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Pneumocystis jirovecii Pneumonia in HIV-Negative, Non-transplant Patients: Epidemiology, Clinical Manifestations, Diagnosis, Treatment, and Prevention

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Abstract

Purpose of Review—*Pneumocystis jirovecii* pneumonia (PJP) is an opportunistic fungal infection that is increasingly seen in HIV-negative patients with immune compromise due to other etiologies. We lack comprehensive clinical recommendations for this population.

Recent Findings—In non-HIV cases, PJP has a mortality rate of up to 50%, which is unacceptable despite the presence of safe and effective prophylaxis and therapy. Steroid use is one of the most common risk factors for disease development. New data suggests that lower doses of the preferred treatment regimen, TMP-SMX, may be equally effective for treatment while limiting side effects. While commonly used, the benefit of corticosteroids for the treatment of PJP has recently been called into question, with a recent multicenter cohort demonstrating no benefit among solid organ transplant recipients.

Summary—A high suspicion of PJP in individuals with pneumonia during immunosuppressant use is crucial. Therapeutic options are evolving to decrease potential side effects while maintaining efficacy in this highly morbid disease.

Keywords

Pneumonia; Pneumocystis; *Pneumocystis jirovecii* ; HIV-negative; Non-transplant patients

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Declarations

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Introduction

The opportunistic and human-specific fungus *Pneumocystis jiroveci*, formerly *Pneumocystis carinii*, was first identified as a cause of severe pneumonia following World War II in children with congenital T-cell abnormalities and shortly afterward in individuals with hematologic malignancies [1]. *Pneumocystis jirovecii* pneumonia (previously PCP, now PJP) has evolved as a significant cause of morbidity and mortality among immunocompromised individuals. According to several recent studies, the prevalence of PJP in non-HIV-infected individuals has been increasing and, at present, is thought to account for up to $686 million in healthcare costs annually in the USA alone [2–5]. We lack more clinical information on PJP among HIV-negative, transplant-negative (NHNT) patients. We aim to review the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of the disease in this population.

Case Presentation

While admitted to the hospital awaiting a liver transplant, a 34-year-old woman with autoimmune hepatitis developed dyspnea and a new oxygen requirement of 2L via nasal cannula. The patient was previously on daily prednisone, ranging from 30–50 mg per day, for 5 months. She did not receive PJP prophylaxis.

Epidemiology and Population at Risk

While some studies suggest that up to 20% of the general population exhibits evidence of *Pneumocystis* colonization, invasive disease is almost always seen in immunocompromised individuals [6, 7]. During the 1980s and 1990s, pneumocystis pneumonia became closely associated with uncontrolled HIV/AIDS infection. Now, however, PJP is increasingly found in immunocompromised individuals without HIV, with up to 60% of the over 400,000 worldwide annual cases found in the non-HIV population [8]. As the incidence of PJP increases worldwide, there is growing awareness of both disease states and medications that predispose to PJP.

The most identified disease states predisposing to PJP in NHNT adults are typically chronic lung disease or malignancy, both solid tumor and hematopoietic. Other cell-mediated immunocompromised conditions increase the risk of PJP — either due to underlying disease immune dysregulation or the need to use immunosuppressive medications — including autoimmune or inflammatory diseases (AIIDs), connective tissue disease, and pulmonary fibrosis [9]. Malignancy is present in up to 46% of cases [10, 11•]. Among children, congenital cardiopulmonary disease and severe combined immunodeficiency (SCID) are the disease states most frequently seen with PJP, accounting for 22% and 19% of cases, respectively [12].

The use of immunosuppressive medications is increasingly recognized as the most significant risk factor for developing non-HIV pneumocystis pneumonia in adults. The use of systemic glucocorticoids is arguably the most well-known risk factor for the development of PJP in HIV-negative patients, and they may be present in up to 76% of the patients

[13]. However, insufficient evidence exists for a specific dose or duration that elevates an individual's risk.

