



# *Pneumocystis jirovecii* Pneumonia and Other Infections in Idiopathic Inflammatory Myositis

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## Abstract

**Purpose of Review** The management of patients with idiopathic inflammatory myositis (IIM) can be complex and challenging due to the myriad of complications they can experience. The continued use of corticosteroids, in addition to the rise of combination immunosuppressive therapy, has contributed to the ongoing concern for infection. Perhaps the most feared infection in IIM patients is *Pneumocystis jirovecii* pneumonia (PJP) given its infrequent occurrence yet high mortality. The field has been, and continues to be, without evidence-based guidelines to help clinicians determine which patients with IIM to prescribe prophylaxis. Herein, we review this literature to provide the clinician with an up-to-date view of infections in IIM.

**Recent Findings** In the past 5 years, a number of studies have been reported highlighting various infectious complications, which help us better understand their frequency and associated risk factors. In addition, data has been published on the potential harms of PJP prophylaxis, to better inform the risk/benefit of our decision-making.

**Summary** Infection remains a major contributor to morbidity and mortality in IIM. A better understanding of which patient subgroups are at risk for particular infections will inform optimal management strategies.

**Keywords** Inflammatory myositis · Antisynthetase syndrome · Immunosuppression · Infection · *Pneumocystis jirovecii* pneumonia

## Introduction

Infection remains a paramount concern in the management of patients with idiopathic inflammatory myopathies (IIM), including polymyositis (PM), dermatomyositis (DM), and immune-mediated necrotizing myopathies (IMNM). Balancing the risks of infection from immunosuppression with the consequences of increased myositis disease activity continues to challenge physicians. In recent years, studies

continue to identify infection as a leading cause of morbidity and mortality in patients with IIM [1–4]. Our aim in this report is to provide an updated review of literature as it pertains to infections in IIM, with particular focus on *Pneumocystis jirovecii* pneumonia (PJP).

## The Magnitude of the Problem

The incidence of infection and causative organisms varies greatly depending on the environment in which patients are studied, that is, intensive care unit (ICU) vs general ward vs the outpatient setting. In more acute settings (hospitals and ICUs), infections are remarkably common and carry a high morbidity. In a retrospective review of 102 Chinese IIM patients admitted to the ICU over an 8-year period, 68 (67%) were diagnosed with an infection, which was the most common reason for admittance to the ICU. The most common infection site was the lung, with pneumonia accounting for over 85% of infections. Causative organisms were identified in 43 patients, the majority of which were opportunistic

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infections, the three most common being pulmonary aspergillosis, PJP, and cytomegalovirus (CMV) pneumonia [2]. Of note, 40% of the patients studied received IV pulse solumedrol in the month prior to admission, and 86% were on at least 0.5 mg/kg of daily prednisone.

The frequency of opportunistic infections in the abovementioned Chinese study was not observed in a US study examining hospitalization records for patients with DM/PM (Healthcare Cost and Utilization Project Nationwide Inpatient Sample) [4]. Over 15,000 hospitalizations of DM and PM patients were studied with an inpatient mortality of approximately 5%. Infection was significantly associated with mortality in these IIM patients (OR 3.4, 95% CI 2.9–4.0). The most common infections were pneumonia and bacteremia. Overall, 28% of myositis patients had an infection recorded during their hospitalization; the majority of which were bacterial. Approximately 2% of patients had a viral infection (HSV, VZV, CMV), 1% had an opportunistic fungal infection (candidiasis, Cryptococcus, histoplasmosis, and aspergillosis), and < 1% had a mycobacterial infection. The degree of immunosuppression patients received is not contained within the Nationwide Inpatient Sample and, thus, was not reported.

An outpatient study was performed on a French IIM population examining 279 IIM patients from three medical centers. Of the 279, 104 (37%) developed an infection over a median follow-up of 36 months. The most common diagnosis was aspiration pneumonia. Of those patients who experienced an opportunistic infection, the authors identified an array of causative pathogens, including *Candida albicans*, PJP, aspergillus fumigatus and atypical mycobacterial organisms among others [5]. Another outpatient study examined the charts of IIM patients over a 10-year period totaling 631 patients with neuromuscular disease (149 of which had dermatomyositis). Prior et al. report a 19% rate of infection over a 10-year period [6]. Pneumonia and sepsis were the two most common infections. Notably, approximately 1/3 of patients had an opportunistic infection, the most common of which was varicella zoster (VZV).

