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REVIEW OF THERAPEUTICS

Prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with inflammatory bowel disease: A systematic review

Caroline M. Sierra[1] | **Krishna C. Daiya**[2]

[1]Loma Linda University School of Pharmacy, Loma Linda, California, USA

[2]Loma Linda University Health, Loma Linda, California, USA

Correspondence
Caroline M. Sierra, Department of Pharmacy Practice, Loma Linda University, 24745 Stewart Street, Loma Linda, CA 92350, USA.
Email: csierra@llu.edu

Abstract

Patients with inflammatory bowel disease (IBD) are at increased risk of developing *Pneumocystis jirovecii* pneumonia (PJP) than the general population. Many medications utilized for the treatment of IBD affect the immune system, potentially further increasing the risk of PJP. Recommendations for prophylaxis against PJP in this patient population are based upon limited evidence, and risk factors for PJP development are not well-agreed upon. The purpose of this systematic review was to consolidate and evaluate the evidence for PJP prophylaxis in patients with IBD. An electronic literature search was performed, and 29 studies were included in the review, of which 24 were case reports or case series. Combined data from five cohort studies showed an absolute risk of developing PJP to be 0.07%. The majority of patients who developed PJP were receiving corticosteroids at the time of diagnosis (76%). The number of concomitant immunosuppressants received at time of PJP diagnosis varied from one to four. All studies reporting treatment of PJP utilized sulfamethoxazole-trimethoprim. Of the 27 studies reporting mortality data, 19% of patients died. Given the lack of conclusive data regarding risk factors for PJP development and the overall low incidence of PJP in patients with IBD, it is recommended to assess the patient's risk on a case-by-case basis to determine whether PJP prophylaxis is warranted.

KEYWORDS
antibiotic prophylaxis, Crohn's disease, inflammatory bowel diseases, *Pneumocystis jirovecii*, *Pneumocystis pneumonia*, ulcerative colitis

1 | INTRODUCTION

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic, airborne infection that can lead to life-threatening pneumonia and respiratory failure by targeting T lymphocytes.[1,2] Historically, PJP risk was often associated with patients with human immunodeficiency virus (HIV), malignancies including acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma, and solid organ or bone marrow transplant.[3] However, inflammatory bowel disease (IBD), including Crohn's disease (CD) or ulcerative colitis (UC), can also increase the risk of PJP.[4] Before the routine use of prophylaxis and antiretroviral therapy, there was a higher prevalence of opportunistic infections (OI) especially among patients with acquired immunodeficiency syndrome.[5] Patients with CD4 T lymphocyte (CD4) counts of less than 200 cells/m^3 or CD4 cell percentage <14% were at higher risks of OI due to significant immunosuppression.[5,6] Studies suggest that mortality from PJP in patients receiving immunomodulators may be higher than in patients with HIV.[7–9]

A retrospective review evaluated 475 patients who developed PJP (442 HIV patients, 33 non-HIV patients) from 1985 to 1995 at

a tertiary teaching hospital. Patients with HIV and PJP had a lower overall mortality than non-HIV patients with PJP (9.6% vs. 39.4%, respectively, $p < .0001$).[9] Patients with organ transplant, hematologic or oncologic disease states, chronic inflammatory disease, and prednisone use leading to immunocompromised state made up the non-HIV population. The risk of PJP infection is often augmented when multiple immunosuppressive medications are used.[10] Solid organ transplant recipients are at risk of PJP predominantly within the first 6-month posttransplant.[11,12] Certain medications may contribute to this higher risk, including treatment with 20 mg of prednisone equivalent for 3–6 months, antibody therapy such as alemtuzumab, and calcineurin inhibitors (CNIs) to prevent rejection.[11] In recognition of this increased risk, the American Transplant Society recommends prophylaxis with sulfamethoxazole-trimethoprim (5–10 mg/kg of trimethoprim given once daily or divided twice daily given two or three times a week for at least 6–12 months after transplant).[11] In addition, malignancies such as high-risk ALL and patients undergoing hematopoietic stem cell transplant require highly immunosuppressive regimens, which also increases risk of developing PJP.[13,14] PJP has also been associated with use of chemotherapy agents such as methotrexate and fluorouracil due to prolonged neutropenia.[15]

Some classes of molecular-targeted medications such as mTOR inhibitors, tyrosine kinase inhibitors, and Janus kinase (JAK) inhibitors necessitate PJP prophylaxis due to the known profound risk.[14] Some of these medications overlap with the treatment of IBD and contribute to the PJP risk. A case report showed that 23 of 84 patients (27%) who developed PJP while receiving infliximab died.[8] The majority of these patients received infliximab for rheumatoid arthritis ($n = 29$) followed by Crohn's disease ($n = 14$). Despite the increasing documentation of PJP in patients with IBD, there is limited guidance on if and when to initiate prophylaxis against PJP and duration of prophylaxis.