Beyond glucocorticoids, therapeutic advances in treating autoimmune disease and maintaining solid organ transplants have led to increased use of immunosuppressive therapy that is increasingly shown to convey a higher risk of PJP infection (Table 1). One study of individuals with inflammatory bowel disease (IBD) demonstrated increased cases of PJP in those receiving thiopurines, infliximab, cyclosporine, and methotrexate, medications which have also been implicated in the development of PJP [14–16]. New anti-neoplastic therapies for a variety of malignancies have also demonstrated associations with increased risk for PJP [17]. Kinase inhibitors such as idelalisib used for the treatment of chronic lymphocytic leukemia (CLL), and related Bruton's tyrosine kinase inhibitors (BTKi) such as ibrutinib and acalabrutinib have been associated with PJP, independent of other anti-neoplastic therapy [18, 19]. We recently found an increased proportion of PJP (0.5% vs. 0.3%, $p = 0.02$) at 5 years with the use of a BTKi among patients with chronic lymphocytic leukemia (CLL) compared to those treated with non-BTKi therapy [20].

Apart from the direct effects on immune function from anti-neoplastic drugs, the development of complications from these therapies has also been associated with the development of PJP. Individuals on immune checkpoint inhibitors (ICI) may develop pneumonitis as a complication, which typically manifests with cough, dyspnea, and nonspecific imaging findings and is challenging to diagnose. Many patients are treated for presumed pneumonitis with a prolonged course of daily corticosteroids, with a minimum recommendation of 4 weeks, which places them at greater risk of developing PJP [20].

The PJP risk associated with these therapies has been demonstrated to increase significantly with concomitant glucocorticoid use, as shown in one study of individuals on rituximab for rheumatoid arthritis in whom the incidence of PJP per 100 person-years rose from 0.40 on rituximab alone to 7.93 for individuals receiving glucocorticoids as well [21]. Similar increased rates of PJP have been observed in individuals receiving methotrexate and etanercept [22, 23]. As typically displayed in our case, long-term corticosteroid exposure was the main predisposing factor for PJP in this patient.

Clinical and Radiographic Findings

Pneumocystis pneumonia most commonly manifests with fever, cough, and shortness of breath that progresses throughout the disease. Chest discomfort or pain can also be present. Individuals without HIV typically have a more rapidly progressive course, with symptoms developing over days rather than the weeks [13]. Some degree of hypoxia is typically seen, with many patients progressing to respiratory failure requiring mechanical ventilation. Cough and fatigue are often present. Some patients may present with a subclinical course with minimal to absent systemic symptoms.

Radiographically, PJP most classically manifests as diffuse, bilateral ground glass opacities, often more prominent in the apices, and the perihilar regions (Fig. 1). Traction bronchiolectasis and reticulation may develop but typically resolve within 2 months of

infection. In patients without HIV, consolidative opacities are more likely and tend to develop rapidly [24]. Cystic lesions are seen in only 3% of non-HIV cases, as opposed to up to 56% of individuals with HIV-associated PJP [25].

Mortality of PJP among HIV-negative patients is very high. Mortality ranges from 30 to 40%, higher compared to HIV-positive patients. Additional clinical factors associated with increased mortality include prior steroid use, worse hypoxemia at presentation, pneumothorax, underlying lung disease, hematologic malignancy, and older age [26–28].

> Our patient's symptoms began with fever and shaking chills. Two days later, she was increasingly breathless with a nonproductive cough and a new oxygen requirement of 1 L/min. Over the following 3 days, her oxygen requirement rapidly increased, and she required endotracheal intubation and ventilation for Acute Respiratory Distress Syndrome (ARDS). CT chest imaging showed diffuse opacities (Fig. 1). For our patient, an induced sputum PCR sample was sent, followed by a BAL PCR sample after intubation. Both resulted positive for PJP within 2 days.

