Salvage treatment of *Pneumocystis jirovecii* pneumonia with micafungin and clindamycin: a case report

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Background: *Pneumocystis jirovecii* pneumonia (PJP) causes significant morbidity and mortality in immunocompromised patients. Current therapeutic options for PJP may be limited by toxicities, and alternate therapeutic options with fewer side effects are limited. We report a unique case of PJP in a non-human immunodeficiency virus (HIV) patient who successfully completed treatment with a combination of micafungin and clindamycin.

Case Description: A 76-year-old male with granulomatosis with polyangiitis presented with dyspnea on exertion and was diagnosed with PJP based on computed tomography (CT) findings of ground glass opacities and a positive polymerase chain reaction (PCR) for PJP from a bronchoalveolar lavage (BAL) specimen. He developed significant nephrotoxicity from trimethoprim/sulfamethoxazole (TMP/SMX) leading to the need for hemodialysis. He was transitioned off of TMP/SMX to clindamycin and primaquine. The patient then developed methemoglobinemia from primaquine, which led to intubation and difficult liberation from the mechanical ventilator. On day 20 of admission, the patient transitioned to clindamycin 900 mg IV every eight hours and micafungin 100 mg IV daily, which were continued for six days (to complete a total 21-day course). His methemoglobin levels trended down, allowing for extubation. Clinical cure was achieved without toxicities with micafungin and clindamycin. He required intermittent hemodialysis and oxygen from hospital discharge through two months post-discharge. Currently, he no longer requires dialysis or oxygen, and he had no recurrence of PJP.

Conclusions: Echinocandins and clindamycin may represent a safe and effective alternative treatment for PJP in patients who develop intolerances to traditional therapies.

Keywords: Case report; echinocandin; clindamycin; *Pneumocystis jirovecii* pneumonia (PJP); beta-d glucan

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Introduction

Pneumocystis jirovecii (PJ) is an opportunistic fungal pathogen with a biphasic life cycle that can cause severe pneumonia in immunocompromised hosts including patients with human immunodeficiency virus (HIV) and non-HIV (malignancies, solid organ transplant, and chronic inflammatory diseases) (1). *Pneumocystis jirovecii* pneumonia (PJP) can be fatal and is associated with complications including acute respiratory distress syndrome and chronic decrease in pulmonary function (2). Patients with non-HIV PJP often have more severe disease leading to mortality rates of up to 75.6% for those admitted to the intensive care unit (1).

The first-line treatment of PJP is trimethoprim/sulfamethoxazole (TMP/SMX) 15 to 20 mg/kg/day intravenous (IV) or oral (PO) based on the TMP component (3,4). This dose is associated with high rates of adverse effects such as hyperkalemia, cytopenias, rash, and renal dysfunction. Tritle *et al.* reported a frequency of 30.8% of adverse effects with conventional dosing (≥15 mg/kg/day). While dose reduction (<15 mg/kg/day) may reduce the risk for adverse effects (risk ratio =0.7 compared to >15 mg/kg/day), they still can occur with a reported frequency of 7%. These challenges highlight the need for safe and effective alternative treatment options (5).

Highlight box

Key findings

- We report successful treatment with the combination of micafungin and clindamycin in a patient with non-human immunodeficiency virus *Pneumocystis jirovecii* pneumonia (PJP) after intolerance to several first-line therapies.

What is known and what is new?

- The first-line treatment for PJP pneumonia is high-dose trimethoprim/sulfamethoxazole, which is associated with significant adverse effects. In the event of further intolerance or allergy, second-line agents (clindamycin and primaquine, dapsone and trimethoprim, atovaquone, or intravenous pentamidine) must be used.
- This manuscript adds supporting evidence for echinocandin therapy in combination with clindamycin as a safe and effective salvage treatment regimen for PJP after failure and/or intolerance to first-line therapies.

What is the implication, and what should change now?

- The use of micafungin in combination with another agent should be considered as a safe and effective option for salvage treatment of PJP if failures or intolerances to other therapies occur.

Second-line treatment options for moderate PJP in order of preference include primaquine and clindamycin followed by dapsone and TMP. For severe disease, alternatives include primaquine and clindamycin followed by intravenous pentamidine. However, these therapies may result in lower efficacy and their use is similarly limited by toxicities (2,3). Echinocandins are well-tolerated antifungals that work by inhibiting synthesis of beta-d-glucan (BDG), a structural polysaccharide within the cell wall of PJ's cystic form and have been suggested as possible therapeutic alternatives for PJP (6-8). We report a patient who successfully completed PJP treatment with micafungin and clindamycin after developing intolerances to traditional therapies. We present this article in accordance with the CARE reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-131/rc).

