-091 Warsaw, Poland
ORCID ID: 0009-0003-5105-8798

Irmina Grygutis
Nicolaus Copernicus Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0008-2863-3471

Urszula Jarzęcka
Medical Centre for Postgraduate Education, Professor W. Orlowski Memorial Hospital, Czerniakowska 231, 00-416 Warsaw, Poland
ORCID ID: 0009-0009-1160-8541

ABSTRACT

Pneumocystis jirovecii pneumonia (PJP) remains a clinically significant opportunistic infection in solid organ transplant (SOT) recipients despite advances in prophylaxis, diagnostics, and treatment. This review aims to summarize current knowledge regarding epidemiology, risk factors, diagnosis, treatment, and prevention of PJP in this population, with particular emphasis on evolving concepts of risk stratification. Although universal trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has significantly reduced incidence, breakthrough and late-onset infections continue to occur, particularly in the context of fluctuating immunosuppression. The risk of PJP is primarily determined by the net state of immunosuppression rather than time since transplantation alone. Key risk factors include lymphopenia, cytomegalovirus infection or reactivation, treatment of acute rejection with high-dose corticosteroids or lymphocyte-depleting agents, hypogammaglobulinemia, and advanced age. Clinically, PJP in SOT recipients is often acute and rapidly progressive, frequently leading to severe hypoxemic respiratory failure and higher mortality compared with HIV-associated disease. Diagnosis requires integration of clinical findings, high-resolution computed tomography, and microbiological analysis of bronchoalveolar lavage. Molecular assays improve sensitivity, but differentiation between active infection and colonization remains challenging. Serum (1→3)-β-D-glucan may support diagnosis but lacks specificity. Trimethoprim-sulfamethoxazole remains first-line therapy and prophylaxis, while alternative agents are less effective. Emerging molecular and immunological tools may improve risk stratification and guide individualized prophylaxis strategies.

KEYWORDS

Pneumocystis Jirovecii Pneumonia, Solid Organ Transplantation, Opportunistic Infections, Immunosuppression, Prophylaxis

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1. Introduction

Pneumocystis jirovecii pneumonia (PJP) is a potentially life-threatening opportunistic fungal infection caused by the atypical fungus *Pneumocystis jirovecii*. It primarily affects individuals with impaired cellular immunity, including solid organ transplant (SOT) recipients, hematopoietic stem cell transplant recipients, patients with HIV infection, and those receiving prolonged or intensive immunosuppressive therapy. PJP is characterized by diffuse interstitial pneumonia that may progress to severe hypoxemic respiratory failure and remains an important cause of morbidity and mortality in immunocompromised populations [1,2]. Despite significant advances in prophylaxis and management, PJP continues to occur in high-risk groups, particularly among SOT recipients [3]. The widespread use of trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis has markedly reduced its incidence; however, cases are still observed, especially after prophylaxis discontinuation and during periods of intensified immunosuppression [2,4,5]. Late-onset PJP, occurring months or even years after transplantation, has become an increasingly recognized clinical challenge, often associated with delayed diagnosis due to a lower index of clinical suspicion [3]. In solid organ transplant recipients, PJP is associated with substantial morbidity and mortality [2,4]. Clinical presentation ranges from mild respiratory symptoms to rapidly progressive respiratory failure requiring intensive care unit admission and mechanical ventilation [4]. Mortality is still substantial, particularly in patients with delayed diagnosis, severe hypoxemia, or concomitant allograft dysfunction [5]. Beyond its direct clinical impact, PJP also imposes a significant healthcare burden due to prolonged hospitalization, intensive care utilization, and increased healthcare costs [3,4]. Moreover, severe infection may negatively affect graft outcomes through necessary modifications in immunosuppressive therapy and associated complications [2,5]. Historically, the highest risk of PJP in SOT recipients was observed within the first six months after transplantation, corresponding to the period of maximal immunosuppressive intensity. However, in the era of routine prophylaxis, the epidemiology

has shifted [4,5]. An increasing proportion of cases now occurs beyond the first post-transplant year, most commonly after discontinuation of prophylaxis or during episodes of augmented immunosuppression, such as treatment of acute rejection or administration of lymphocyte-depleting therapies [2,5,6]. As a result, the risk of PJP is no longer confined to the early post-transplant period and may persist throughout long-term follow-up [3,6]. These evolving epidemiological patterns challenge traditional time-based approaches to prophylaxis and support the development of individualized preventive strategies based on dynamic assessment of immunological risk. This review summarizes current evidence regarding the epidemiology, risk factors, clinical presentation, diagnosis, treatment, and prevention of PJP in solid organ transplant recipients, with particular emphasis on late-onset disease and risk-adapted prophylaxis.

2. Methodology

This study is a literature review of published research on Pneumocystis jirovecii pneumonia in solid organ transplant recipients. A structured search of the literature was conducted using the PubMed database to identify relevant articles published between 2009 and 2026. Keywords used included “Pneumocystis jirovecii pneumonia,” “solid organ transplantation,” “immunosuppression,” and “prophylaxis.” A total of 19 articles were selected based on their relevance to the epidemiology, risk factors, clinical presentation, diagnosis, treatment, and prevention of PJP in transplant populations. Only English-language publications were included. The selected studies were analyzed and synthesized to provide an overview of current knowledge on Pneumocystis jirovecii pneumonia in solid organ transplant recipients.

