Clinical, Diagnostic, and Treatment Disparities between HIV-Infected and Non-HIV-Infected Immunocompromised Patients with *Pneumocystis jirovecii* Pneumonia

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Keywords

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Abstract

The substantial decline in the *Pneumocystis jirovecii* pneumonia (PCP) incidence in HIV-infected patients after the introduction of antiretroviral therapy (ART) in resource-rich settings and the growing number of non-HIV-infected immunocompromised patients at risk leads to considerable epidemiologic changes with clinical, diagnostic, and treatment consequences for physicians. HIV-infected patients usually develop a subacute course of disease, while non-HIV-infected immunocompromised patients are characterized

by a rapid disease progression with higher risk of respiratory failure and higher mortality. The main symptoms usually include exertional dyspnea, dry cough, and subfebrile temperature or fever. Lactate dehydrogenase may be elevated. Typical findings on computed tomography scans of the chest are bilateral ground-glass opacities with or without cystic lesions, which are usually associated with the presence of AIDS. Empiric treatment should be initiated as soon as PCP is suspected. Bronchoalveolar lavage has a higher diagnostic yield compared to induced sputum. Immunofluorescence is superior to conventional staining. A combination of different diagnostic tests such as microscopy, polymerase chain reaction, and (1,3)- β -D-glucan is recommended. Trimethoprim/sulfamethoxazole for 21 days is the treatment of choice in adults and children. Alternative treatment regimens include dapsone with trimethoprim, clindamycin with

primaquine, atovaquone, or pentamidine. Patients with moderate to severe disease should receive adjunctive corticosteroids. In newly diagnosed HIV-infected patients with PCP, ART should be initiated as soon as possible. In non-HIV-infected immunocompromised patients, improvement of the immune status should be discussed (e.g., temporary reduction of immunosuppressive agents). PCP prophylaxis is effective and depends on the immune status of the patient and the underlying immunocompromising disease.

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Case Report

A 48-year-old previously healthy man was admitted to our hospital with a 5-week medical history of increasing exercise-induced shortness of breath. He had lost 6 kg of weight within the last 2 months. During the past 3 weeks he had experienced night sweats. He reported increasing dry cough over 4 days prior to admission.

Upon admission his body mass index was 22.8 (180 cm, 74 kg). He was in a trained physical condition. Musculoskeletal system examination and neurological examination were without pathological findings. On the skin of his forehead there was an efflorescence compatible with seborrheic dermatitis. There was no jaundice, anemia, finger clubbing, or cyanosis present. On the neck, both axillas, and groins there were pea-sized palpable lymph nodes. He was febrile with a temperature of 39.5 °C. Cottage cheese-like plaques were visible on the hard palate and pharynx, compatible with *Candida* stomatitis and pharyngitis. His heart rate was 92 beats/min and his blood pressure 120/70 mm Hg. His respiration rate at rest was 23 breaths/min. The breath sounds were vesicular over both lung fields. Arterial blood gas analysis showed

a pO₂ of 62 mm Hg, a pCO₂ of 31 mm Hg, and a pH of 7.47 on room air. Oxygen saturation was 92% and dropped to 86% after 3 min of walking horizontally. Lung function test showed a reduced forced vital capacity of 64% with a nonobstructive forced expiratory volume in 1 s/forced vital capacity ratio of 96%, indicating a restrictive spirometry pattern with a reduced diffusing capacity of the lung of 35%.

Routine laboratory values were within normal limits, except for a serum lactate dehydrogenase (LDH) level of 338 U/L (normal <252 U/L), a hemoglobin concentration of 12.1 g/dL (normal 13.5–17.5 g/dL), and a C-reactive protein level of 2.08 mg/dL (normal <0.5 mg/dL). An HIV screening test was reactive with a positive HIV-1 Western blot test result. The HIV RNA concentration was 34,618 copies/mL. The number of circulating CD4+ T lymphocytes was 124/μL (7%) and the number of CD8+ T lymphocytes was 1,276/μL (67%), resulting in a CD4:CD8 ratio of 0.1 (normal 1.2–2.7).

Chest X-ray showed bilateral perihilar ground-glass opacities with interstitial thickening. There was no pleural effusion or cavitation visible. A computed tomography (CT) scan of the chest showed multifocal ground-glass opacities, compatible with the diagnosis of alveolitis (Fig. 1).

On bronchoscopy the visual aspect of the trachea and bronchial tree was without pathological findings. Bronchoalveolar lavage (BAL) demonstrated 16 × 10⁶ cells/100 mL (normal 3–12 × 10⁶ cells/100 mL), with a differential cell count of 13% lymphocytes (normal <10%), 26% macrophages (normal >85%), 60% neutrophils (normal <3%), and 1% eosinophils (normal <0.5%). Grocott-Gomori methenamine silver staining of the BAL fluid identified multiple spherical, oval asci/cysts 5–6 μm in diameter, compatible with the diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) (Fig. 2). Treatment with trimethoprim/sulfamethoxazole (TMP/SMX) for 21 days as well as antiretroviral therapy (ART) was initiated. After 8 weeks the patient's symptoms and radiological changes had resolved completely.