Case presentation (*Table 1*)

A 76-year-old Caucasian male weighing 81 kilograms with granulomatosis with polyangiitis was initiated on prednisone 30 mg PO daily and rituximab six weeks prior to admission. Atovaquone 1,500 mg PO daily was initiated two weeks prior to admission for PJP prophylaxis. He presented on the day of admission (D1) with dyspnea on exertion and an oxygen saturation of 96% on room air. He was afebrile with a blood pressure of 124/56 mmHg, heart rate of 70 beats/minute, and respiratory rate of eighteen breaths/minute. Notable laboratory findings included a serum creatinine (SCr) of 2.9 mg/dL (baseline 2.4 mg/dL) and a white blood cell count (WBC) of 13.9×10^9/L. His chest X-ray and computed tomography (CT) chest scan on D1 demonstrated diffuse bilateral ground glass opacities with consolidated areas in the bilateral lung base (*Figure 1*). A point-of-care SARS-CoV2 nasal swab was negative, and a serum BDG assay was collected.

On D2, his dyspnea worsened at rest, and he was placed on 1 L/min by nasal cannula (NC). The primary team consulted infectious diseases. On D4, he underwent bronchoscopy with bronchoalveolar lavage (BAL). On D5, the patient's serum BDG returned as >500 pg/mL, and his oxygen requirements increased to 3 L/min NC. He was started on TMP/SMX 5 mg/kg/dose every twelve hours (two double-strength tablets PO twice daily), which was a renally-adjusted dose. His *Pneumocystis* polymerase chain reaction (PCR) from the BAL was positive.

On D8, the patient's oxygen requirement increased to 6 L/min NC. His potassium increased to 5.4 mg/dL,

Table 1 Diagnostic and therapeutic timeline

Day of care	Events	Oxygen requirements	Antimicrobial therapy
1	• Chest X-ray: bibasilar heterogeneous opacities • CT: diffuse bilateral ground glass opacities with consolidated areas in the bilateral lung base • SARS-CoV2 swab negative	–	–
2	• Infectious diseases consulted	1 L nasal cannula	–
4	• Bronchoscopy with BAL performed and cultures sent • BDG: >500 pg/mL	3 L nasal cannula	–
5	• PCR for pneumocystis DNA returns positive	3 L nasal cannula	Started SMX/TMP 5 mg/kg PO (2 DS tablets) q12h
8	• Develops AKI and hyperkalemia (serum potassium: 5.4 mg/dL, SCr: 4.2 mg/dL, BUN: 89 mg/dL, urine output 0.2 mL/kg/h)	6 L nasal cannula	Stopped SMX/TMP
	• G6PD deficiency: negative		Started primaquine 30 mg PO daily and clindamycin 900 mg IV q8h due to AKI
9	–	8–11 mL/min high flow nasal cannula	Primaquine 30 mg PO daily and clindamycin 900 mg IV q8h
10	• Admitted to the medical ICU	50 mL/min high flow nasal cannula	Primaquine 30 mg PO daily and clindamycin 900 mg IV q8h
11	• Chest X-ray: worsening bilateral opacities	50 mL/min high flow nasal cannula	Primaquine 30 mg PO daily and clindamycin 900 mg IV q8h
12	• Patient is intubated • Develops methemoglobinemia: % CO methemoglobin: 17.4%	Mechanical ventilation (FiO_2 40%, PEEP 8)	Stopped primaquine 30 mg PO daily and clindamycin 900 mg IV q8h
	• Received methylene blue 150 mg IV × 1 for methemoglobinemia		Re-started SMX/TMP 5 mg/kg VT q12h
13	• % CO methemoglobin: 11.5%	Mechanical ventilation (FiO_2 40%, PEEP 8)	SMX/TMP 5 mg/kg q12h VT
14	• % CO methemoglobin: 10.9% • Patient was proned • Received vitamin C 1.5 g IV q6h × 6 doses for methemoglobinemia	Mechanical ventilation (FiO_2 40%, PEEP 8)	SMX/TMP 5 mg/kg q12h VT
15	• % CO methemoglobin: 10.1% • CRRT initiated	Mechanical ventilation (FiO_2 40%, PEEP 8)	Stopped SMX/TMP 5 mg/kg VT q12h Started dapsone 100 mg VT daily + TMP 300 mg VT daily
20	• % CO methemoglobin: 10.4% • Unable to liberate patient from mechanical ventilation	Mechanical ventilation (FiO_2 40%, PEEP 8)	Stopped dapsone 100 mg VT daily + TMP 300 mg VT daily Started micafungin 100 mg IV daily and clindamycin 900 mg IV every 8 hours