Diagnostic Testing

While suspicion of PJP is typically based on clinical factors and imaging results, confirmation of PJP requires specific laboratory testing, including serum markers and organism-specific testing. Lactate dehydrogenase (LDH) is present in many human cells, particularly leukocytes. Elevated serum LDH is a sensitive but not specific marker for PJP, as serum LDH typically rises with any lung injury process. The value of serum LDH as a test for PJP is reportedly lower outside of HIV-infected patients. The sensitivity of elevated serum LDH (any elevation) for PCP has been estimated to be 66–91% and specificity to be 36–52%, with most data obtained from HIV patients [29]. Tasaka et al. reported the positive predictive value (PPV) and negative predictive value (NPV) of LDH (cutoff 268 IU/L) at 0.24 and 0.94, respectively [30]. (1,3)-beta-D-glucan (BDG) is the most advantageous serum biomarker for PJP assessment. BDG is a polysaccharide found in the cell walls of many (but not all) bacteria and fungi. In the USA, the Fungitell® assay (Associates of Cape Cod, Inc.) is most often performed, whereas in Japan and Europe, other testing systems are commercially available (Fungitec-G, Seikagaku Biobusiness, Tokyo, Japan; Wako, Wako Pure Chemical Industries, Osaka, Japan). The BDG assay is a serum marker for invasive fungal infection, detecting BDG released into serum by many invasive fungi besides PJP. These fungi include *Aspergillus*, *Histoplasma* (but not *Blastomyces*), *Candida*, *Coccidioides*, *Fusarium*, *Trichosporon*, and multiple other fungi. Invasive bacteria such as *S. pneumoniae* and *P. aeruginosa* can also elevate serum BDG. Thus, at the outset, serum BDG testing is not specific to PJP among fungi. Notably, testing of BDG in BAL fluid has been studied, but specificity (BAL 39%; serum 92%) deteriorated due to the frequent airway colonization with other fungi and bacteria, and sensitivity (BAL 95%; serum 91%) appeared only slightly better than serum BDG testing in both HIV-negative and HIV-positive populations [31, 32]. The PPV and NPV in that study were 61% and 98%, respectively. The sensitivity and specificity of serum BDG reported by Karageorgopoulos et al. were 95% and 86%, respectively, with positive and negative likelihood ratios of 6.9 and 0.06 [33].

Esteves et al. reported better operating characteristics when combined testing of BDG and LDH was performed in HIV patients with pneumonia. This study determined the best cutoff levels for PJP diagnosis were 350 U/l of LDH and 400 pg/ml of BDG. When combined with clinical data, the authors reported 93% sensitivity and 84% specificity [29]. Thus, the very low PPV of serum LDH testing does not compensate for its higher NPV. BDG testing has better operating characteristics for PJP diagnosis and thus has supplanted serum LDH testing in most situations. Serum LDH testing still has a role in resource-limited settings that cannot perform serum BDG testing or where serum BDG testing is a send-out test with an unacceptable turnaround time. LDH and BDG can increase pretest probability and are typically widely available with quick turnaround times. Procalcitonin (PCT) and C-reactive protein (CRP) do not have value in PJP diagnosis [34, 35].

Sputum testing is appealing as the main pathway for specific tests for PJP. HIV-positive patients have a much higher burden of fungal organisms in their lungs, which results in increased diagnostic yield of sputum and BAL to confirm PJP [36]. In contrast, non-HIV patients typically have lower fungal burdens, lowering test sensitivity [37]. Sputum can be tested after spontaneous cough (non-induced), after cough induction by hypertonic saline (induced sputum, or IS), by endotracheal aspirates (in already intubated patients), or by bronchoscopy. Bronchoalveolar lavage (BAL) without prior sputum testing is performed in many cases. Of note, adding transbronchial lung biopsy increases risk and does not appear to increase sensitivity for detecting the majority of fungal infections versus BAL alone, although data regarding the yield of transbronchial biopsy for PJP specifically is limited [38]. Oral rinses (saline gargles of up to 50 ml for 10–30 s), targeted at detecting residual upper airway organisms in coughing patients, have been reported as nearing sputum testing in utility for PJP diagnosis but appear best suited to pediatric populations where IS and bronchoscopy are more difficult to perform (sampling of nasal secretions may be useful in infants) [39]. The use of non-induced, expectorated sputum is a simple approach that has been reported to have high sensitivity that approaches IS in HIV patients. Still, the higher concentration of mucins in non-induced sputum may limit PCR efficiency. Thus, many hospitals and regional reference labs do not recommend using non-induced sputum for *Pneumocystis* testing [40]. In high-resource areas and cases of high suspicion of PCP, a BAL is recommended if negative IS results are obtained. Like other tests, a long turnaround time for results may diminish the appeal of the lower-yield IS method in favor of the higher-yield BAL approach.