3. Results

3.1. Epidemiology

Before the widespread implementation of prophylactic strategies, Pneumocystis jirovecii pneumonia represented one of the most common opportunistic infections among transplant recipients [5]. The highest incidence was observed during the first six months following transplantation, corresponding to the period of greatest immunosuppressive exposure [4,5]. During this phase, induction therapy, high-dose maintenance immunosuppression, and frequent treatment of early rejection episodes collectively contributed to profound impairment of cellular immunity [2,5]. The introduction of routine TMP-SMX prophylaxis substantially altered the epidemiology of PJP [7]. Multiple studies demonstrated substantial reductions in disease incidence across all major transplant populations, leading to universal recommendations for prophylactic therapy during the early post-transplant period [5,7]. Nevertheless, the risk of infection has not been eliminated [3,4]. Contemporary cohorts continue to report cases of PJP despite widespread prophylaxis, emphasizing that prevention reduces but does not completely abolish susceptibility [2,3,6]. A major epidemiological shift has been the growing recognition of late-onset PJP [3,4]. Increasing numbers of infections now occur beyond the first post-transplant year, frequently after completion of standard prophylactic regimens [5,6]. This observation has challenged traditional concepts that viewed PJP primarily as an early post-transplant complication [3,5]. Instead, accumulating evidence suggests that infection risk persists throughout long-term follow-up and is driven primarily by dynamic changes in immunosuppressive burden rather than time from transplantation alone [2,5,6]. Late-onset disease is frequently associated with identifiable clinical events that increase the net state of immunosuppression [5]. These include treatment of acute rejection, CMV infection or reactivation, intensified maintenance immunosuppressive regimens, and prolonged lymphopenia [2,5,8]. As a result, contemporary understanding increasingly emphasizes dynamic immunological risk rather than chronological time after transplantation as the principal determinant of susceptibility [3,5]. Beyond its direct clinical consequences, PJP imposes a significant healthcare burden [3,4]. Patients frequently require hospitalization, advanced respiratory support, intensive care management, and extensive diagnostic evaluation [4,5]. These factors contribute substantially to healthcare utilization and costs. Furthermore, severe infection may necessitate modification of immunosuppressive regimens, potentially affecting long-term graft outcomes and increasing the risk of rejection [2,5].

3.2. Pathogenesis and Immunopathogenesis

The pathogenesis of PJP remains incompletely understood despite decades of investigation. Historically, the disease was believed to arise primarily through reactivation of latent infection acquired during childhood. This concept was supported by serological studies demonstrating widespread exposure to Pneumocystis organisms early in life. According to this model, asymptomatic colonization persists within the respiratory tract and progresses to active disease when host immune defenses become sufficiently impaired [10]. More recent molecular and epidemiological evidence has challenged this traditional paradigm, suggesting that Pneumocystis infection is better understood as a dynamic process influenced by both environmental exposure and host immune status. Multiple outbreak investigations have identified genetically similar strains among epidemiologically linked patients, particularly within transplant and hematology units. These findings strongly support the possibility of de novo acquisition through airborne transmission. Consequently, current understanding favors a dual-pathway model in which both latent reactivation and recent acquisition contribute to disease development [10]. Host defense against Pneumocystis relies predominantly on cell-mediated immunity. CD4+ T lymphocytes play a central role in coordinating the immune response through cytokine production and activation of effector cells. In transplant recipients, impairment of these cells is often functional rather than purely quantitative, reflecting the effects of immunosuppressive therapy [10]. This dysfunction represents the principal immunological defect predisposing to infection [5]. However, susceptibility cannot be explained solely by absolute CD4+ cell counts, particularly among transplant recipients, where functional impairment of immune responses may be equally important [2,3,5]. In solid organ transplant recipients, pharmacological immunosuppression—particularly corticosteroids and T-cell–depleting agents—plays a central role in disrupting these immune pathways. Alveolar macrophages serve as the principal effector cells responsible for fungal clearance. Their phagocytic and microbicidal activity depends heavily on signaling from activated T lymphocytes [10]. When adequate T-cell help is absent, macrophage function becomes impaired, permitting unchecked proliferation of Pneumocystis organisms within alveolar spaces [5]. The cytokine environment also plays a critical role in determining disease outcome. The cytokine milieu plays an important role in shaping the immune response, with Th1-associated signaling promoting macrophage activation and pathogen clearance, whereas dysregulated or Th2-skewed responses may impair host defense [10]. The balance between these immune pathways appears to influence both pathogen control and disease severity [5,10]. In addition to microbial proliferation, host-mediated inflammatory injury contributes substantially to pulmonary dysfunction [10]. Activation of inflammatory pathways leads to disruption of the alveolar-capillary membrane, increased vascular permeability, and accumulation of protein-rich exudates within the alveolar space [5,10]. These processes impair oxygen diffusion and contribute directly to the development of hypoxemia [5,10]. Pneumocystis infection disrupts pulmonary surfactant function, impairing alveolar stability and gas exchange and contributing to respiratory failure [10]. Together, these mechanisms produce the characteristic clinical picture of diffuse interstitial pneumonia and progressive respiratory failure [5]. In solid organ transplant recipients, these mechanisms act in the context of pharmacologically induced immune dysfunction, resulting in rapidly progressive disease, severe respiratory failure, and substantial mortality.

3.3. Risk Factors in Solid Organ Transplant Recipients

The development of Pneumocystis jirovecii pneumonia in transplant recipients reflects the net state of immunosuppression, encompassing the cumulative effects of immunosuppressive medications, underlying immune dysfunction, concurrent infections, and host-related factors [3,5]. Among the most consistently identified risk factors, lymphopenia occupies a central position [2,5]. Numerous studies have demonstrated an association between reduced absolute lymphocyte counts and increased susceptibility to opportunistic infections, including PJP [2,3,8]. Although CD4+ T-cell depletion is classically associated with HIV-related disease, impaired T-cell function in transplant recipients may occur even in the presence of relatively preserved lymphocyte counts. Therefore, both quantitative and qualitative defects in cellular immunity contribute to infection risk [5,10]. Cytomegalovirus (CMV) infection or reactivation represents another major determinant of PJP susceptibility [2,5]. CMV exerts broad immunomodulatory effects that extend beyond its direct viral replication. Through impairment of antigen presentation, induction of T-cell exhaustion, and disruption of normal immune regulation, CMV contributes to a state of functional immunodeficiency that predisposes patients to secondary opportunistic infections [3,5]. Multiple observational studies have consistently demonstrated CMV infection as one of the strongest independent predictors of subsequent PJP development [2,4,8]. Treatment of acute allograft rejection is strongly associated associated with increased risk [2,5]. Management of rejection frequently involves high-dose corticosteroid therapy and, in more severe cases,