Current therapies to treat IBD may include combinations of corticosteroids, thiopurines, immunomodulators, antitumor necrosis factors (anti-TNF), and JAK inhibitors. Anti-TNFs with steroid therapy or immunomodulators increase the risk of OI.[16] Anti-TNFs inhibit the pro-inflammatory cytokines that lead to disease progression in rheumatoid arthritis and IBD.[17] Following the approval of infliximab in the United States in 1998, several case reports described the incidence of various OI, including aspergillosis, mycobacterium, and PJP. A Japanese study evaluated the incidence of adverse effects of infliximab in 5000 patients with rheumatoid arthritis within 6 months of starting therapy and found that 21 patients had PJP confirmed by bronchoalveolar lavage (BAL).[18] A multivariate analysis from a comparative study showed an increased odds ratio (OR) of OI when a single agent (corticosteroids, infliximab, azathioprine, or 6-mercaptopurine) was used for IBD; this risk increased fivefold when two or three drugs were used simultaneously.[19] The European Crohn's and Colitis Organization (ECCO) Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis Part 1 guidelines identify predisposing risk factors for OIs in patients with UC. These risk factors include older patient age and corticosteroid use of doses at least 20 mg of prednisolone equivalent daily for more than 2 weeks.[20] ECCO guidelines recommend that patients on triple immunomodulators, including steroids, methotrexate, thiopurines, and biologics or double immunomodulator including a CNI should receive prophylaxis with sulfamethoxazole/trimethoprim.[21] Lymphopenia has also been observed in non-HIV patients who developed PJP.[1] A prospective observational study demonstrated that a subset of immunocompromised patients without HIV infection (39%–46%) who received long-term therapy with steroids developed PJP and had CD4+ counts less than 300 cells/μL.[22] This finding is reinforced in the recommendations of another study, which suggests that CD4 monitoring may be beneficial in determining patients with IBD who are at high risk of OI and for guiding chemoprophylaxis.[23] These data suggest that low CD4 cell counts may be an important clinical marker when identifying patients at high risk of developing PJP.

Due to the high morbidity and mortality associated with PJP infection, certain preventative measures can be considered. The ECCO guidelines for patients with IBD recommend starting PJP prophylaxis in patients treated with triple immunosuppression, which includes anti-TNF inhibitors or CNIs. Prophylaxis may also be considered if patients are on two immunomodulators, particularly if one is a CNI.[21] The recommended prophylaxis regimen is sulfamethoxazole/trimethoprim administered on alternate days or for 3 days of the week. The American College of Gastroenterology guideline for treatment of ulcerative colitis in adults fails to mention the risks of PJP infection or indications for prophylaxis.[24] This review summarizes the literature regarding the incidence of PJP in patients with IBD and seeks to identify common risk factors in efforts to guide decisions related to PJP prophylaxis.

2 | METHODS

2.1 | Study selection

A literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] Databases utilized for the search included Embase and PubMed from inception through March 24, 2022. A literature search was conducted utilizing the MeSH terms “inflammatory bowel diseases” AND “pneumonia, pneumocystis” to find studies regarding the incidence of PJP in patients with IBD. Included studies involved adult and pediatric patients with a history of CD or UC who developed PJP while receiving single or multiple immunosuppressive agents. Studies regarding PJP associated with immunosuppressive medications in patients with other diagnoses such as rheumatoid arthritis, cancer, transplant, or HIV without IBD were excluded. Acceptable study designs were retrospective or observational cohorts and case reports or case series. Review articles, meta-analyses, abstracts, posters, and reports, such as unpublished manuscripts, were excluded. Studies had to be published in a journal with full text available in English. Three articles not available online were retrieved from Loma Linda University Library.