Fig. 1. Axial computed tomography scan of the chest showing diffuse bilateral ground-glass opacities due to an alveolitis in *Pneumocystis jirovecii* pneumonia.

Fig. 2. Microscopic image of black *Pneumocystis jirovecii* cysts of 5–6 μm in a bronchoalveolar lavage fluid cell pellet after centrifugation. Grocott-Gomori methenamine silver staining, ×1,000.

Epidemiology and Risk Groups

HIV-Infected Patients

While PCP was rarely described before the HIV/AIDS epidemic, the incidence of PCP increased rapidly during the 1980s, with PCP occurring in 75% of individuals with AIDS, resulting in mortality rates up to 40% [1]. Given the fact that >90% of PCP cases occurred in patients with CD4+ T lymphocyte counts <200 cells/mm³, the infection became one of the main AIDS-defining illnesses [1]. Since then, the widespread use of PCP prophylaxis with TMP/SMX and early ART have led to a substantial decline in the PCP incidence among individuals with HIV infection. Studies in the early 2000s reported an incidence of PCP among HIV-infected individuals below 1 case per 100 person-years [2–8]. Given the trend towards earlier diagnosis of HIV infection and immediate ART independent of CD4+ T cell count, the incidence of PCP in HIV patients has likely decreased further during recent years [9–12].

Despite its decreasing incidence, PCP is still a serious health concern for people living with HIV/AIDS [13]. Since there is no national surveillance for PCP in the United States and other resource-rich countries, the exact number of cases is difficult to determine. While fewer HIV-infected individuals develop opportunistic infections in resource-rich settings overall, PCP is still one of the most common opportunistic infections in HIV patients in the United States, Canada, and Europe [2, 13]. It mainly affects individuals who are unaware of their HIV infection or who get diagnosed late (i.e., late presenters) or are not receiving ongoing care for HIV infection [14, 15]. Late HIV diagnosis as the major risk factor for PCP is significantly more frequent among populations suffering from healthcare disparities [16]. PCP remains also very common as an opportunistic infection among people living with HIV/AIDS in resource-limited countries (see PCP from a Global Health Perspective with Emphasis on Resource-Limited Settings) [17].

Non-HIV-Infected Patients with Other Immunocompromising Reasons

PCP is increasingly diagnosed in non-HIV-infected immunocompromised patients, indicating new challenges for the diagnosis, treatment, and prophylaxis in a larger susceptible population [18–20]. In contrast to HIV-infected patients, there is evidence for a more acute onset of symptoms, faster progression of disease, poorer outcome, higher mortality, and higher risk of coinfections [9, 21–24].

Posttransplant Patients. Both patients undergoing hematopoietic stem cell transplantation (HSCT) and patients undergoing solid organ transplantation (SOT) are at risk of PCP (5–15% of cases), which is higher after allogeneic versus autologous HSCT and after heart and/or lung SOT versus for instance renal transplantation [19, 20, 25, 26].

Hematooncologic Patients. Particularly patients with leukemia (such as acute lymphatic leukemia) and lymphoproliferative disorders (such as chronic lymphatic leukemia and non-Hodgkin lymphomas) have a substantial risk of developing PCP. Certain chemotherapeutic agents are more predisposing to PCP, including corticosteroids, cyclophosphamide, methotrexate, vincristine, cytarabine, fludarabine, temozolomide, rituximab, alemtuzumab, ibrutinib, and idelalisib [27–30].

Patients under Immunosuppressive Drugs due to Autoimmune Diseases. Inflammatory diseases, their complications, and immunosuppressive regimens contribute to the risk of PCP. Up to 20% of PCP cases occur in patients with inflammatory diseases, the incidence being especially high in cases of polyarteritis nodosa, granulomatosis with polyangiitis, dermatomyositis/polymyositis, and interstitial lung diseases in patients with rheumatoid arthritis [31, 32]. Furthermore, it depends on the administered immunosuppressant, with following drugs most frequently mentioned: prolonged medium- to high-dose glucocorticoids, cyclophosphamide, rituximab, alemtuzumab, and tumor necrosis factor alpha antagonists [33, 34].

Clinical and Radiological Presentation of PCP

Signs and Symptoms

The classic triad of PCP symptoms in AIDS patients includes (1) subacute onset of exertional dyspnea, (2) dry and nonproductive cough, and (3) fever or subfebrile temperatures (Table 1). The subacute course over several days and even weeks often allows differentiation from bacterial pneumonia. Oral thrush and substantial weight loss are also frequently seen in AIDS patients with PCP, as demonstrated in our patient. However, despite the subacute course, deterioration may occur rapidly.