administration of lymphocyte-depleting agents such as antithymocyte globulin or alemtuzumab [3,5]. These interventions produce profound and often prolonged impairment of cellular immunity, substantially increasing vulnerability to opportunistic pathogens [2,5]. Importantly, the increased risk may persist for months after completion of anti-rejection therapy [3,5,8]. The type of transplanted organ also influences susceptibility [3,4]. Lung transplant recipients require the most intensive and prolonged immunosuppression due to continuous exposure of the allograft to environmental antigens and a high risk of rejection, and consequently exhibit the highest incidence of PJP. Heart and intestinal transplant recipients are also considered high-risk populations [4,5]. Although kidney transplant recipients generally receive less intensive maintenance immunosuppression, their risk increases substantially following rejection episodes or additional immunomodulatory interventions [2,8]. Additional risk factors include advanced age, hypogammaglobulinemia, chronic allograft dysfunction, prolonged corticosteroid exposure, and the use of newer immunomodulatory agents [2,3,5]. Collectively, these observations reinforce the concept that PJP reflects cumulative immunological vulnerability rather than exposure to a single risk factor [5]. Particular attention has recently been directed toward risk factors in kidney transplant recipients. A systematic review and meta-analysis demonstrated that CMV infection, BK virus viremia, lymphopenia, acute rejection episodes, ABO-incompatible transplantation, older recipient age, and impaired graft function are all associated with increased susceptibility to PJP [6]. These findings emphasize the importance of ongoing risk assessment throughout long-term follow-up and support individualized approaches to prophylaxis and surveillance [3,5,6].

3.4. Clinical Manifestations

The clinical presentation of PJP varies according to the underlying type and intensity of immunosuppression and the tempo of disease progression [3,12]. In solid organ transplant recipients, symptoms are often nonspecific during the early stages of infection, which may contribute to delays in diagnosis and treatment [4,5]. The most common manifestations include fever, nonproductive cough, progressive dyspnea, and exercise intolerance. Patients frequently describe gradually worsening dyspnea over days to weeks. Hypoxemia is a hallmark feature and may initially be evident only during exertion before becoming apparent at rest as disease severity increases [4,5,12]. Physical examination findings are often surprisingly limited relative to the degree of respiratory impairment. Lung auscultation may reveal only subtle crackles and can be unremarkable despite significant radiological abnormalities. Tachypnea and increased work of breathing become more prominent as disease progresses [5,12]. Compared with HIV-associated PJP, which typically evolves over several weeks, disease in transplant recipients follows a more acute and fulminant course, with deterioration often occurring within days [4,12]. This accelerated progression is thought to reflect differences in host immune responses and patterns of inflammatory injury [10]. Severe cases may progress to acute hypoxemic respiratory failure requiring high-flow oxygen therapy, noninvasive ventilation, or invasive mechanical ventilation [4]. Acute respiratory distress syndrome (ARDS) may develop in severe cases and is associated with particularly poor outcomes [12]. The rapid progression of respiratory compromise underscores the importance of maintaining a high index of suspicion in immunocompromised patients presenting with compatible symptoms [3,4,5].

3.5. Diagnostic Evaluation

The diagnosis of PJP requires integration of clinical findings, radiological abnormalities, microbiological evidence, and laboratory data. No single diagnostic modality is sufficient in isolation, and clinicians must interpret results within the broader clinical context [12,13]. Imaging studies represent a cornerstone of diagnostic evaluation. Conventional chest radiography may demonstrate bilateral interstitial infiltrates, although findings can be subtle or even absent during the early stages of disease. High-resolution computed tomography (HRCT) is considerably more sensitive and is the imaging modality of choice. The characteristic appearance consists of diffuse bilateral ground-glass opacities, often distributed symmetrically throughout both lungs. Interlobular septal thickening may coexist with ground-glass changes, producing the classic “crazy-paving” pattern. Less common findings include cystic lesions, nodules, or areas of consolidation [4,12,14]. Laboratory abnormalities are generally nonspecific but may provide supportive evidence. Elevated serum lactate dehydrogenase levels are frequently observed and are thought to reflect diffuse alveolar epithelial injury [12,13]. Although LDH lacks both sensitivity and specificity, markedly elevated levels often correlate with extensive pulmonary involvement. Arterial blood gas analysis typically demonstrates hypoxemia and an increased alveolar-arterial oxygen gradient, findings that may also have prognostic significance [5,12]. Serum beta-D-glucan has emerged as an important adjunctive biomarker, demonstrating high sensitivity for PJP but