In intubated patients, particularly those with severe hypoxemia, testing for PJP with suctioned endotracheal aspirates (EA) may be appealing as the risks of clinical deterioration during bronchoscopy and BAL are higher. Moreover, EA appears more cost-effective if it does not delay diagnosis and treatment or lengthen ICU stay. The sensitivity and specificity of EA have been reported as approaching BAL by one group, where 92% of BAL (+) PJP subjects were also identified by EA. In this study, immunofluorescence antibody sensitivity for PJP was better than histologic techniques using calcofluor-white stain [41]. BAL has the highest sensitivity for diagnosing PJP. However, bronchoscopy to obtain samples has attendant risks and costs that may diminish its appeal in certain patients. BAL has the additional value of diagnosing other conditions and providing cell count and differential data that may aid diagnosis and management. BAL is most appealing to perform

in patients already intubated and not on high FiO2. Bronchial aspirates obtained during bronchoscopy may yield increased fungal loads compared to BAL fluid in patients with pneumocystis pneumonia [42]. The diagnosis of PJP on lung histology is typically made only serendipitously when other diagnoses are being considered or when lung biopsy or resection are performed for different reasons.

Histology stains include Grocott-Gömöri's methenamine silver stain (GMS, "silver stain") and calcofluor white (CWS, a fluorescent blue dye that binds to cellulose and chitin). During the HIV pandemic in the 1990s, multiple antibodies to *Pneumocystis jirovecii* were developed and utilized to improve detection sensitivity. This technique is called direct fluorescent antigen (DFA) testing [43]. These assays stain trophozoites and cysts, an advantage over nonimmune stains, as trophozoite life forms are much more abundant than cysts (10:1 ratio) in PJP. Visualizing ≥ 1 cluster of fungi with *Pneumocystis jirovecii* morphology with any staining method is considered a positive result. Other fungi typically stain poorly or not at all with immune stains. Sensitivity ranges from 48 to 100%, but with a high specificity of 82–100%. Multiple studies report a higher sensitivity for DFA than nonimmune stains, particularly in HIV patients [43, 44]. These stains require a fluorescent microscope, often precluding their use in resource-limited settings or making these tests feasible only in a reference laboratory (as opposed to other nonimmune stains such as GMS), and the cost of DFA may be higher than for nonimmune staining.

Due to the limitations and expertise required for staining techniques and interpretation and the lower amounts of PJP organisms in early infection and non-HIV hosts, PCR detection has become the dominant testing technique in many hospitals and reference laboratories in resource-rich countries. PCR testing is the most sensitive technique available. However, it is limited by its possible misidentification of low-level colonization versus actual infection and by PCR inhibitors in secretions that can block gene amplification [45].

PCR testing is more sensitive than DFA in most reports. Hauser et al. reported PCR sensitivity, specificity, PPV, and NPV of 93%, 90%, 65%, and 98%, while DFA testing values were 93%, 100%, 100%, and 98%, respectively [46]. Due to its tendency to amplify colonizing fungi DNA, PCR has a lower PPV for PJP than DFA. Similarly, compared to nonimmune staining, the sensitivity and specificity of PCR were reported by Flori et al. to be 100% and 87%, while nonimmune staining values were 60% and 100%, respectively [47]. In most reports, a negative qualitative PCR (qPCR) assay (Ct > 45) rules out PCP. A strongly positive PCR (Ct < 32) confirms PCP [48]. Curation of specific Ct cutoffs differentiated colonized (often referred to by an "indeterminate" result) and infected HIV-positive patients with 100% sensitivity and specificity in BAL samples. However, Ct results are not typically available to clinicians within many test reports [49].

Unbiased blood assay for any infection is a novel technique where circulating DNA (cfDNA) can be identified by shotgun DNA sequencing in a hospital or referral laboratory. Such methods are among the most expensive (particularly for equipment purchase), but such expenses may soon be less than that of BAL. Diagnoses of PJP have been reported with this technique, which is attractive, as blood PCR for *Pneumocystis* was previously reported as not being useful [50•, 51].