A diagnostic hallmark is respiratory insufficiency, which should be confirmed by arterial blood gas analysis. LDH is often elevated and may have limited use as a predictive parameter for the course of disease. However, a high LDH level is an unfavorable sign and may reflect the severity of the PCP. In contrast, C-reactive protein is of-

Table 1. Disease characteristics of PCP in HIV-positive patients compared to patients with other reasons of immunosuppression

Disease characteristics	HIV-positive/AIDS patients	HIV-negative immunocompromised patients	Commentary
Signs and symptoms	the classic triad in AIDS patients includes (1) exertional dyspnea, (2) dry, nonproductive cough, and (3) fever or subfebrile temperatures	the main symptoms include fever, dyspnea, and nonproductive cough; hypoxia/respiratory failure are more frequent; dyspnea and cough are less frequent; elevation of LDH is less frequent	LDH is of poor predictive value
Severity and course of disease	subacute onset of symptoms; subacute/chronic course (several days to weeks); risk to suddenly deteriorate after a long stable phase of disease	acute onset of clinical symptoms; rapid disease progression (days)	higher mortality in HIV-negative immunocompromised patients (35–50%)
Radiological pattern			
Chest X-ray	perihilar, bilateral, interstitial infiltrates more often cystic lesions/cavities	initial chest X-ray may be unremarkable; alveolar or alveolo-interstitial patterns are less frequent; more often nodules, consolidations, and pleural effusions	consider underlying respiratory disorders and coinfections
CT scan of the chest	bilateral ground-glass opacities (perihilar, diffuse, and/or mosaic pattern) thin-walled cystic lesions of variable size and forms more associated with AIDS	typically widespread ground-glass opacities; less frequently associated with cystic lesions; nodules, consolidations, and pleural effusions may be seen more often	
CT, computed tomography; LDH, lactate dehydrogenase; PCP, <i>Pneumocystis jirovecii</i> pneumonia.			

ten normal, provided there are no other concurrent infections.

Numerous studies have compared the clinical features and the outcome of HIV-infected and non-HIV-infected cases. These comparisons should be considered with caution, as the clinical and therapeutic background of PCP in non-HIV-infected patients with variable immunocompromising disorders is very diverse. In large retrospective cohort studies of PCP cases, however, non-HIV-infected patients were less symptomatic at diagnosis than AIDS patients [19]. On the other hand, the progression of PCP seems to be faster and higher mortality rates have been reported in non-HIV-infected immunocompromised patient compared to HIV-infected patients [35]. The latter may be due in part to the delay of the initiation of a specific anti-infective therapy [9, 19].

Radiological Pattern

X-ray of the chest may show characteristic findings with a perihilar interstitial infiltrate (Fig. 3; Table 1). In non-HIV-infected immunocompromised patients, the initial chest X-ray may be normal due to the acute onset of symptoms and more rapid progression, but generally the features of the chest X-ray are very similar to those found in HIV-infected patients. Sometimes radiological changes are discreet and the X-ray is often inconclusive or does not show lung pathologies seen on CT scan.

High-resolution CT of the chest should be preferred if available, offering a precise description of the radiological pattern with differentiation to other pulmonary diseases [36]. Ground-glass opacities, often with a central distribution as demonstrated by our patient (Fig. 1), are a common radiological pattern of PCP on CT scans, but the distribution can vary from a mosaic pattern to a

Fig. 3. Chest X-ray showing diffuse bilateral infiltrates due to *Pneumocystis jirovecii* pneumonia in an HIV-infected patient with AIDS with a CD4+ T lymphocyte count of 15/μL.

more diffuse pattern. Upper lobe predominance has been described [36]. Other less common manifestations include nodules, consolidations, or thin-walled cystic lesions, sometimes classified as pneumatocele formation, which are usually associated with the presence of AIDS, whereas non-HIV-infected immunocompromised patients usually present with widespread ground-glass opacities [37–39]. Cystic lesions are often small, bilateral, and multiple, but larger pulmonary cystic lesions with the risk of developing a spontaneous pneumothorax have also been reported (Fig. 4) [40]. The name pneumocystis refers to the microscopic image of the fungus and not to the radiological pattern of the disease. In a prospective study including 30 AIDS patients with respiratory symptoms and an uncertain X-ray, the sensitivity and specificity of high-resolution CT was 100 and 83%, with a positive and negative predictive value of 90.5 and 100%, respectively [36].

Diagnosis of PCP

In ill patients with clinical suspicion of PCP, empiric treatment should be started immediately. There is no need to delay treatment initiation for diagnostic assessment since cysts persist for several days in respiratory material, even under PCP-specific treatment [41, 42].