limited specificity due to elevation in a variety of fungal and non-fungal conditions. [12,13,15]. However, because elevated levels may occur in numerous other fungal infections and noninfectious conditions, the test lacks sufficient specificity to establish the diagnosis independently [12,14,15]. Its greatest value lies in supporting or excluding the diagnosis when interpreted alongside clinical and radiological findings [5,12,14]. Definitive diagnosis generally requires direct detection of Pneumocystis organisms or their genetic material within respiratory specimens [12,13]. Bronchoalveolar lavage obtained during bronchoscopy remains the preferred diagnostic sample because of its high yield and ability to provide material for multiple testing modalities [5,12,13]. Traditional methods include direct immunofluorescence staining and microscopic visualization of the organism [10,13]. Although highly specific, these techniques are less sensitive than molecular approaches and depend heavily on operator expertise. Polymerase chain reaction (PCR) assays have revolutionized the diagnosis of PJP. Their superior sensitivity allows detection of small amounts of fungal DNA that might be missed by conventional microscopy [10,12,13]. As a result, PCR has become an integral component of contemporary diagnostic algorithms [5,12,14]. However, its high sensitivity complicates interpretation, as positive results may reflect colonization rather than active infection. [10,12,13]. Quantitative PCR has therefore attracted increasing attention as a means of improving diagnostic specificity [13,16]. Higher fungal loads correlate more strongly with clinically significant disease, whereas low-level positivity may reflect colonization [10,17]. However, differences among assays and the absence of universally accepted thresholds currently limit standardization across institutions [17]. Metagenomic next-generation sequencing (mNGS) represents a promising emerging technology [13]. By enabling unbiased detection of microbial nucleic acids, it may facilitate diagnosis in complex cases and identify coinfections that would otherwise remain undetected. Although currently limited by cost and availability, its role in future diagnostic strategies is expected to expand [18]. Overall, the diagnosis of PJP requires a multimodal approach integrating clinical, radiological, and microbiological data, with increasing reliance on molecular techniques to improve diagnostic accuracy while maintaining specificity.

3.6. Diagnostic Challenges and Differential Diagnosis

The diagnosis of PJP in non-HIV immunocompromised patients is associated with several unique challenges. The disease often manifests with nonspecific symptoms that overlap substantially with other infectious and noninfectious pulmonary disorders [12,13]. Furthermore, the rapid progression characteristic of transplant recipients may limit the diagnostic window and necessitate empiric treatment before definitive confirmation is obtained [5]. One of the most important challenges is distinguishing active infection from colonization. Detection of Pneumocystis DNA by PCR does not necessarily indicate clinically significant disease, particularly in patients with chronic lung disease or prolonged immunosuppression [10,13,17]. Interpretation therefore requires careful consideration of fungal burden, radiological findings, biomarker results, and clinical presentation [12,13,17]. The differential diagnosis is broad and includes numerous conditions commonly encountered in transplant populations [5]. CMV pneumonia is particularly important, as it may present with fever, hypoxemia, and diffuse ground-glass infiltrates that closely resemble PJP [5,12]. Coinfection with CMV and Pneumocystis may also occur, further complicating diagnosis and management [5]. Organizing pneumonia, whether cryptogenic or secondary to infection, drug exposure, or allograft dysfunction, may produce similar radiological patterns [5,12]. Viral pneumonias caused by influenza virus, respiratory syncytial virus, adenovirus, or SARS-CoV-2 may also mimic PJP clinically and radiographically. Invasive fungal infections, including aspergillosis, should likewise be considered, particularly in patients with severe immunosuppression [3,5]. Because of these overlapping clinical and radiological features, accurate diagnosis requires a multimodal approach integrating clinical assessment, imaging, laboratory biomarkers, and microbiological testing [12,13]. Reliance on any single diagnostic modality may lead to misclassification, delayed treatment, or unnecessary exposure to potentially toxic therapies [10,13,17].

3.7. Treatment Strategies

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the cornerstone of therapy for PJP and is recommended as first-line treatment across all disease severities [14]. The superiority of TMP-SMX over alternative regimens has been demonstrated in multiple clinical studies, and no other available agent has consistently shown comparable efficacy [12]. In addition to its activity against *P. jirovecii*, TMP-SMX provides coverage against several other opportunistic pathogens, including *Toxoplasma gondii* and *Nocardia* species, making it particularly valuable in transplant populations [5]. Early initiation of therapy is critical, as delayed treatment is consistently associated with worse outcomes [4,12]. In many cases, empiric therapy is

initiated based on compatible radiological findings and progressive respiratory failure, before microbiological confirmation is available [5,12,14]. Given the fulminant nature of disease in transplant recipients, waiting for definitive microbiological confirmation may result in clinically significant delays [4,5]. A major consideration in clinical practice is the evaluation of reported sulfonamide allergy. Many patients carry a historical label of "sulfa allergy" based on nonspecific or poorly documented reactions or mild cutaneous eruptions occurring years earlier. Such reactions do not necessarily preclude future use of TMP-SMX. Careful reassessment of allergy history is therefore essential before selecting alternative therapy. In patients with uncertain or mild reactions, supervised drug rechallenge or formal desensitization protocols may permit administration of the preferred treatment. In contrast, re-exposure to TMP-SMX is contraindicated in patients with a history of severe hypersensitivity reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), or anaphylaxis. In these situations, alternative therapies must be used despite their lower efficacy [11,19]. Several second-line treatment options are available. Atovaquone may be used in patients with mild-to-moderate disease who cannot tolerate TMP-SMX. Its oral administration and favorable safety profile make it an attractive alternative; however, efficacy is generally considered inferior and depends on adequate gastrointestinal absorption. Intravenous pentamidine is reserved for severe disease when TMP-SMX cannot be used [14]. Although effective, pentamidine is associated with significant toxicity, including nephrotoxicity, pancreatitis, electrolyte abnormalities, and cardiac arrhythmias. Another alternative regimen is the combination of clindamycin and primaquine, often used in moderate to severe disease when first-line therapy is contraindicated. Because primaquine may cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, appropriate screening is required before treatment [12,14]. The recommended duration of therapy is generally 21 days, although treatment should be individualized according to clinical response, degree of immunosuppression, and tolerability [5,12,14]. Close monitoring during treatment is essential, as adverse effects are common and may necessitate dose adjustment or changes in therapeutic strategy [12].