Table 1 (*continued*)

Table 1 (*continued*)

Day of care	Events	Oxygen requirements	Antimicrobial therapy
23	• Patient is extubated • Methemoglobinemia resolves. % CO methemoglobin: 1.3%	–	Micafungin 100 mg IV daily and clindamycin 900 mg IV every 8 hours
25	• Transitioned from CRRT to intermittent hemodialysis	–	Micafungin 100 mg IV daily and clindamycin 900 mg IV every 8 hours
26	• Completed therapy for PJP	–	–
27	• Transitioned from the ICU to the medical ward	–	–
36	• Discharged home	–	–

CT, computed tomography; BAL, bronchoalveolar lavage; BDG, beta-d-glucan; PCR, polymerase chain reaction; SMX, sulfamethoxazole; TMP, trimethoprim; PO, oral; DS, double strength; AKI, acute kidney injury; SCr, serum creatinine; BUN, blood urea nitrogen; G6PD, glucose-6-phosphate deficiency; PEEP, positive end-expiratory pressure; VT, via tube; CRRT, continuous renal replacement therapy; PJP, *Pneumocystis jirovecii* pneumonia.

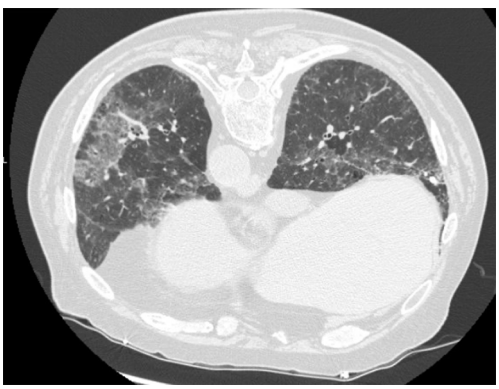

Figure 1 The computed tomography chest scan on the day of admission shows diffuse bilateral ground glass opacities with consolidated areas in the bilateral lung base.

SCr increased to 4.2 mg/dL, blood urea nitrogen (BUN) increased to 89 mg/dL, and urine output decreased to 0.2 mL/kg/h. Due to acute kidney injury (AKI), therapy was transitioned from TMP/SMX to primaquine 30 mg PO daily and clindamycin 900 mg IV every eight hours. He tested negative for glucose-6-phosphate deficiency (G6PD).

Although renal function improved with discontinuation of TMP/SMX, the patient's oxygen requirement increased over the next several days, resulting in transfer to the intensive care unit and intubation. On D12, venous blood gas revealed a methemoglobin level of 17.4% attributed to primaquine. He was transitioned back to TMP/SMX 5 mg/kg via tube (VT) every twelve hours, and his methemoglobinemia was treated with a single dose of IV methylene blue 1.5 mg/kg. While he initially responded to methylene blue, he subsequently received IV vitamin C 1,500 mg every six hours for six doses for persistently elevated methemoglobin levels.

After re-initiation of TMP/SMX, the patient's AKI again worsened and continuous renal replacement therapy (CRRT) was started on D15. To avoid further renal injury, he was switched to dapsone 100 mg VT daily and TMP 300 mg VT daily. From D13 to D20, the patient's methemoglobin levels fluctuated between 8.4% and 11.5% while the patient remained intubated with a stable fraction of inspired oxygen (FiO_2) of 40% and positive end-expiratory pressure (PEEP) of 8 cm H_2O.

Due to persistently elevated methemoglobin levels limiting liberation from mechanical ventilation, dapsone and TMP were discontinued, and combination therapy with micafungin 100 mg IV daily and clindamycin 900 mg IV every eight hours was initiated on D20 (9-11). Over the next several days, methemoglobin levels decreased from 6.5% to 1.3% and he was extubated on D23.

On D26, after six days of micafungin and clindamycin, the patient completed his treatment for PJP. He transitioned to the medical ward on D27 and was discharged home on D36 with atovaquone 1,500 mg PO daily for secondary PJP prophylaxis. He required intermittent hemodialysis and oxygen from hospital discharge through two months post-discharge. Currently, he no longer requires dialysis or oxygen, and he had no recurrence of PJP.