If possible, bronchoscopy with BAL should be performed, because analysis of BAL fluid provides not only a higher diagnostic yield, but also allows exclusion of alternative diagnoses or coinfections, e.g., tuberculosis (TB), histoplasmosis, cytomegalovirus (CMV), etc. In-

Fig. 4. Axial computed tomography scan of the chest showing large cavities with predominance of the right side and diffuse bilateral ground-glass opacities in an HIV-infected patient with AIDS.

Fig. 5. Microscopic image of an indirect immunofluorescence staining using monoclonal antibodies against the asci/cyst form of *Pneumocystis jirovecii* (green, $\times 200$) in a bronchoalveolar lavage fluid of an HIV-positive patient. Clusters of cysts can be observed.

duced sputum with hypertonic saline is a less invasive alternative, but has a lower sensitivity of 55–90% [41, 43].

Active pulmonary TB can be excluded either by microscopic smear, by polymerase chain reaction (PCR) (e.g., GenXpert MTB/rifampicin assay; Cepheid Inc., Sunnyvale, CA, USA), and/or by culture from respiratory samples. For most systemic endemic mycoses causing pulmo-

Table 2. Diagnostic methods for PCP

Diagnostic tests	Material	Pros and cons	Commentary
Microscopy: IF; conventional staining	BAL fluid; induced sputum	<i>Pros:</i> conventional staining commonly available and affordable; IF superior to conventional staining <i>Cons:</i> variable sensitivity of 55–90% for staining (depending on material, specific staining, laboratory experience); less sensitive in HIV-negative immunocompromised patients (lower number of cysts and higher number of inflammatory cells in BAL fluid); consider false-negative test results	BAL should be preferred due to higher diagnostic yield compared to sputum examination; different staining methods with comparable diagnostic performance (e.g., calcofluor white, cresyl violet, Giemsa, Grocott-Gomori methenamine silver, toluidine blue O, or Papanicolaou staining)
PCR	BAL fluid; induced sputum	<i>Pros:</i> sensitivity of PCR > microscopy (conventional staining and IF); qPCR in BAL fluid [46, 72, 73]: sensitivity 94–99%, specificity 89–91% <i>Cons:</i> consider false-positive results (e.g., contamination/colonization); clinical cutoffs not validated	cutoff: 8 copies/5 µL (area under the ROC curve 0.92) [46]; genotyping using multilocus sequence marker for epidemic investigations
(1,3)-β-D-glucan	BAL fluid; serum	<i>Pros:</i> high negative predictive value; useful to exclude PCP; useful to diagnose PCP in patients where a bronchoscopy is not possible <i>Cons:</i> unspecific with the standard cutoff (= panfungal marker); positive (1,3)-β-D-glucan test results should be followed by additional diagnostic tests; not available in many settings	meta-analysis and systematic review [47, 49]: pooled sensitivity of 95–96% and specificity of 84–86%; personal experience shows that (1,3)-β-D-glucan levels in PCP patients are mostly >500 or even >1,000 pg/mL, i.e., much higher than the cutoff of 80 pg/mL

BAL, bronchoalveolar lavage; IF, immunofluorescence; PCP, *Pneumocystis jirovecii* pneumonia; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; ROC, receiver operating characteristic.

nary disease including histoplasmosis, culture or histology from BAL fluid or lung tissue is the method of choice (Salzer et al., *Respiration* 2018, accepted for publication). To exclude CMV pneumonitis, histology from lung tissue may demonstrate characteristic inclusion bodies, and BAL fluid can be used for CMV culture or for viral load testing using quantitative PCR (qPCR) assays.

P. jirovecii does not grow on culture media in vitro. Therefore, PCP diagnosis historically relied on the visualization of cysts or trophic forms from respiratory material (Table 2). Direct or indirect immunofluorescence assay (mainly anticyst antibodies) is the most sensitive microscopic method (Fig. 5) and superior to conventional staining methods (e.g., Grocott-Gomori methenamine silver staining) (Fig. 2). The sensitivity of microscopy is lower in non-HIV-infected compared to HIV-infected patients due to a lower fungal load [42, 44].

PCR is an important additional diagnostic method, especially in non-HIV-infected patients, and may add an additional 7% diagnostic yield compared to staining methods alone [45]. Real-time qPCR should be preferred as the only PCR method compatible with diagnosis and

the Minimum Information for Publication of Quantitative Real-Time PCR Experiments guidelines, but evidence on the validation of clinical cutoffs is limited [45, 46]. This method enables the detection of very low fungal loads, which can be considered as colonization.