3.8. Adjunctive Corticosteroid Therapy

Adjunctive corticosteroids are well established in the treatment of moderate-to-severe PJP in patients with HIV infection [1,12]. Randomized controlled trials have demonstrated significant reductions in respiratory deterioration and mortality when corticosteroids are initiated early in patients with substantial hypoxemia [1,12,14]. The beneficial effect is thought to result from attenuation of the inflammatory response triggered by antimicrobial-induced destruction of Pneumocystis organisms [12]. In contrast, evidence supporting corticosteroid use in non-HIV immunocompromised populations remains limited [1,2,3]. Most available data originate from retrospective studies, observational cohorts, and expert opinion rather than randomized trials [1,3,4]. Consequently, uncertainty persists regarding the magnitude of benefit in transplant recipients, and recommendations are largely extrapolated from studies conducted in HIV-infected populations [3,4,5]. Current recommendations generally support consideration of adjunctive corticosteroids in selected patients with severe respiratory impairment, particularly those with significant hypoxemia [1,5,13]. Common clinical thresholds include a partial pressure of arterial oxygen below 70 mmHg on room air or an alveolar-arterial oxygen gradient ≥35 mmHg [1,12,14]. In such cases, corticosteroids may reduce inflammatory lung injury and limit progression to respiratory failure [12]. Nevertheless, potential benefits must be balanced against important risks in this population [3,4,5]. Transplant recipients are already profoundly immunosuppressed, and additional corticosteroid exposure may increase susceptibility to secondary bacterial, viral, and fungal infections [2,3,5]. Moreover, corticosteroid therapy may complicate the management of concurrent opportunistic infections and contribute to metabolic complications. Decisions regarding adjunctive corticosteroid use should therefore be individualized, taking into account disease severity, competing infectious risks, and the overall level of immunosuppression, and ideally made in consultation with transplant infectious disease specialists [1,5,14].

3.9. Prevention and Prophylaxis

Prevention remains the most effective strategy for reducing the burden of PJP in transplant recipients [1,3,5]. The introduction of routine prophylaxis has transformed the epidemiology of disease and represents one of the major successes of transplant infectious disease practice [3,4,5]. TMP-SMX is universally regarded as the preferred prophylactic agent because of its superior efficacy, favorable cost-effectiveness profile, and broad antimicrobial spectrum [5,14]. Beyond preventing PJP, TMP-SMX provides clinically important protection against toxoplasmosis, nocardiosis, urinary tract infections, and selected bacterial pathogens [1,12].

These additional benefits further support its role as the first-line prophylactic regimen in transplant populations [2,3,5]. Current guidelines generally recommend prophylaxis for a minimum of six to twelve months following transplantation [1,3]. This period corresponds to the phase of greatest immunosuppressive burden, during which susceptibility to opportunistic infections is highest [2,5]. However, the optimal duration of prophylaxis remains an area of active debate [3,7]. Increasing evidence suggests that fixed-duration prophylaxis may be insufficient for many transplant recipients, prompting growing interest in risk-adapted strategies based on the net state of immunosuppression [2,5,6]. Such an approach recognizes that susceptibility may fluctuate substantially over time and that periods of heightened risk often occur long after the initial transplant procedure [2,3,6]. Re-initiation or extension of prophylaxis should therefore be considered in patients undergoing treatment for acute rejection, receiving lymphocyte-depleting therapies, developing CMV disease, or experiencing persistent lymphopenia [2,4,5]. This evolving approach reflects a broader shift from time-based prophylactic strategies toward individualized prevention based on ongoing assessment of immunological vulnerability. Particularly high-risk populations may warrant prolonged or even lifelong prophylaxis [3,6]. Lung transplant recipients are frequently cited as an example because of their sustained immunosuppressive requirements, continuous environmental exposure of the allograft, and consistently elevated incidence of opportunistic infections [3,5]. Similar considerations may apply to selected intestinal transplant recipients and patients with recurrent episodes of rejection requiring repeated intensification of immunosuppressive therapy [2,5]. Alternative prophylactic regimens are available for patients who cannot tolerate TMP-SMX. Atovaquone is commonly used because of its favorable safety profile and ease of administration [1,5]. Dapsone represents another oral alternative but requires prior testing for glucose-6-phosphate dehydrogenase deficiency to reduce the risk of hemolytic complications. Aerosolized pentamidine may be considered in selected patients who are unable to tolerate oral agents, although its lack of systemic antimicrobial activity limits protection against extrapulmonary opportunistic infections [5,14]. Despite the effectiveness of prophylaxis, breakthrough infections continue to occur [3,6]. Such cases are usually associated with profound immunosuppression, treatment interruptions, inadequate drug exposure, or poor adherence [2,6]. These observations emphasize that prophylaxis substantially reduces risk but cannot completely eliminate susceptibility in highly immunocompromised individuals, further underscoring the need for ongoing risk assessment throughout long-term follow-up [5,6].