2.2 | Data charting and synthesis methods

All studies including data regarding prophylaxis in patients with IBD were evaluated for inclusion. Two independent researchers screened the remaining abstracts to determine inclusion; differences in opinion were resolved via discussion between the researchers. Data were collected independently by two reviewers in efforts to identify common variables among patients diagnosed with PJP. Data collected included demographic information, including age, sex, diagnosis history, comorbidities, and incidence of PJP. Other data collected for case reports included laboratory values including white blood cell count, absolute neutrophil count, and lymphocytes; immunosuppressive medications, prednisone equivalent dose, duration of therapy, and diagnosis and treatment of PJP were also collected. Two tables were created utilizing Excel to collect this information: one for case reports and case series and a second for retrospective cohorts. For case reports and case series, laboratory values and the specific medication(s) that the patient(s) received were included. The second table intended for retrospective cohorts included the number of patients who developed PJP, number of patients who received corticosteroids, thiopurines, aminosalicylic acids, immunomodulators, CNIs, anti-TNFs or JAK inhibitors, and number of concomitant agents. Specific laboratory values or medication names were not included for retrospective studies as this information was often not available. All steroid doses were converted to prednisone equivalent to maintain consistency. Summation and means were utilized to present the results. One author examined and consolidated the data collected by both individual reviewers. Descriptive analysis was used to summarize the findings.

Risk of bias assessment was conducted by one author using the Joanna Briggs Institute (JBI) Critical Appraisal Tools Checklist for cohort studies,[26] case series,[27] and case reports.[28] Each checklist contained a series of different questions (found in Appendix S1) to assess the quality of the study and determine the probability of bias. A percentage score was calculated based on the number of "yeses" after assessment and categorized with a low, moderate, or high risk. Percentage scores of up to 49% were considered high risk of bias, 50%–69% moderate risk, and 70% or greater low risk.

3 | RESULTS

Figure 1 depicts the PRISMA flow diagram for the screening and inclusion of articles in this study. A literature search resulted in 365 records, of which 163 were screened for eligibility and 29 were included in this review. Information from the 20 case reports is presented in Table 1; data from the case series and retrospective cohort studies are presented in Tables 2 and 3, respectively.

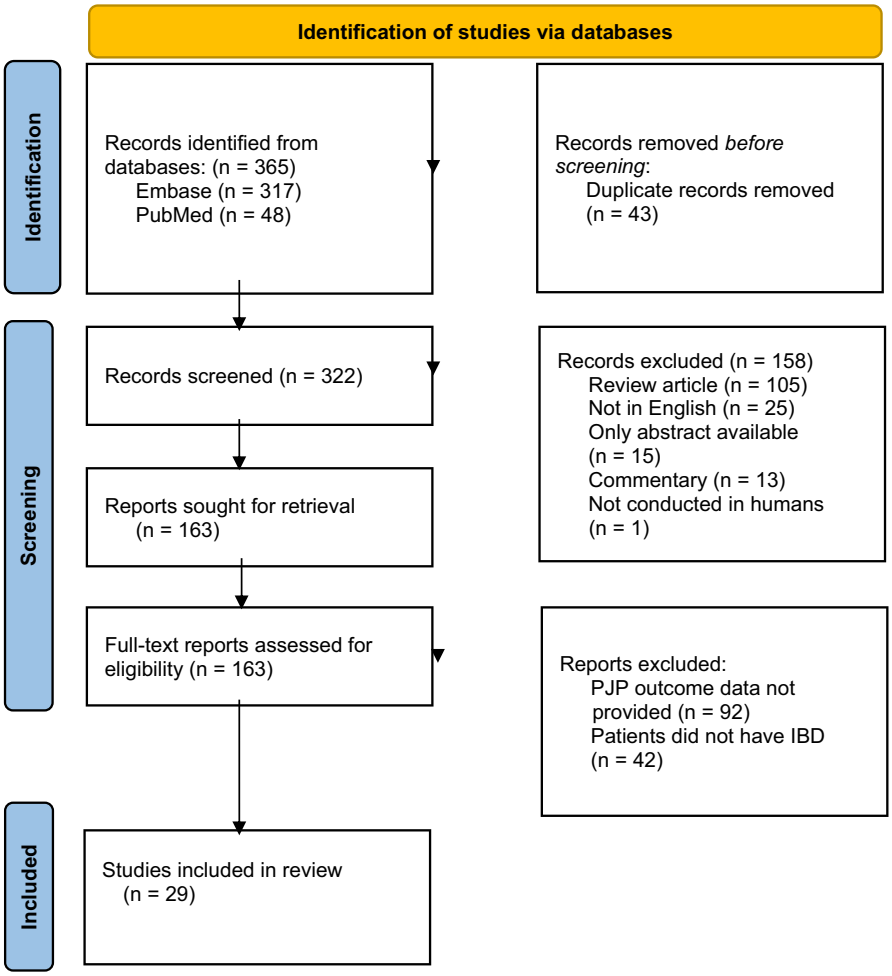

FIGURE 1 PRIMSA flow diagram for searching of records of PJP in patients with IBD. From reference [55]. IBD, inflammatory bowel disease; PJP, *Pneumocystis jirovecii*