A highly sensitive diagnostic method is the serum (1,3)-β-D-glucan assay characterized by its high negative predictive value that makes a PCP infection unlikely in patients with a negative test result [47]. However, it should not be used as a single diagnostic test for PCP, and positive results should trigger a bronchoscopy with BAL [48, 49]. A limitation is that (1,3)-β-D-glucan testing is frequently not available (at least with time to results of <24 h). However, it is rather easy to establish the test on a coagulation automate and do single-sample testing [50]. Diagnostic guidelines commonly recommend combining different methods, e.g., microscopy (immunofluorescence and conventional staining) and qPCR [42]. When analyzed in parallel with qPCR fungal load, a correlation between both markers is observable, suggesting that circulating (1,3)-β-D-glucan levels reflect the fungal load in the lungs [51].

Table 3. Treatment regimens for acute PCP

Treatment regimens	Route	Dosage	Duration	Commentary
First choice				
TMP/SMX	i.v.; p.o.	TMP 15–20 mg and SMX 75–100 mg/kg/day given (i.e., divided up) every 6 or 8 h	21 days	for mild to moderate PCP: p.o. in 3 divided doses or TMP/SMX DS – 2 tablets t.i.d.; for moderate to severe PCP: start i.v. and switch to p.o. after clinical improvement
Alternative				
Dapsone + TMP	p.o.	dapsone 100 mg p.o. daily + TMP 15 mg/kg/day p.o. (3 divided doses)	21 days	option for mild to moderate disease
Clindamycin + primaquine	i.v.; p.o.	clindamycin (i.v. 600 every 6 h or 900 mg every 8 h) or (p.o. 450 mg every 6 h or 600 mg every 8 h) + primaquine 30 mg (base) p.o. once daily	21 days	option for mild to moderate PCP and for moderate to severe PCP; in case of mild to moderate PCP: primarily clindamycin p.o.
Atovaquone	p.o.	750 mg p.o. b.i.d. with food	21 days	option for mild to moderate disease
Pentamidine	i.v.	4 mg/kg i.v. once daily given over at least 60 min	21 days	option for moderate to severe disease; may reduce the dose to 3 mg/kg i.v. once daily in case of toxicity
Caspofungin (alone or in combination with TMP/SMX)	i.v.	caspofungin 70 mg on day 1/50 mg starting on day 2	21 days	second-line (salvage) treatment
Additional treatment				
Prednisone	p.o.	days 1–5: 40 mg b.i.d.; days 6–10: 40 mg daily; days 11–21: 20 mg daily	21 days	for moderate to severe PCP if (1) PaO ₂ <70 mm Hg at room air or (2) alveolar-arterial O ₂ gradient ≥35 mm Hg

b.i.d., twice daily; DS, double strength; i.v., intravenous; p.o., per os; PCP, *Pneumocystis jirovecii* pneumonia; SMX, sulfamethoxazole; t.i.d., three times daily; TMP, trimethoprim.

Management of PCP

Treatment of Acute PCP

TMP/SMX is the treatment of choice for PCP in adults and children, being as effective as parenteral pentamidine and more effective than other regimens. Treatment is generally administered over 21 days (Table 3) [52]. In patients with mild to moderate disease, oral outpatient therapy with TMP/SMX may be considered. The TMP/SMX dosage needs to be adjusted to renal function (Table 4). TMP/SMX is usually also effective in patients who have PCP despite TMP/SMX prophylaxis [42].

Clinical deterioration may occur during the first 4–8 days of treatment. It is important that this deterioration has been frequently seen in the era before the introduction of highly active ART. Deterioration usually neither indicates immune reconstitution inflammatory syn-

drome (IRIS) (very rare) nor treatment failure. It is probably due to an inflammatory response caused by antimicrobial-induced lysis of organisms in the lung (that is why steroids may be helpful). Patients can deteriorate rapidly during treatment, so close monitoring of respiratory rate and arterial oxygenation are essential. Nevertheless, physicians must be aware that clinical worsening rebound phenomena after initial improvements have also been observed in HIV-coinfected patients treated with ART that have been attributed to IRIS [53].

Alternative therapeutic regimens for mild to moderate and moderate to severe disease are depicted in Table 3. Dosages for renal impairment and dosage recommendations for children, as well as the most common adverse events and costs of the therapeutic regimens, are displayed in Table 4. All patients with documented or suspected PCP and moderate to severe disease should receive

Table 4. Renal adaption, child dosage, side effects, and costs of PCP treatment regimens