3.10. Limitations and Controversies in Prophylaxis

Although prophylactic strategies have dramatically reduced the incidence of PJP, several important limitations remain [3,5]. Drug-related toxicity represents one of the most significant challenges. TMP-SMX may cause leukopenia, neutropenia, thrombocytopenia, renal dysfunction, hyperkalemia, and hypersensitivity reactions [1,5,19]. These adverse effects are particularly relevant in transplant recipients, who often receive multiple medications with overlapping toxicities [4,5]. Medication adherence constitutes another important concern. Long-term prophylaxis may be affected by pill burden, treatment fatigue, adverse effects, and complex medication schedules [1,3,5]. Even brief interruptions in prophylaxis may increase susceptibility to opportunistic infection, particularly in patients with severe immunosuppression [2,6,8]. Perhaps the most important unresolved question concerns the optimal duration of prophylaxis. While six to twelve months remains the standard recommendation for most transplant recipients, increasing recognition of late-onset disease has raised concerns that this approach may be insufficient in selected populations [3,6]. Some experts advocate prolonged prophylaxis in patients with persistent risk factors, whereas others emphasize individualized decision-making guided by ongoing assessment of immunological status [2,5,6]. However, there is currently no universally accepted strategy for identifying transplant recipients who would derive the greatest benefit from extended prophylaxis [2,3,5,6]. A major limitation of risk-adapted approaches is the lack of validated biomarkers capable of accurately defining an individual patient's risk of PJP and guiding prophylaxis duration [2,3,6]. In addition, increasing use of highly sensitive molecular diagnostic methods has highlighted the challenge of distinguishing colonization from active infection, complicating interpretation of epidemiological data and assessment of prophylactic effectiveness [10,16,17]. The absence of an alternative agent with efficacy equivalent to TMP-SMX further complicates management. Although several second-line options exist, all appear less effective and provide narrower antimicrobial coverage [5,14]. Consequently, whenever possible, efforts should be made to maintain patients on TMP-SMX through careful management of adverse effects, allergy evaluation, and desensitization strategies when appropriate [5,11,19]. These challenges highlight the need for more precise approaches to risk stratification and prophylaxis optimization in transplant recipients [2,3,5,6].

3.11. Late-Onset Pneumocystis Pneumonia After Transplantation

One of the most important developments in the contemporary understanding of Pneumocystis jirovecii pneumonia among solid organ transplant recipients has been the recognition of late-onset disease [3,6]. Historically, PJP was considered primarily an early post-transplant complication, with the majority of infections occurring during the first six months after transplantation. This perception was largely based on observations from the pre-prophylaxis era, when the intensity of immunosuppression was greatest during the early post-transplant period and preventive strategies were not routinely employed [3,4,5]. In recent years, however, the epidemiology of PJP has shifted substantially, with late-onset disease emerging as one of the most important contemporary challenges in transplant infectious diseases [3,6,8]. Many of these infections occur after discontinuation of standard prophylactic regimens, highlighting the fact that protection afforded by TMP-SMX is limited to the period during which prophylaxis is administered and does not permanently eliminate susceptibility [5,6]. Recent meta-analytic data in kidney transplant recipients further demonstrated that a substantial proportion of PJP cases occur beyond the first post-transplant year and are strongly associated with identifiable risk factors such as CMV infection, lymphopenia, acute rejection, and impaired graft function [6]. Late-onset PJP reflects the dynamic nature of immunological risk in transplant recipients. Rather than representing a failure of prophylaxis, most late cases appear to be associated with subsequent events that alter the net state of immunosuppression. Among these, treatment of acute allograft rejection remains one of the most important risk factors [2,6,8]. Anti-rejection therapy often involves high-dose corticosteroid pulses, lymphocyte-depleting antibodies, or intensified maintenance immunosuppression, all of which can profoundly impair host defenses against opportunistic pathogens [3,5]. Cytomegalovirus infection represents another major contributor to late disease. CMV exerts complex immunomodulatory effects that extend beyond direct viral replication [2,5,6]. Through impairment of T-cell function, disruption of antigen presentation, and promotion of immune exhaustion, CMV creates a state of functional immunodeficiency that may persist long after apparent virological control has been achieved [5]. Numerous studies have demonstrated a strong association between CMV infection and subsequent development of PJP, supporting the concept that CMV acts both as a marker and mediator of excessive immunosuppression [2,5,6,8]. Persistent lymphopenia has also emerged as an important predictor of late-onset infection [2,6,8]. Reduced lymphocyte counts may reflect prolonged effects of immunosuppressive therapy, chronic viral infections, or underlying immune dysfunction [3,5]. Several observational studies have identified severe or persistent lymphopenia as an independent risk factor for opportunistic infections, including PJP. Consequently, persistent lymphopenia has been proposed as a practical marker for identifying transplant recipients who may benefit from prolonged or reinitiated prophylaxis [2,6,8]. The recognition of late-onset disease has important clinical implications. Physicians may be less likely to consider PJP in patients who are several years removed from transplantation, particularly when prophylaxis was completed successfully and no previous infectious complications have occurred [3,6]. Reduced clinical suspicion may contribute to delays in diagnosis and treatment, potentially worsening outcomes [3]. Collectively, these findings support a paradigm shift from fixed-duration prophylaxis based on time after transplantation toward individualized prevention strategies guided by dynamic assessment of immunological risk [2,3,6]. These observations have increasingly challenged traditional guideline recommendations based solely on time since transplantation.

3.12. Outcomes and Prognostic Factors

Despite significant advances in prevention, diagnosis, and treatment, PJP remains a major cause of adverse outcomes among solid organ transplant recipients [3,4]. Clinical prognosis is influenced by multiple factors, including disease severity at presentation, timeliness of diagnosis, underlying immunological status, and the presence of concurrent complications [3]. Mortality rates among non-HIV immunocompromised patients remain substantially higher than those reported in individuals with HIV infection, with contemporary studies continuing to report considerable mortality among transplant recipients, particularly among those requiring intensive care support [1,3,12]. This difference is generally attributed to a more acute disease course, delayed recognition, and a reduced capacity to mount effective immune responses once infection becomes established. The severity of respiratory failure at presentation is consistently identified as the most important determinant of outcome. Patients presenting with profound hypoxemia, acute respiratory distress syndrome, or extensive radiological involvement are significantly more likely to experience adverse outcomes [12]. The requirement for intensive care unit admission represents a particularly strong marker of disease severity and is associated with markedly increased mortality. Similarly, the need for invasive mechanical ventilation has repeatedly been associated with adverse clinical outcomes and high mortality [4]. Once respiratory failure