TABLE 1 Case reports from systematic review

Author and year	Age (year)	Sex assigned at birth	Diagnosis	Time from IBD diagnosis to PJP onset (years)	Number of ISMs at time of PJP diagnosis	Daily prednisone equivalent dose at PJP diagnosis (mg)	ISMs at time of PJP diagnosis	WBC at time of PJP diagnosis (bil/L)	How PJP diagnosis was confirmed	Were ISMs continued during PJP treatment	Mortality
Watanabe 2022[31]	74	M	UC	0.08	2	70	Corticosteroids Mesalamine	15.64	PJP suspected	NA	No
Verstockt 2020[36]	53	F	UC	10	2	12.8	Corticosteroids Tofacitinib	10.98	BAL	Partially	No
Golan 2019[32]	30	M	CD	1	1	NA	Adalimumab	NA	BAL	No	No
DeFillippis 2015[34]	56	F	CD	38	3	NA	Corticosteroids Methotrexate Adalimumab	10.6	BAL	NA	No
Omer 2014[33]	76	M	CD	NA	1	NA	Corticosteroids	NA	BAL	No	No
Desales 2012[37]	36	M	CD	0.29	3	10	Corticosteroids Azathioprine Adalimumab	1.4	BAL	No	No
Tschudy 2010[38]	8	M	CD	6	1	NA	Infliximab	NA	Thoracostomy	NA	No
Lee 2009[39]	21	M	UC	3	2	40	Corticosteroids Azathioprine	2.8	BAL	Yes	No
Estrada 2009[40]	45	M	UC	1	4	16	Corticosteroids Mesalamine Azathioprine Infliximab	3.8	BAL	Partially	No
Oshitani 2008[41]	32	M	UC	NA	1	NA	Corticosteroids	NA	BAL	Yes	No
Itaba 2007[42]	57	F	CD	21	3	25	Corticosteroids Mesalamine Infliximab	4.37	BAL	NA	No
Sharma 2007[43]	36	F	CD	12	4	NA	Corticosteroids Mesalamine Mercaptopurine Infliximab	4	BAL	NA	No
Stratakos 2005[35]	77	F	CD	0.75	2	20	Corticosteroids Infliximab	12.6	BAL	NA	No
Velayos 2004[44]	19	M	CD	NA	2	NA	Azathioprine Infliximab	3.5	BAL	NA	No
Seddik 2003[45]	29	M	CD	NA	3	60	Corticosteroids Azathioprine Infliximab	3.1	BAL	NA	No
Scott 1997[46]	43	M	UC	4	2	37.5	Corticosteroids Cyclosporine	2.2	PCR	Yes	No
Quan 1997[29]	63	M	UC	0.25	2	NA	Corticosteroids Cyclosporine	NA	Histology	Yes	Yes
Khatchatourian 1997[30]	68	M	UC	28	1	NA	Mercaptopurine	6.5	BAL	Yes	Yes
Smith 1992[47]	32	M	UC	0.17	3	30	Corticosteroids Mesalamine Cyclosporine	NA	BAL	NA	No
Peters 1983[48]	27	F	CD	NA	1	NA	Corticosteroids	NA	PJP suspected	NA	No

Abbreviations: BAL, bronchoalveolar lavage; CD, Crohn's Disease; IBD, inflammatory bowel disease; ISM, immunosuppressive medications; NA, not available; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii*; UC, ulcerative colitis; WBC, white blood cells.

TABLE 2 Case series from systematic review

Author and year	Total patients (*n*)	Patients with PJP (*n*)	Mean age at PJP diagnosis (years)	% Males	Patients with CD (*n*)	Patients with UC (*n*)	Confirmed PJP diagnosis (*n*)	Suspected PJP diagnosis (*n*)	Mortality (*n*)
Escher 2010[49]	2	2	73	100	0	2	2	0	2
Lawrance 2010[52]	2	2	26	50	2	0	NA	NA	0
Takenaka 2004[50]	3	3	41	33	0	3	3	0	0
Bernstein 1993[51]	2	2	53	100	0	2	2	0	1

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; NA, not available; PJP, *Pneumocystis jirovecii*; UC, ulcerative colitis.