In some of these studies, the authors sought to identify the magnitude of risk individual immunosuppressive agents confer on infection rates. In the same French study of 279 IIM patients, the authors examined which medications patients were taking at the time their infection was diagnosed. Comparing patients who developed an infection ( $N = 94$ ) to those who did not ( $N = 185$ ), they reported that methotrexate and IVIG were both statistically associated with infection, OR 2.12 (95% CI 1.22–3.68) and OR 3.58 (95% CI 2.06–6.25), respectively. Upon adjusting for other factors in multivariable regression (malignancy, myalgia, ventilator insufficiency, and esophageal involvement), only methotrexate was statistically associated with infection (OR 2.0, 95% CI 1.1–3.66,  $p = 0.02$ ) [5]. Different results were obtained from Prior and colleagues,

who reported in a time-to-event analysis that plasmapheresis (PLEX), mycophenolate, and corticosteroids were all statistically significantly associated with an increased risk of infection. The multivariable HRs after adjusting for disease, sex, age, and drug exposure were 1.31 (95% CI 1.17–1.47,  $p < 0.0001$ ) for corticosteroids, 1.77 (95% CI 1.33–2.34,  $p < 0.0001$ ) for PLEX, and 1.38 (95% CI 1.07–1.77,  $p = 0.012$ ) for mycophenolate.

Taken together, a number of general statements can be made from these studies. For one, there appears to be consensus that infection remains a main driver of morbidity and mortality in IIM patients. The lung is the most common site of infection, and opportunistic infections are not infrequent. Given the heterogeneity of opportunistic infections reported, it would be prudent to cast a wide diagnostic net when evaluating a patient with IIM where infection is suspected, including viral PCR and fungal staining on biospecimens. It remains unclear which disease characteristics and specific immunosuppressants place a patient at highest risk. Given the lung is a common site of infection, factors such as interstitial lung disease and dysphagia seem likely to confer risk. Similarly, while prednisone use appears to be a risk factor for many infections, the risk of other disease-modifying anti-rheumatic drugs and biologics is less clear.

### ***Pneumocystis jirovecii* Pneumonia**

The incidence of PJP in PM/DM is uncommon, having been estimated at 3.6/100,000 patient-years [7]. Still, it remains a grave concern in patients with autoimmune and rheumatic diseases due to its high mortality rate, ranging from 33 to 60% depending on the cohort examined [8, 9]. Despite these mortality rates, many rheumatologists and other healthcare providers do not routinely administer prophylaxis [10, 11]. This is at least in part due to the lack of evidence-based guidelines to help clinicians appropriately provide prophylaxis.

A recent study reviewed published PJP recommendations for autoimmune diseases [12•] (Table 1). The majority of the studies recommended consideration of PJP prophylaxis based on similar factors including the absolute lymphocyte count (ALC), presence of lymphopenia, and corticosteroid dose/duration. Some studies advocated for considering other risk factors such as intrinsic lung disease and older age. The authors went on to perform a small case-control study of 11 patients with autoimmune disease who developed PJP (two of which had inflammatory myositis). Upon adjusting for corticosteroid use, they showed that lymphopenia remained a statistically significant independent risk factor ( $p = 0.02$ ), suggesting this may be a risk factor regardless of whether the patient is on corticosteroids.

A population-based study from the USA examined PJP prophylaxis prescribing patterns in patients with vasculitis,