progresses to the point of requiring ventilatory support, mortality remains high despite appropriate antimicrobial therapy and modern intensive care management [12]. This observation highlights the importance of early recognition and treatment before irreversible pulmonary injury develops [3]. Delayed diagnosis is another major determinant of outcome. Because symptoms are often nonspecific and may overlap with numerous other pulmonary disorders, diagnostic consideration is frequently postponed, particularly in patients who present outside the traditional early post-transplant period [3,12]. Delays in initiating appropriate anti-Pneumocystis therapy have consistently been associated with worse clinical outcomes and increased mortality. Several laboratory markers have also been associated with prognosis. Severe hypoxemia at presentation, elevated serum lactate dehydrogenase concentrations, persistent lymphopenia, and evidence of systemic inflammatory activation have all been associated with increased mortality and adverse clinical outcomes [12]. Although no single biomarker provides reliable prognostic discrimination, these findings collectively reflect extensive pulmonary injury and profound immune dysfunction [3,12]. Concurrent infections may further worsen prognosis. CMV coinfection is particularly important because it may contribute both to direct pulmonary injury and to additional impairment of immune function [2,4,5]. Patients with CMV disease often experience more severe clinical courses and increased mortality compared with patients with PJP alone [2,3,5]. Beyond its impact on survival, PJP may adversely affect allograft outcomes. Severe infection frequently necessitates modification of immunosuppressive therapy, potentially increasing the risk of rejection [3,4,5]. Furthermore, prolonged hospitalization, systemic inflammation, and multiorgan dysfunction may contribute to long-term graft injury. Although graft loss directly attributable to PJP is uncommon, severe infection may indirectly compromise long-term transplant outcomes through its impact on patient health and immunosuppressive management [4,5].

3.13. Comparison with HIV and Other Immunocompromised Populations

Although Pneumocystis jirovecii is the causative pathogen across all patient populations, clinical manifestations and outcomes vary considerably depending on the underlying cause of immunosuppression [1,12]. These differences illustrate the importance of the broader immunological context in determining disease phenotype and prognosis [12]. In patients with HIV infection, PJP typically develops in the setting of progressive CD4+ T-cell depletion [10,12]. The disease usually follows a subacute course characterized by gradual worsening of cough, dyspnea, and constitutional symptoms over several weeks, which often allows earlier clinical recognition and intervention, despite the possible presence of severe hypoxemia at diagnosis [1,12]. Mortality rates have declined substantially in the era of effective antiretroviral therapy and are generally lower than those observed in non-HIV populations [3,10,12]. In contrast, transplant recipients frequently experience a more acute and rapidly progressive illness [3,12]. Pharmacologically induced immunosuppression in this population affects multiple components of the immune system and may fluctuate considerably over time [5]. Episodes of rejection treatment, CMV infection, and other complications create dynamic changes in immune function that can predispose patients to abrupt disease onset [2,3,6]. As a result, respiratory deterioration often occurs more rapidly, and mortality remains significantly higher than in HIV-associated disease [3,12]. Patients with hematologic malignancies and hematopoietic stem cell transplantation represent another important population at risk [13,14]. These patients often exhibit profound defects in both cellular and humoral immunity, particularly in the presence of graft-versus-host disease or intensive chemotherapy [14]. Among major immunocompromised populations, they are often associated with the highest mortality rates and the most severe clinical presentations [3,12]. These differences support the concept that susceptibility to PJP is determined not simply by CD4+ T-cell depletion but by the overall functional integrity of the immune system [5]. The notion of a net state of immunosuppression provides a more comprehensive framework for understanding disease risk and explains why patients with similar lymphocyte counts may experience markedly different clinical outcomes depending on the underlying cause of immune dysfunction [2,5].

3.14. Future Directions

The future management of PJP is likely to be shaped by advances in molecular diagnostics, immunological monitoring, and personalized preventive strategies [3,13]. One of the most important priorities is improving the ability to distinguish active infection from asymptomatic colonization [10,17]. Although PCR has transformed diagnostic practice, its inability to reliably differentiate these states remains an important limitation. Establishing standardized quantitative thresholds and integrating fungal burden measurements into diagnostic algorithms may improve specificity and reduce diagnostic uncertainty [16,17]. Metagenomic next-

generation sequencing represents another promising area of development [3,18]. This technology enables comprehensive pathogen detection without predefined targets and may be particularly valuable in patients with atypical presentations or mixed infections [3,17,18]. As costs decrease and accessibility improves, mNGS is expected to become increasingly integrated into clinical practice [3,18]. Growing interest also surrounds the development of immunological biomarkers capable of more accurately reflecting the net state of immunosuppression [5]. Traditional approaches relying primarily on absolute lymphocyte counts provide only a partial assessment of immune competence [2]. Future strategies may incorporate functional immune assays, markers of T-cell exhaustion, cytokine profiles, and broader measures of immune function to better identify patients at highest risk for opportunistic infections [3,5]. Preventive strategies are also evolving toward greater individualization. Rather than applying uniform prophylactic durations to all transplant recipients, future approaches are likely to rely on dynamic risk assessment incorporating clinical events, immunological biomarkers, viral infections, and patterns of immunosuppressive exposure [2,6,8]. Such personalized strategies may improve protection while minimizing unnecessary antimicrobial exposure and treatment-related toxicity [3,5]. Despite decades of research, no vaccine against *Pneumocystis jirovecii* is currently available. The unique biology of the organism, including its inability to be continuously cultured in vitro, has complicated vaccine development efforts [10]. Nevertheless, advances in molecular biology and immunology continue to identify potential targets that may eventually support vaccine-based preventive strategies [3]. Emerging biomarkers beyond beta-D-glucan also represent an active area of investigation [16,17]. Host-response signatures, transcriptomic profiling, proteomic approaches, and multi-omics technologies may eventually improve both diagnosis and prognostication [3]. These innovations have the potential to transform PJP management by enabling earlier detection, improved risk stratification, and more individualized therapy [3,5].