All procedures performed in this study were in accordance with the ethical standards of the institutional

and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient consent according to the Duke University Hospital ethics committee/institutional review board.

Discussion

Echinocandins, in combination with clindamycin, represent a novel PJP treatment option based on their mechanism of action. PJ is structurally distinct from other fungi in that it lacks ergosterol within its cell membrane. For this reason, PJ cannot be treated with polyenes or azole antifungals (6). With a unique biphasic life cycle, PJ exists in either a trophic or cystic form. The trophic form is the primary form in the alveolar space during an active infection, and the cystic form is primarily responsible for human transmission. Only the cystic form of PJ contains BDG within its cell wall, which is the target for echinocandins. Since echinocandins do not have activity against the trophic form, addition of a traditional treatment option such as TMP/SMX or clindamycin should be considered; however, successful treatment of PJP with echinocandin monotherapy has been reported (9-11).

Treatment guidelines suggest caspofungin monotherapy or in combination with TMP/SMX as an alternative or salvage treatment option for PJP based on retrospective case series and case reports (3,4). Most data on echinocandin therapy for PJP is with caspofungin or anidulafungin. Cushion *et al.* reported that these two agents reduced cyst burden in mice to a greater extent compared to micafungin, which required higher doses (one mg/kg/day) to show similar reduction in burden compared to the other echinocandins (6). Yang *et al.* described a successful case of PJP treated with caspofungin 50 mg IV daily and clindamycin 600 mg IV twice daily. They also reviewed 22 other cases of immunocompromised patients with PJP treated with caspofungin monotherapy, or in combination with other agents as either first, second, or third-line therapy. Four patients (18%) failed therapy while the others (82%) fully recovered (9). There were no apparent differences in baseline characteristics between those who failed and those who recovered.

Huang *et al.* performed a retrospective cohort study of 34 patients with PJP receiving echinocandins either as monotherapy or in combination with TMP/SMX (10). There was no difference in all-cause and PJP-related in-hospital mortality between echinocandin and TMP/SMX combination therapy versus echinocandin monotherapy (16.7% *vs.* 17.4%, P>0.999). Factors such as severity of illness (70.6% moderate-severe), duration of echinocandin therapy (median twelve days), and specific echinocandin (anidulafungin: 68%, caspofungin 21%, micafungin 11%) did not statistically differ between those who survived and those who did not. Data using micafungin as the echinocandin of choice is limited, and this study only included four patients who received micafungin (10). There have been sixteen case reports describing echinocandin use for treatment in non-HIV patients with PJP (*Table 2*) (9,11-18). None of these cases utilized micafungin, and most cases either used TMP/SMX (N=12) in combination with echinocandins versus an alternate agent (N=2). Therefore, our case adds to the literature by demonstrating safety and efficacy in a non-HIV patient treated with micafungin and clindamycin.

Specific levels of serum BDG may predict the efficacy of echinocandin therapy. Higher levels of BDG during PJP infection indicate a higher burden of organisms in the cystic phase which is why echinocandins may be effective (6). Jin *et al.* reviewed 126 patients with PJP who received caspofungin and TMP/SMX or TMP/SMX monotherapy. In patients with a BDG of >800 pg/mL (N=54), three-month mortality was significantly lower in the echinocandin combination therapy group compared to the monotherapy group (20% *vs.* 56%; P=0.010). Echinocandin combination therapy also had higher rates of positive response in this group (80% *vs.* 38%, P<0.001) (19). In the case reported by Yang *et al.*, the patient presented with an initial BDG of 984.6 pg/mL (9). Our patient's BDG was >500 pg/mL (upper limit of detection), which may have been a positive predictor for his response to echinocandin therapy.