**Table 1** Adapted and modified with permission from Tadros et al. [12•]

Study Name	Factors guiding PJP prophylaxis initiation in patients with systemic autoimmune rheumatic disease					PJP prophylaxis recommendation from study
	Lymphopenia	Lymphocyte count cut off	Corticosteroids	Corticosteroids dose and duration	Other	
Okade et al.	X					Pulmonary fibrosis Suggest PJP prophylaxis in patients with at least one risk factors for PJP (ILD, lymphopenia)
Ogawa et al.	X		X	≥ 30 mg/day prednisolone		PJP in patients at high risk for PJP (medium- or high-dose corticosteroids with an immunosuppressant with decreased ALC)
Inokuma et al.	X	ALC < 500/ $\mu$ L	X	≥ 1.2 mg/kg/day prednisolone or those receiving corticosteroids equivalent to ≥ 0.8 mg/kg/day along with other immunosuppressive agents	Age > 50	PJP in patients with age > 50 receiving corticosteroids as described, or whose ALC < 500 during immunosuppressive therapy.
Sowden et al.	X	CD4+ < 200	X	≥ 15 mg prednisolone/day		Perform CD4+ counts after 1 month of immunosuppression in patients who are on steroids (> 15 mg prednisolone/day), > 3 months corticosteroids treatment and total ALC < 500 cells/mm <sup>3</sup> . CD4 count < 200 may warrant the use of prophylaxis if annual risk of PJP in these patients is > 9%
Park et al./Winthrop and Baddley	X		X	> 30 mg prednisone for ≥ 4 weeks OR ≥ 15–30 mg daily with one additional risk factor (baseline lymphopenia, low CD4, cyclophosphamide use, anti-TNF or rituximab use, or initial steroid dose > 60 mg/day)	Cyclophosphamide, TNFi, or rituximab	> 30 mg prednisone for ≥ 4 weeks OR ≥ 15–30 mg daily with one additional risk factors (baseline lymphopenia, low CD4, cyclophosphamide use, anti-TNF or rituximab use, or initial steroids dose < 15 mg/day)

systemic lupus, and IIM. A total of 316 patients (72 of which had IIM) were followed for approximately  $24 \pm 14$  months. During follow-up, not a single case of PJP was identified in this study. The study provides data on the adverse event rate due to prophylactic agents used by clinicians, with trimethoprim/sulfamethoxazole (TMP/SMX) being the most commonly (73%) used prophylaxis followed by dapsone and atovaquone. The authors calculated an adverse event incidence rate of 2.2% per person-year (among 124 patients who received prophylaxis, 12 had an adverse event during the study period). Since this ascertainment was based on reported allergies in the electronic medical record for the adverse event rate, this is likely an underestimate [11].

A French study examined 129 patients who developed PJP, 27 of which had an autoimmune/inflammatory disorder and examined the absolute lymphocyte and CD4 count [13]. Of the 27 patients, 70% developed PJP with CD4 > 200/mm<sup>3</sup>, 50% with CD4 > 300, and 25% with CD4 > 450. Over 60% of patients developed PJP with absolute lymphocyte counts (ALC) > 600/mm<sup>3</sup>, and 18.5% developed PJP with ALC > 1200/mm<sup>3</sup>. The two patients with dermatomyositis who developed PJP both had ALC > 800 and CD4 > 500/mm<sup>3</sup>.

A large Korean study was performed to evaluate the use of TMP/SMX PJP prophylaxis in patients with a rheumatic disease [14]. A total of 1522 steroid treatment episodes (defined as steroid ≥ 30 mg/day for ≥ 4 weeks) in 1092 patients were

studied over a 12-year period. Of these treatment episodes, 262 were associated with TMP/SMX prophylaxis. Propensity score matching was utilized to account for differences between the two populations (group receiving prophylaxis versus group who did not). Expectedly, patients who received prophylaxis were more likely to be older, have lymphopenia, have a “high risk” rheumatic disease (granulomatosis with polyangiitis, microscopic polyangiitis, DM), and to be treated with secondary immunosuppressive agents. Thirty PJP cases were identified in 30 patients (15 on  $\geq 30$  mg/day prednisone, 12 on 15–30 mg/day, and 3 cases  $< 15$  mg/day). The authors reported a dose responsiveness of PJP risk; the incidence rate ratio (vs 30–45 mg prednisone/day) was 2.26 for 45–60 mg/day and 3.35 for  $\geq 60$  mg/day. The authors also reported that TMP/SMX was very effective (HR 0.17, 95% CI 0.02–1.22) in preventing PJP. A valuable aspect about the work is the reporting of all adverse drug reactions which occurred in 34 patients (21.2/100 person-years), two of which were serious (pancytopenia and Stevens-Johnson syndrome). From this information, the authors were able to calculate the number needed to harm (NNH) being 131, in contrast to the number needed to treat (NNT) to prevent one case of PJP, which was 52.

Despite the study limitations (largely Korean cohort, use of daily single strength TMP/SMX as opposed to the more often prescribed thrice weekly double-strength dosing, imperfect matching of groups using propensity scoring), this work provides valuable information to inform clinicians’ decision-making. In an accompanying editorial to the article by Park et al., Winthrop and Baddley proposed guidelines for patients with DM/PM [15]. Prophylaxis with TMP/SMX should be provided for patients on  $> 30$  mg prednisone for  $\geq 4$  weeks, and also for those patients taking 15–30 mg daily, provided they have at least one additional risk factor (baseline lymphopenia, low CD4, cyclophosphamide use, anti-TNF or rituximab use, or initial glucocorticoid dose of  $> 60$  mg/day). They also recommend discontinuing prophylaxis when the glucocorticoid dose drops below 15 mg daily.