While specific PJP tests may have appealing sensitivity and specificity, cost and the need for local investment or alternate use of a reference laboratory should be considered at an administrative level in deciding the best techniques to employ at individual institutions. In one modeling study with a 50% PJP pretest prevalence, procedures using expectorated sputum with PCR, or IS with PCR, were all highly cost-effective — successfully treating 77–90% of patients at $26–51 per life-year gained. Procedures using BAL specimens were significantly more expensive — without added benefit, successfully treating 68–90% of patients at $189–232 per life-year gained [52].

> As in our patient, intubation facilitated the performance of BAL for specific PJP testing. BAL was performed as results for the IS sample performed a day prior were not yet available. LDH and BDG may serve as initial stratification and consideration for empiric therapy if elevated while waiting for confirmatory testing.

Our patient began treatment with 15 mg/kg/day TMP-SMX and prednisone 60 mg/day with a plan for subsequent taper. Therapy was initiated before confirmation of PJP infection, given the great concern and severity of the illness. Despite treatment, she unfortunately passed away from respiratory failure due to PJP.

Treatment

When PJP is suspected or confirmed, treatment should be initiated with trimethoprim-sulfamethoxazole (TMP-SMX). While traditional dosing recommendations have been to treat with 15–20 mg/kg/day of TMP, patients frequently have renal and hematologic side effects from this dose, most often hyperkalemia and agranulocytosis. New data suggest that lower doses of TMP-SMX, < 12.5 mg/kg/day of TMP, might be just as effective for PJP treatment while decreasing side effects [53, 54••]. The bioavailability of TMP-SMX is excellent, 97.5–101.8%, making oral therapy a safe, effective, and affordable option for treatment [55]. Given that sulfamethoxazole is a CYP2C9 inhibitor metabolized via the CYP450 system, caution should be taken when TMP-SMX is used in individuals on warfarin, phenytoin, and oral diabetic agents in particular, as it may lead to increased concentrations of these medications. In addition, use of TMP-SMX with ACE inhibitors or potassium-sparing diuretics may contribute to the development of hyperkalemia [56]. In severe cases, some experts advocate the use of combination therapy with an echinocandin, although the efficacy of this combination is not proven. There are calls for a potential clinical trial among HIV-negative patients comparing IV TMP-SMX plus caspofungin (intervention group) vs. IV TMP-SMX monotherapy (control group) [57].

The use of adjunctive corticosteroids in treatment does not play a role in treating mild or moderate disease. Still, it has a controversial benefit in HIV-negative patients with severe illness and hypoxemic respiratory failure [58]. A recent multicenter cohort did not observe any benefit of adjunctive corticosteroids on a solid organ transplant population with PJP [59•]. A prior meta-analysis also failed to demonstrate any benefit among HIV-negative patients [60]. Also, the majority of NHNT patients with PJP are already on steroids, suggesting minimal to no additional benefit. The potential benefit of corticosteroids is perhaps mediated by diminished immune-mediated lysis of *Pneumocystis* organism, decreasing surfactant inactivation [61]. While the optimal dose has yet to be determined,

prednisone of at least 60 mg/day or 1 mg/kg/day has been utilized. The most widely utilized recommendation for prednisone duration suggests 5 days of high-dose therapy, followed by 5 days of prednisone 40 mg daily and 20 mg prednisone daily for pneumocystis treatment based on studies in HIV patients [62, 63].

For patients who cannot tolerate TMP-SMX, a combination of clindamycin and primaquine is preferred as a second-line therapy for moderate to severe disease (Table 2). While not established, cases of successful treatment with echinocandins and promising mouse model studies suggest that this may become a future therapeutic option [64].

As reflected in our case, mortality remains elevated for those presenting with severe hypoxemic respiratory failure and on previous corticosteroids.