The strength of this case report is that it provides a reasonable treatment alternative for completing a course for PJP if intolerances or side effects occur. While this patient did experience a favorable outcome, the main limitation to this report is the risk for confounding factors. Echinocandin therapy may be an effective salvage regimen if patients experience intolerance to first-line agents; however, the optimal duration of therapy has not been studied. The duration of therapy in other reports ranges from four to 24 days, which is based on the timing of intolerance and remaining duration of therapy needed to complete the total course. The patient presented in this case report finished the last six days of his 21-day course for PJP with echinocandin combination therapy due to timing of adverse effects. Given that the patient received fifteen days

Table 2 Case reports of echinocandin use for HIV-negative patients with PJP

Author, year	Age (years)/ sex	Underlying disease	Initial treatment	Initial TMP/SMX dose	Reason for EC use	Salvage regimen	BDG (pg/mL)	Time to EC use (days)	Steroid used	Duration of EC (days)	Result
Yang 2019 (9)	66/female	SLE	TMP/SMX + CLI + CA	1 DS tablet TID (weight NR)	Adverse effect	CA + CLI	984.6	0	Yes	24	S
Huang 2018 (11)	71/male	IgG4 Deficiency	TMP/SMX	15 mg/kg/day	Treatment failure	CA + TMP/SMX	NR	14	Yes	21	S
	68/female	SLE	TMP/SMX	15 mg/kg/day	Treatment failure	CA + TMP/SMX	NR	NR	Yes	7	S
Li 2016 (12)	46/male	CKD	TMP/SMX	NR	Allergy to TMP/ SMX	CA + CLI	>1000	NR	Yes	33	S
Kim 2013 (13)	63/male	Liver TP	TMP/SMX	15 mg/kg/day TMP	Treatment failure	CA + TMP/SMX	NR	9	No	4	D
	57/male	Kidney TP	TMP/SMX	15 mg/kg/day TMP	Treatment failure	TMP/SMX + PRI + CLI then CA + TMP/SMX	NR	18	No	11	D
	46/male	Liver TP	TMP/SMX	15 mg/kg/day TMP	Treatment failure	CA + TMP/SMX	NR	6	No	7	S
Tu 2013 (14)	61/male	Kidney TP	TMP/SMX	2 DS tablets TID (weight NR)	Adverse reaction	CA + TMP/SMX (1 SS tablet TID)	NR	>10	Yes	14	D
	35/male	Kidney TP	TMP/SMX	2 DS tablets TID (weight NR)	Adverse reaction	CA + TMP/SMX (1 SS tablet BID)	NR	10	Yes	14	S
	43/male	Kidney TP	CA + TMP/SMX	1 SS tablet TID (weight NR)	Empirical use	N/A	NR	7	No	14	S
Jiang 2013 (15)	46/male	LBC-L	CA	N/A	Allergy to TMP/ SMX	N/A	NR	5	No	NR	S
Mu 2009 (16)	76/male	CML	CA	N/A	Adverse reaction	CA + TMP/SMX	30	9	Yes	21	S
Hof 2008 (17)	60/male	WG	CA	N/A	Treatment failure	N/A	NR	9	No	21	S
Utili 2007 (18)	28/male	Kidney TP	TMP/SMX	17 mg/kg/day	Treatment failure	CA + TMP/SMX (same dose)	NR	7	Yes	16	S
	59/male	Heart TP	TMP/SMX	2 DS tablets 4× daily (weight NR)	Treatment failure	CA + TMP/SMX	NR	6	Yes	7	S
	58/female	Heart TP	CA + TMP/SMX	2 DS tablets 4× daily (weight NR)	Empirical use	N/A	NR	1	Yes	14	S
Present study	76/male	GPA	TMP/SMX	10 mg/kg/day	Treatment failure	MI + CLI	>500	14	Yes	7	S

HIV, human immunodeficiency virus; PJP, *Pneumocystis jirovecii* pneumonia; TMP, trimethoprim; SMX, sulfamethoxazole; EC, echinocandins; BDG, beta-d-glucan; SLE, systemic lupus erythematous; CLI, clindamycin; S, survived; D, mortality; CA, caspofungin; DS, double strength; TID, three times daily; NR, no report; CKD, chronic kidney dysfunction; TP, transplant; PRI, primaquine; SS, single strength; BID, two times a day; LBC-L, large-B-cell lymphoma; CML, chronic myelocytic leukemia; WG, Wegener's granulomatosis; GPA, granulomatosis with polyangiitis; MI, micafungin.

of therapy with first-line agents, the other agents likely contributed to his positive outcome. However, the patient would not have been able to successfully complete the 21-day course with first-line therapy due to intolerance and side effects from several first-line treatment options.

Conclusions

Echinocandins have a favorable safety profile and may be considered as salvage therapy for PJP after failing or experiencing intolerance to other agents. They should be used in combination with an agent active against the trophic form of PJ in the alveoli. Based on the mechanism of action, echinocandins may be particularly useful in patients with a serum BDG of >500 pg/mL.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-131/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-131/coif). The authors have no conflicts of interest to declare.

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