TABLE 3 Retrospective cohort studies from systematic review

Author and year	Total patients (*n*)	Patients with PJP (*n*)	Mean age at PJP diagnosis (year)	% Males	Patients with CD (*n*)	Patients with UC (*n*)	Confirmed PJP diagnosis (*n*)	Suspected PJP diagnosis (*n*)	Mortality (*n*)
Kojima 2020[53]	4525	9	NA	NA	0	9	3	6	2
Nam 2020[54]	6803	6	44	66	6	0	6	0	2
Yoshida 2018[55]	28	28	60	75	4	24	28	0	5
Cotter 2017[4]	937	4	72	100	0	4	4	0	0
Long 2013[56]	108,604	38[a]	49	45	21	15	38[b]	0	NA

[a]Two patients had an unknown IBD diagnosis.

[b]Diagnosis of PJP was determined by ICD-9 code.

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; NA, not available; PJP, *Pneumocystis jirovecii*; UC, ulcerative colitis.

The majority of the retrospective, cohort studies (five of five) was considered low risk of bias based on the JBI Critical Appraisal Checklist for cohort studies.[26] Most of these studies failed to address the occurrence of incomplete follow-up and strategies utilized to manage this. Two of four case series had a high risk of bias due to insufficient demographic information and lack of consecutive inclusion of participants. Sixteen of twenty (80%) case reports included had a low risk of bias. Of note, many case reports did not provide adequate demographic information including ethnicity, past medical history, or comorbidities and also did not specify the occurrence of unanticipated/adverse events. Refer to Table 4 for complete bias assessment scores for each study included.

Twenty unique patients were represented in the case reports, the majority of which were male (70%) and were diagnosed with CD (55%). The mean age of patients at time of PJP diagnosis was 45 years (standard deviation [SD] 21 years). The time from diagnosis of IBD to diagnosis of PJP varied widely, from approximately 1 month to 28 years. Similarly, the number of immunosuppressive medications the patients were receiving at time of PJP diagnosis ranged from one to four medications, the distributions of which are listed in Figure 2. Almost all patients (90%) had a confirmed PJP diagnosis, and only 10% of patients died from PJP.[29,30]

Several patients diagnosed with PJP were also infected with cytomegalovirus at time of PJP diagnosis,[31–33] one of whom also had HIV.[32]

TABLE 4 Joanna Briggs Institute risk of bias assessment

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Raw score	%Y	Risk
Critical appraisal tool for cohort studies[63]														
Kojima 2020[53]	Y	Y	Y	Y	Y	Y	Y	U	U	NA	Y	8/11	73	Low
Nam 2020[54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	10/11	91	Low
Yoshida 2018[55]	NA	NA	Y	Y	Y	Y	Y	N	N	N	Y	6/11	54	Mod
Cotter 2017[4]	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	8/11	73	Low
Long 2013[56]	Y	Y	Y	Y	N	Y	Y	N	Y	U	Y	8/11	73	Low
Critical appraisal tool for case series[64]														
Escher 2010[49]	N	Y	Y	N	N	N	Y	Y	N	NA	–	4/10	40	High
Lawrance 2010[52]	Y	Y	N	Y	Y	Y	Y	N	Y	Y	–	8/10	80	Low
Takenaka 2004[50]	N	Y	Y	N	N	N	Y	N	N	NA	–	3/10	30	High
Bernstein 1993[51]	N	Y	Y	N	N	Y	Y	Y	N	NA	–	5/10	50	Mod
Critical appraisal tool for case reports[65]														
Watanabe 2022[31]	N	Y	Y	Y	Y	Y	N	Y	–	–	–	6/8	75	Low
Verstockt 2020[36]	Y	Y	Y	Y	Y	Y	N	Y	–	–	–	7/8	88	Low
Golan 2019[32]	Y	Y	Y	Y	N	Y	Y	Y	–	–	–	7/8	88	Low
DeFillippis 2015[34]	N	Y	Y	Y	N	Y	Y	Y	–	–	–	6/8	75	Low
Omer 2014[33]	N	N	Y	Y	N	N	N	Y	–	–	–	3/8	38	High
Desales 2012[37]	Y	Y	Y	Y	Y	N	N	Y	–	–	–	6/8	75	Low
Tschudy 2010[38]	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	8/8	100	Low
Lee 2009[39]	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	8/8	100	Low
Estrada 2009[40]	N	Y	Y	Y	Y	Y	NA	Y	–	–	–	6/8	75	Low
Oshitani 2008[41]	N	Y	Y	Y	Y	N	Y	Y	–	–	–	6/8	75	Low
Itaba 2007[42]	Y	Y	Y	Y	N	Y	Y	Y	–	–	–	7/8	88	Low
Sharma 2007[43]	Y	Y	Y	Y	Y	Y	NA	Y	–	–	–	7/8	88	Low
Stratakos 2005[35]	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	8/8	100	Low
Velayos 2004[44]	N	Y	Y	Y	N	Y	NA	Y	–	–	–	6/8	63	Mod
Seddik 2003[45]	N	Y	Y	Y	Y	Y	N	Y	–	–	–	6/8	75	Low
Scott 1997[46]	N	Y	Y	Y	Y	Y	Y	Y	–	–	–	5/8	88	Low
Quan 1997[29]	N	Y	Y	Y	NA	Y	Y	Y	–	–	–	6/8	75	Low
Khatchatourian 1997[30]	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–	8/8	100	Low
Smith 1992[47]	N	Y	N	N	N	Y	U	Y	–	–	–	3/8	38	High
Peters 1983[48]	N	Y	Y	Y	Y	N	U	Y	–	–	–	6/8	63	Mod