Prophylaxis and Prevention

Current recommendations are to start prophylaxis against PJP once a patient has received the equivalent of 20 mg prednisone daily for 4 weeks or longer, particularly if they have an underlying immunosuppressive condition or additional immunosuppressive therapy [65, 66]. However, this threshold may be shifting as the 2022 EULAR recommendations suggest the initiation of prophylaxis for those receiving more than 15 mg daily prednisone for at least 2 weeks [67]. While prednisone has historically been the steroid most associated with the development of PJP, recent literature has additionally demonstrated its occurrence with other steroids, such as dexamethasone [23]. Additionally, the steroid dose at which patients on additional immunosuppression developed PJP was, in many cases, lower than the previously recommended threshold dosing for prophylaxis. These data suggest that combined immunosuppression places patients at greater risk of developing PJP and thus requires careful prophylaxis consideration.

With regards to oncologic therapy and prophylaxis, NCCN guidelines recommend the use of prophylaxis for at least 6 months following hematopoietic cell transplant and for those on CAR T-cell therapy [68]. Those with ALL should be prophylaxed throughout anti-leukemic therapy. Current guidelines also suggest the consideration of PJP prophylaxis for patients on nucleoside analogs such as gemcitabine, anti-CD52 monoclonal antibodies like alemtuzumab, and alkylating agents such as temozolomide until a patient’s CD4 count has recovered to above 200 cells/mcL [66, 68].

The current first-line prophylactic regimen for PJP in at-risk groups is trimethoprim-sulfamethoxazole (TMP-SMX) (Table 2). Dosing should be adjusted for impaired renal function; for patients who are intolerant of TMP-SMX, such as those with sulfa allergies, desensitization can be attempted. If desensitization fails, dapsone is the accepted second-line alternative. Atovaquone is preferred in patients who have undergone hematopoietic cell transplantation. Pentamidine, primaquine, and clindamycin are acceptable alternatives [69]. These second-line therapies are often better tolerated but are generally less effective [70].

Recent research has added nuance to the distribution, clinical implementation, and efficacy of PJP prophylaxis. Recent findings continue to support TMP-SMX as a robust first-line prophylaxis for PJP. A study of 1092 patients with rheumatic disease receiving high-dose

steroids found that patients receiving TMP-SMX prophylaxis had a significantly reduced incidence of PJP and related mortality. The same study demonstrated fewer adverse TMP-SMX reactions, with a number needed to treat of 52 compared to a number needed to harm of 131 [21]. Despite the efficacy of TMP-SMX prophylaxis, clinical implementation can be inconsistent. A 2022 study found that in 617 systemic lupus erythematosus patients receiving immunosuppressive therapy, only 128 (21%) were given prophylaxis [71]. One possible explanation for the inconsistency of prevention may be its expanding range of associated pathology. A 2022 case series found that of 20 confirmed PJP cases in a large Italian hospital, only 9 cases had a main indication for PJP prophylaxis [72]. Additionally, contradictory data is emerging regarding prophylaxis in the setting of emerging new therapies such as immune checkpoint inhibitors (ICI). Another recent study reported a high rate (43%) of breakthrough PJP in patients receiving ICI therapies and glucocorticoids despite prophylaxis [73]. Individuals with primary immunodeficiency syndromes and Acute Lymphoblastic Leukemia (ALL) are recommended to take prophylaxis against PJP infection, given their specifically increased risk [66]. Additional research is warranted regarding the implementation and efficacy of PJP prophylaxis in the expanding spectrum of vulnerable groups. As in our case, implementation of PJP prophylaxis in HIV-negative patients at risk can be cost-effective and lifesaving.

Conclusion

Over the preceding decades, *Pneumocystis jirovecii* pneumonia has transformed from a disease primarily affecting individuals with uncontrolled HIV to one increasingly associated with malignancy and autoimmune disease, as well as the treatments for these conditions. As the incidence of PJP increases, and current therapeutic options remain limited, it is crucially important to understand the factors that place patients at increased risk for this devastating and potentially fatal disease.