Treatment regimens	Renal adaption			Child dosage	Side effects	Costs ^a	Commentary
	GFR 10–30 mL/min	GFR <10 mL/min	dialysis				
TMP/SMX	5 mg/kg (TMP) i.v. every 12 h or TMP/SMX 2 DS tablets p.o. every 12 h	5 mg/kg (TMP) i.v. every 24 h or TMP/SMX DS tablet p.o. every 12 h	5 mg/kg/day (TMP) i.v. or 2 TMP/SMX DS tablets p.o.; dose after dialysis on dialysis days	children aged >2 months: 3.75–5 mg/kg/day (TMP) and 19–25 mg/kg/day (SMX) i.v. every 6 h, given over 1 h for 21 days; for mild to moderate diseases transition to oral treatment with same total daily dose possible; effective therapeutic serum concentrations: 5–10 µg/mL TMP	diarrhea, thrombocytopenia, hyperkalemia, gastrointestinal symptoms, rash, myalgia, arthralgia, fever	USD 0.40 per tablet; USD 40 per i.v. dose	in case of dialysis consider therapeutic drug monitoring to optimize therapy (target TMP concentrations: 5–8 mg/mL)
Dapsone + TMP	dapsone: probably no adjustment needed; TMP: see above	dapsone: probably no adjustment needed; TMP: see above	dapsone: probably no adjustment needed; TMP: see above	adolescents: 100 mg dapsone p.o. once daily; in children aged <13 years: 2 mg/kg dapsone p.o. once daily; TMP: see above	dapsone: hemolysis, toxic hepatitis, hypersensitivity syndrome	dapsone: USD 2 per 25-mg tablet	CAVE: do not use in those with glucose-6-phosphate dehydrogenase deficiency
Clindamycin + primaquine	clindamycin: no adjustment; primaquine: no data	clindamycin: no adjustment; primaquine: no data	clindamycin: no adjustment; primaquine: no data	infants/children: 10 mg/kg/dose i.v./p.o. every 6 h (max. 600 mg i.v., max. 450 mg p.o.) with primaquine (0.3 mg/kg/day base); adolescents: 600 mg i.v. every 6 h or 300 mg p.o. every 6 h or 450 mg p.o. every 8 h with primaquine (0.3 mg/kg/day base)	clindamycin: diarrhea, gastrointestinal intolerance; primaquine: heartburn, itching, skin rash, pain or discomfort in the chest, upper stomach, or throat, stomach cramps	USD 25 per i.v. clindamycin/p.o. primaquine dose	limited pediatric data
Atovaquone	no data	no data	no data	adolescents ≥13 years: 750 mg/dose (5 mL) p.o. twice daily with food; children <3 months and >24 months to 12 years: 30–40 mg/kg/dose p.o. once a day with food; children 2–24 months: 45 mg/kg/dose once daily	cough or hoarseness, difficult or labored breathing, fever or chills, lower back or side pain, painful or difficult urination, tightness in the chest	USD 25 per 5 mL solution	
Pentamidine	for GFR 10–50 mL/min: 3 mg/kg i.v. every 24 h	4 mg/kg i.v. every 48 h	–	4 mg/kg i.v. once daily for 21 days; in case of clinical improvement switch to oral atovaquone or TMP/dapsone after 7–10 days possible	burning pain, dryness, or sensation of lump in throat, chest pain, coughing, difficulty in breathing, difficulty in swallowing, skin rash, wheezing, pancytopenia	USD 45 per dose	
Caspofungin	no adjustment needed			<3 months: safety and efficacy not established, limited data suggest off-label dose of 25 mg/m ² /dose i.v. once daily; ≥3 months: day 1 loading dose of 70 mg/m ² i.v. infused over 1 h, maintenance 50 mg/m ² i.v. infused over 1 h	overall well tolerated; phlebitis, diarrhea, and rash may occur	USD 300–360 per day	

DS, double strength; GFR, glomerular filtration rate; i.v., intravenous; p.o., per os; PCP, *Pneumocystis jirovecii* pneumonia; SMX, sulfamethoxazole; TMP, trimethoprim. ^a Costs depend on each country and are provided for the United States.

adjunctive corticosteroids as early as possible and always within 72 h after starting specific PCP therapy (Table 3). However, this has only been validated in HIV-infected patients and the classification of mild, moderate, and severe disease is not precisely defined. Early predictors of

mortality may be useful to assess the risk of death as shown for HIV-infected patients including older age, second or third episode of PCP, low hemoglobin level, low PaO₂ breathing room air at admission, pulmonary Kaposi sarcoma, and medical comorbidities [54].

Table 5. Primary and secondary prophylaxis in HIV-positive and HIV-negative immunocompromised patients based on available recommendations