While these recommendations are welcome in this area of uncertainty, it must be said that for every proposed rule or guidelines, exceptions invariably exist. Along with other recommendations [15], including those suggested by Winthrop and Baddley, patients who receive steroids for  $\geq 4$  weeks should be given PJP prophylaxis [16••]. However, reports exist of PJP occurring in patients  $< 4$  weeks after prednisone monotherapy [17]. Until prospective, controlled studies are performed investigating different PJP prophylaxis strategies, it is unlikely we will have adequate evidence to make confident recommendations. Additional data will be needed to understand the adverse event rate of PJP prophylaxis agents as was done by Schmajuk and Park et al. Only then will risk/benefit ratios be able to be calculated and an informed discussion with patients can be conducted. In our practice,

patients with IIM are typically prescribed TMP/SMX for PJP prophylaxis with prolonged ( $> 2$  weeks) prednisone use over 20 mg/day. The discontinuation of TMP/SMX occurs when prednisone is less than 20 mg and/or lymphopenia improves. We typically prescribe trimethoprim-sulfamethoxazole DS three times per week or dapsone 100 mg daily, the latter only after ensuring normal G6PD enzyme activity.

## Other Infections

### Progressive Multifocal Leukoencephalopathy

Despite the increasing use of high-dose mycophenolate and rituximab to treat IIM, relatively few cases of PML have been reported [18–21] (both mycophenolate and rituximab have been issued black box warnings for the development of PML). Importantly, a single case has been reported of a patient with untreated DM developing PML, suggesting immunosuppression may not always be required for PML to occur [22]. While IVIG is often considered “protective” for infectious complications due to passive immunity, at least 3 PML cases have been reported in IIM patients receiving IVIG in addition to other immunosuppressants [21]. While patients should be counseled on this potential and rare risk of medications, often it is judged that the potential benefits outweigh the risks.

### Varicella Zoster Virus

One out of every three Americans will develop shingles during their lifetime, and of that group, 1 in 10 patients will develop post-herpetic neuralgia (PHN) that can last months or years [23]. Patients with IIM, even those not on therapy, are at higher risk for developing VZV compared with the general population [24]. With an increasing use of higher dose and combination immunosuppressant therapy, VZV continues to be challenge to physicians treating patients with IIM [6, 24].

A recent case-control Taiwanese study by Tsai et al. examined over 2000 patients with IIM and compared them to age, sex, and comorbidity-matched controls. Upon examining patients with IIM, those who developed VZV were significantly more likely to be receiving immunosuppressants (50% vs 1.67%,  $p < 0.0001$  and corticosteroids 75% vs 23%,  $p < 0.0001$ ). The adjusted hazards ratio for developing VZV in IIM patients compared with matched controls was 3.90 (95% CI 3.18–4.77). The incidence rate for VZV per 1000 person-years was higher in IIM patients even if they were not on immunosuppressive therapy (28.7/1000 person-years) compared with matched controls (5.75/1000 person-years). In IIM patients on corticosteroids and immunosuppression, the incidence rate increased to 40.3/1000 person-years [24].

## Vaccinations

We recommend all patients receive Pneumovax-23 as well as Prevnar-13 given the likelihood they will receive immunosuppression. All patients should also receive the annual flu vaccine unless a contraindication is noted [25, 26]. In 2006, the live attenuated shingles vaccine Zostavax® emerged to help prevent shingles and its complications. More recently, in 2017, a new dead virus vaccine called Shingrix® was released that is more than 90% effective in preventing shingles and PNH, and is the preferred vaccine recommended by the Centers for Disease Control [23]. Adults over 50 are approved for the vaccine, and it is given in a two shot series, administered 2–6 months apart. Even if patients have had the original shingles vaccine (Zostavax®) or shingles itself, they can still receive Shingrix®. Unlike Zostavax, which is a weakened live virus, Shingrix uses a dead virus, so in theory, the use in immunosuppressed patients is safe.

## Conclusions

Infection remains a major concern in the management of IIM. A better understanding of which patient subgroups are at risk for particular infections will inform future guidelines on who to prophylaxis and the optimal use of combination immunosuppressant therapy.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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