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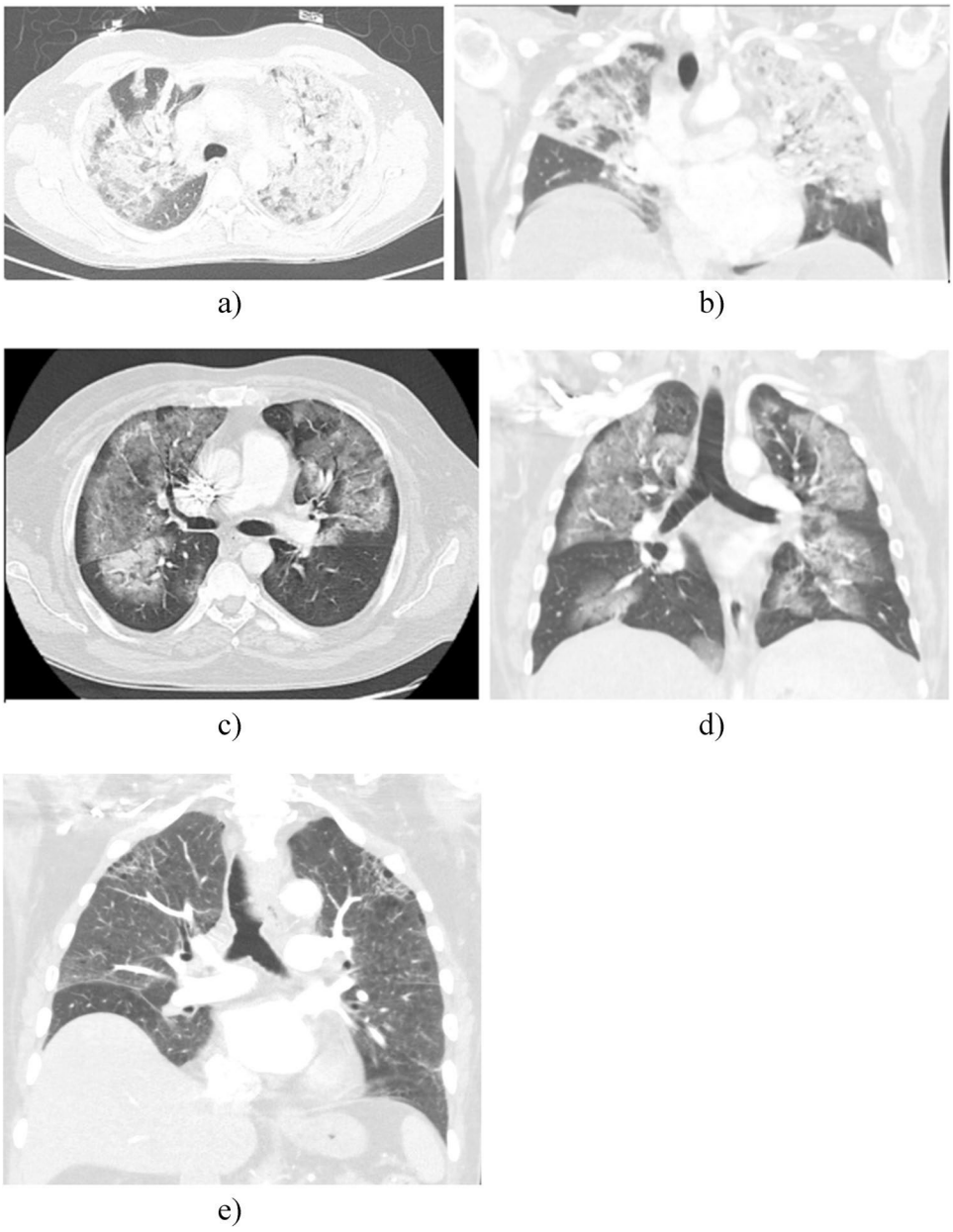

Fig. 1.