	HIV-positive patients	HIV-negative immunocompromised patients
When to start prophylaxis?	CD4 count <200/ μ L (or <14% of the total lymphocyte count); recurrent thrush or relevant concomitant immunosuppression	<p>allogenic and selected autologous HSCT recipients: from engraftment at least for 6 months and if immunosuppression is ongoing [9]</p> <p>SOT recipients: for at least 6–12 months post transplantation; consider longer durations (e.g., lung and small bowel transplant, cytomegalovirus disease [26])</p> <p>hematooncologic patients [58]: glucocorticoids: dose equivalent ≥ 20 mg of prednisone/day for 1 month or longer alone or in combination with additional immunosuppressive drugs specific recommendations mentioned for alemtuzumab, temozolomide, purine analogs (e.g., fludarabine) acute lymphoblastic leukemia: from induction to end of maintenance all patients treated successfully for PCP should receive a secondary anti-PCP prophylaxis (same regimens preferred as for primary prophylaxis)</p> <p>patients with anti-neutrophil cytoplasmic antibody-associated vasculitis receiving cyclophosphamide [32]</p> <p>consider prophylaxis in immunocompromised patients with a combination of risk factors such as older age and pulmonary comorbidity with higher doses of glucocorticosteroids (≥ 15–20 mg/day) for a longer time period or other immunosuppressive drugs (e.g., TNFα antagonists in inflammatory diseases) or patients with an idiopathic immunodeficiency (e.g., severe combined immunodeficiency or idiopathic CD4 T lymphocytopenia with CD4 cells <200/μL)</p>
Stopping rule for prophylaxis	CD4 count >200 cells/ μ L over 3 months or CD4 count 100–200 cells/ μ L and HIV viral load undetectable for 3 months	a stopping rule is generally not defined and the decision should be made on an individual basis (e.g., end of immunosuppressive therapy) [57]
Treatment of choice	TMP/SMX 400/80 mg tablet daily or 800/160 mg 3 times per week	
Alternative treatments	<p>There is no widely accepted consensus of a preferred regimen as an alternative to the treatment of choice. In HIV-positive patients with a positive serology for toxoplasmosis, a pyrimethamine (+ folinic acid)-containing regimen should be preferred.</p> <p>pentamidine: inhalation, 300 mg in 6 mL aqua 1–2$\times$/month dapsone: 1 $\times$ 2 tablets $\times$ 50 mg (CAVE: dapsone: check for G6PD deficiency) dapsone 1 $\times$ 50 mg plus pyrimethamine 50–75 mg 1$\times$/week plus folinic acid 25–30 mg 1$\times$/week p.o. atovaquone suspension: 1 $\times$ 1,500 mg together with food atovaquone suspension: 1 $\times$ 1,500 mg together with food + pyrimethamine 50–75 mg 1$\times$/week + folinic acid 25–30 mg 1$\times$/week p.o.</p>	

HSCT, hematopoietic stem cell transplantation; p.o., per os; PCP, *Pneumocystis jirovecii* pneumonia; SMX, sulfamethoxazole; SOT, solid organ transplantation; TMP, trimethoprim; TNF, tumor necrosis factor.

ART in Newly Diagnosed HIV-Infected Patients with Acute PCP

In newly diagnosed HIV-infected patients with PCP, ART should be initiated as soon as possible. In a large multicenter trial (ACTG A5164), a total of 282 subjects with an acute opportunistic infection (69% PCP) were randomized to initiate ART immediately or after treatment of the opportunistic infection [55]. Immediate ART resulted in less AIDS progression and deaths, with no increase in adverse events or loss of virologic response compared to deferred ART. This study provided clear arguments for immediate initiation of ART when PCP is diagnosed.

The risk of a PCP-associated IRIS is low. Given the rapid decay of plasma viremia seen with integrase strand transfer inhibitors (INSTIs), the low prevalence of transmitted INSTI resistance, and the favorable safety profile, INSTI-based regimens seem to be a reasonable option. Antiretroviral drugs with a potential allergenic potential and/or high risk of resistance (non-nucleoside reverse transcriptase inhibitors, abacavir) should be avoided in patients with acute PCP.

Immunosuppressive Drugs during Acute PCP in Non-HIV-Infected Immunocompromised Patients

During therapy of acute PCP, it is crucial to reflect all comedications due to many possible drug-drug interactions. As the treatment of choice in patients with acute PCP according to national and international guidelines (see above) is TMP/SMX, methotrexate should be avoided because of potentially increasing adverse drug effects. If possible, immunocompromising treatment should be reduced, paused, or stopped, but this should be an individual approach (depending for instance on the activity of the underlying disease).

Furthermore, it remains unclear whether adjunctive therapy with glucocorticosteroids in non-HIV-infected patients (e.g., in the intensive care unit setting) leads to any benefit for this subgroup [20, 56, 57]. If patients are already treated with glucocorticosteroids for another reason, there should not be an abrupt discontinuation, though an individual adjustment seems mandatory.

Prophylactic Treatment of Patients at Risk

Several guidelines give specific recommendations for prophylaxis in HIV-infected patients, and there are recommendations available for hematologic and post-transplant patients as well as for patients with anti-neutrophil cytoplasmic antibody-associated vasculitis receiving cyclophosphamide (Table 5) [30, 32, 58]. Otherwise,

there is a lack of consensus for otherwise immunocompromised patients [20]. Most evidence exists for regimens containing TMP/SMX [59]. Alternative prophylactic options (e.g., dapsone, atovaquone, or pentamidine) lack evidence for these patients (Table 5) [58]. One of the major challenges is the identification of patients susceptible to *P. jirovecii* infection at an earlier stage of risk to start proper prophylaxis [19]. Monitoring CD4+ T lymphocytes, as in HIV-infected patients, appears to be insufficient to predict the risk of PCP [30].