4. Discussion

This review highlights that PJP in solid organ transplant recipients is best understood as a dynamic consequence of cumulative and fluctuating immunosuppression, rather than a time-dependent post-transplant complication. Pneumocystis jirovecii pneumonia (PJP) remains one of the most important opportunistic infections affecting solid organ transplant (SOT) recipients despite substantial advances in prophylaxis, diagnostics, and treatment. The introduction of routine trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis has significantly reduced disease incidence; however, PJP continues to occur and is still associated with considerable morbidity, mortality, and healthcare utilization [3,5,8]. Current evidence indicates that susceptibility to infection is determined primarily by the net state of immunosuppression rather than time elapsed since transplantation alone [5]. Multiple risk factors contribute to infection risk, including lymphopenia, cytomegalovirus (CMV) infection or reactivation, treatment of acute allograft rejection, exposure to high-dose corticosteroids, and use of lymphocyte-depleting agents [2,5,8]. Increasing recognition of late-onset PJP further highlights the dynamic nature of immunological risk and challenges traditional time-based prophylaxis strategies [6,8]. These observations reflect the complexity of pharmacologically induced immunosuppression, which affects multiple components of the immune system and may fluctuate significantly over time. Episodes of rejection treatment, viral infections—particularly CMV—and intensification of immunosuppressive regimens result in transient but profound immune dysfunction, predisposing patients to opportunistic infections [5]. Clinically, PJP in transplant recipients often follows a more acute and rapidly progressive course compared with HIV-associated disease. In contrast to the subacute presentation typically seen in HIV-positive patients, SOT recipients may experience rapid respiratory deterioration, leading to a higher risk of respiratory failure and death [3,12]. Several studies have demonstrated higher mortality rates in non-HIV immunocompromised populations compared with HIV-infected individuals [12]. Patients with hematologic malignancies and hematopoietic stem cell transplantation (HSCT) represent another high-risk group. Profound defects in both cellular and humoral immunity, often compounded by graft-versus-host disease (GVHD) and intensive chemotherapy, result in particularly severe disease and the highest reported mortality rates among immunocompromised populations [13,14]. From a pathophysiological perspective, susceptibility to PJP cannot be explained solely by CD4+ T-cell depletion but instead reflects overall immune dysfunction. The concept of the net state of immunosuppression provides a more comprehensive framework for risk assessment and better explains interindividual variability in susceptibility despite similar immunological parameters [5,7]. Overall, PJP risk in transplant recipients should be considered dynamic rather than strictly time-dependent. Diagnosis requires integration of clinical, radiological, microbiological, and molecular findings. Although PCR-based assays have significantly improved diagnostic sensitivity, distinguishing active infection from colonization remains a major challenge [10,16,17]. Quantitative

approaches, interpreted alongside imaging and clinical context, may improve diagnostic specificity. TMP-SMX remains the first-line agent for both treatment and prophylaxis and continues to represent the cornerstone of contemporary management [5,14]. Despite its effectiveness, increasing evidence supports a shift from fixed-duration prophylaxis toward individualized, risk-adapted strategies based on continuous assessment of immunological and clinical risk factors [2,6,9]. Future advances are expected to arise from improvements in molecular diagnostics, development of novel biomarkers, and implementation of personalized preventive strategies. Immunological biomarkers may provide a more accurate reflection of immune competence than conventional parameters such as absolute lymphocyte counts [18]. In addition, metagenomic next-generation sequencing (mNGS), transcriptomic profiling, and proteomic approaches may enable earlier diagnosis and improved risk stratification [17,18]. Despite extensive research, no vaccine against Pneumocystis jirovecii is currently available, largely due to biological limitations of the organism, including its inability to be continuously cultured in vitro [10]. Nevertheless, advances in molecular biology and immunology continue to identify potential antigenic targets that may support future vaccine development strategies.

5. Conclusions

Pneumocystis jirovecii pneumonia remains one of the most important opportunistic infections in solid organ transplant recipients, despite substantial advances in prophylaxis, diagnostics, and treatment [3,4,5]. Although routine TMP-SMX prophylaxis has dramatically reduced disease incidence, PJP continues to occur and is associated with significant morbidity, mortality, and healthcare utilization [2,3,8]. Current evidence indicates that susceptibility to infection is determined primarily by the net state of immunosuppression rather than by time elapsed since transplantation alone [5]. Lymphopenia, CMV infection or reactivation, treatment of acute rejection, exposure to high-dose corticosteroids, and administration of lymphocyte-depleting agents represent the most important risk factors for disease development [2,8]. The increasing recognition of late-onset PJP further underscores the dynamic nature of infection risk and challenges traditional approaches based solely on fixed post-transplant timelines [3,4,6]. Diagnosis requires integration of clinical, radiological, microbiological, and molecular findings [3,13]. Although PCR-based assays and novel molecular techniques have substantially improved diagnostic sensitivity, differentiation between active infection and colonization remains a key challenge [16,17]. Early recognition and prompt initiation of therapy are critical, as delayed diagnosis is strongly associated with adverse outcomes [3,4]. TMP-SMX remains the first-line agent for both treatment and prophylaxis and continues to represent the foundation of contemporary management [5,14]. However, growing evidence supports a shift from fixed-duration prophylaxis toward individualized, risk-adapted strategies guided by ongoing assessment of immunological status and clinical risk factors [2,5,6]. Future advances are expected to arise from improvements in molecular diagnostics, development of novel biomarkers, and implementation of personalized approaches to prevention and risk stratification [3,17,18]. Together, these innovations may further reduce the burden of PJP and improve outcomes among transplant recipients in the years ahead [2,3,5].

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