CT Findings of pneumocystis pneumonia. **a** Axial view and **b** coronal view of severe PJP with diffuse apical predominant consolidative opacities in a 34-year-old female with autoimmune hepatitis (AIH) on prednisone. **c** Axial view and **d** coronal view of PJP with diffuse ground glass opacities and subpleural sparing in a 56-year-old female on dexamethasone. **e** Coronal view of PJP with cystic lesions in a 72-year-old male with rheumatoid arthritis on rituximab

Table 1

Conditions and medications associated with the development of pneumocystis pneumonia in non-HIV, non-transplant patients

Diseases	Example	Associated risk
Malignancy, solid organ	CNS cancer, breast cancer	< 25 cases per 100,000 [7]
Malignancy, hematopoietic	Acute Lymphoblastic Leukemia (ALL), non-Hodgkin's lymphoma	Incidence 25–42% in ALL, up to 25% in non-Hodgkin's lymphoma [19]
Vasculitis	Granulomatosis with polyangiitis, polyarteritis nodosa	72 per 100,000 cases in GPA, 92 per 100,000 cases in PAN [2]
Cardiac disease	Cardiomyopathy, Tetralogy of Fallot	22% of pediatric cases [2]
Primary immunodeficiency	SCID	SCID in 19% of pediatric cases [2]
Medication class	Examples	Factors increasing PJP risk
Corticosteroid	Prednisone, dexamethasone	Equivalent of prednisone 20 mg/day for 4 weeks [67]
Monoclonal antibody	Rituximab	Consider ppx if on rituximab alone, recommended if also on steroid [21]
Antimetabolites	Methotrexate	Concomitant steroid or additional DMARD use, serum albumin < 3.5 risk factors [22]
Thiopurines	Azathioprine, 6-MP	Up to 42% of PJP cases in patients with IBD, typically in conjunction with corticosteroids. Majority have lymphopenia [15]
TNF-alpha inhibitors	Infliximab	Risk increases with concomitant immunosuppression. Mean time of onset 21 days, mortality for infliximab-associated PJP 27% [16]
Immune checkpoint inhibitor	Nivolumab, pembrolizumab	ICI toxicity treatment with glucocorticoids increases risk of PJP. No definite associations with ICI use alone [9]
Kinase inhibitors	Idelalisib, ibrutinib	PJP occurs in up to 3.5% not on prophylaxis, risk increased with concomitant steroid use [18, 19]
Nucleoside analog	Gemcitabine	Up to 18% of lymphoma patients not on prophylaxis, fewer with breast/lung/GI malignancy. Concomitant steroids increase risk [17]
Alkylating agents	Temozolomide	Recommended to utilize prophylaxis if combined with radiotherapy due to concomitant steroid use [66]

CNS central nervous system, *SCID* severe combined immunodeficiency, *Ppx* prophylaxis, *DMARD* disease modifying antirheumatic drug, *IBD* inflammatory bowel disease, *ICI* immune checkpoint inhibitor, *GI* gastrointestinal, *PAN* Polyarteritis nodosa, *PPx* prophylaxis, *GPA* Granulomatosis with polyangiitis

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Table 2

Prophylaxis and treatment for pneumocystis pneumonia

Prophylaxis	Dose	Duration	Special considerations
TMP-SMX	1 SS tablet daily or 1 DS tablet 3 × / week	During use of immune suppressant	Anti-folate activity may contribute to macrocytic anemia, thrombocytopenia, leukopenia
Dapsone	100 mg daily		Hemolytic anemia if G6PD deficiency
Atovaquone	1500 mg once daily with food		Liquid
Pentamidine	300 mg monthly		Nebulized
Dapsone, pyrimethamine, and leucovorin	200 mg, 75 mg, and 25 mg weekly		
Treatment	Dose	Duration	Special considerations
Trimethoprim-sulfamethoxazole (TMP-SMX)	15–20 mg/kg/day TMP divided TID or QID	21 days	Rash (rare SJS), hyperkalemia
TMP + dapsone	5 mg/kg/day TMP 3/day + 100 mg dapsone daily		
Primaquine + clindamycin	30 mg primaquine daily + Clinda IV 900 mg Q8H or 600 Q6H, or PO 600 TID		
Atovaquone	750 mg BID		Must take with food
Pentamidine	4 mg/kg IV daily		Nephrotoxicity, arrhythmia, pancreatitis, hypoglycemia, hypotension

SS single strength, *DS* double strength, *G6PD* glucose-6-phosphate dehydrodgenase, *SJS* Stevens-Johnson syndrome