PCP from a Global Health Perspective with Emphasis on Resource-Limited Settings

Along with the high burden of HIV infection, particularly in sub-Saharan Africa, PCP infection contributes significantly to HIV-related morbidity and mortality in children and adults. The widespread introduction of PCP prophylaxis as a programmatic intervention as well as the significant rollout of ART has reduced the incidence of PCP infections [60]. Although detailed data are scarce, reports about PCP are available from all continents [61]. In a recent meta-analysis, Wasserman et al. [60] describe a case fatality of 18% for HIV-infected patients with PCP in sub-Saharan Africa.

The diagnosis of PCP is mostly a presumptive diagnosis in resource-limited settings. Clinical signs and symptoms, particularly dyspnea, fever, dry cough, and hypoxia in absence of an alternative diagnosis in an immunocompromised patient with a CD4+ T lymphocyte count <200 cells/mL and concurrent radiological changes lead to the initiation of PCP treatment [62]. Very limited availability of diagnostic stains and PCP-specific PCR only infrequently allow a definite diagnosis. Bronchoscopy, bronchial wash, BAL, or transbronchial biopsy, which increase the diagnostic yield over sputum diagnosis, are often not available [60]. A high level of awareness and clinical suspicion is required. A South African autopsy study documented that PCP was not recognized prior to death in 89% of PCP cases [63]. Due to the high incidence of TB in many resource-limited settings, patients are treated with anti-TB drugs instead. No data can be found on patients requiring invasive or noninvasive ventilation in resource-limited settings, but limited access to such facilities in many settings contributes to higher mortality rates.

Increased LDH levels support the diagnosis and the test is often available. Rising LDH during treatment is associated with poor prognosis [64]. (1,3)- β -D-glucan is a helpful test to support the diagnosis in absence of a defi-

nite diagnosis in HIV-infected and non-HIV-infected patients, but is not widely available [48]. Very promising reports about the S-adenosylmethionine serum level as a diagnostic marker for PCP could not be independently validated [65, 66]. A recent approach used real-time qPCR in oral wash to detect PCP tried to establish a cutoff value for infection versus colonization, but this approach needs further studies [67].

TB is an important differential diagnosis for PCP, but coinfections should also be considered [68]. One autopsy study in South African miners describes cryptococcal pneumonia and bacterial pneumonia as the most frequent coinfections with PCP [63].

Prophylactic treatment with TMP/SMX also reduces the incidence of toxoplasmosis, malaria, and bacterial pneumonias. Particularly in HIV-infected children aged <5 years, the World Health Organization recommends a continuous PCP prophylaxis, while in areas with a high incidence of malaria and bacterial pneumonias, this is also an option for adults. In other settings, the prophylaxis can be stopped if the CD4+ T lymphocyte count is >400 cells/ μ L for more than 3 months or if the viral load is undetectable and the CD4+ T lymphocyte count is 100–200 μ L for more than 3 months [69].

Conclusions and Discussion

PCP is presently at a transitional stage with substantial epidemiologic changes. The widespread use of ART has led to an important decline in the PCP incidence in HIV-infected patients worldwide, while the medical progress leads to a growing number of non-HIV-infected immunocompromised patients susceptible for PCP infection. Therefore, physicians should be aware that PCP is an important infectious complication in hematologic and posttransplant patients, including SOT or allogeneic and

autologous HSCT, and in patients under immunosuppressive drugs due to autoimmune diseases. Considering the rapid course of the disease in non-HIV-infected immunocompromised patients, early diagnosis and treatment of acute PCP infection is crucial and can decrease morbidity and mortality. However, we also would like to draw attention to PCP prophylaxis, which sometimes seems to be disregarded in these heterogeneous patient cohorts, although it is effective and helps to combat rising trends.

In case of HIV infection, especially in late presenters who are unaware of their HIV infection and who often present with very low CD4+ T lymphocyte counts, there is a high risk of developing PCP. Community-based screening methods, partner services, and simple risk scores can be effective tools to find HIV-unaware individuals [70, 71]. PCP prophylaxis is of outmost importance and should be initiated in HIV-infected patients with CD4+ T lymphocyte counts <200/ μ L.

It remains unclear why PCP varies between HIV-infected patients and non-HIV-infected immunocompromised patients, but physicians should be aware of the clinical, diagnostic, and management disparities of acute PCP infection in these heterogeneous patient cohorts.

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The authors declare that no competing interests exist. All authors have submitted the ICMJE Form for Disclosure of Potential Conflict of Interest.

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