Abbreviations: Mod., moderate; N, No; NA, not applicable; Q1–Q11, questions from the specified JBI critical appraisal tool available (Appendix S1); U, Uncertain; Y, Yes.

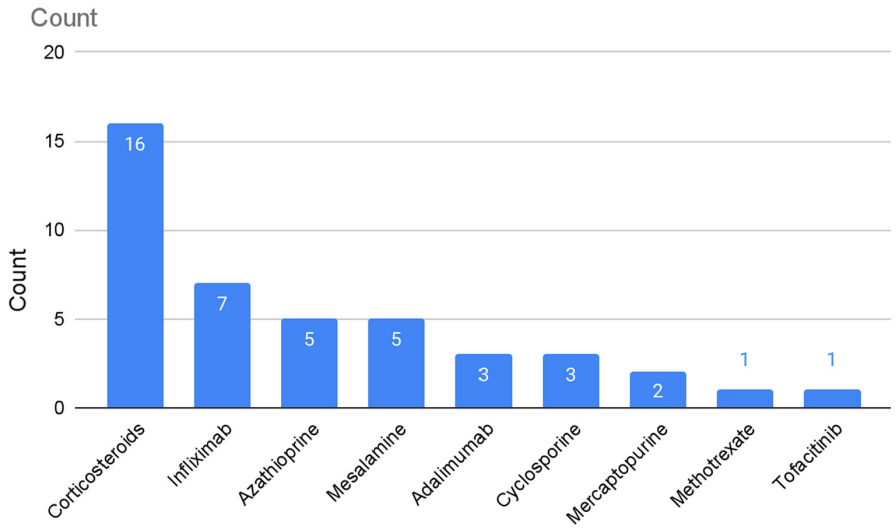

FIGURE 2 Case studies from systematic review—ISMs received at time of PJP diagnosis. ISM, Immunosuppressive medications; PJP, *Pneumocystis jirovecii*

Other patients had comorbidities of parastomal pyoderma gangrenosum[34] and one patient had type II diabetes, arterial hypertension and also grew *Acinetobacter baumannii* and *Proteus mirabilis* from airway and urine cultures, respectively.[35] Another patient also had a positive blood culture for *Nocardia farcinica*.[36] However, the majority of patients (70%) had no comorbidities documented at time of diagnosis.

Of the 18 case reports that listed the medication used for PJP treatment, all utilized sulfamethoxazole/trimethoprim.[30,31,33–48] Continuation of immunosuppressive medications was inconsistently documented in the case reports, but several of the patients[29,30,39,46] had all their immunosuppressive agents continued during PJP treatment; two of these patients were the only documented patients with mortality.[29,30] Ten studies reported the daily prednisone equivalent dose the patient was receiving at time of diagnosis; the mean daily dose was 32 mg at time of PJP diagnosis.[31,35–37,39,40,42,45–47] Of the six patients who were receiving infliximab at time of PJP development, the average duration of therapy was 8 months.[35,38,40,42,44,45]

Four case series reported on nine patients with PJP, the majority of which (77.8%) were in patients with UC[49–51] and who were male (55.6%).[49–52] Two studies reported the patients' white blood cell count at time of PJP diagnosis; the mean white blood cell count was 4.0 bil/L[50] and 10.4 bil/L,[51] respectively. Three of the four case series had confirmed PJP diagnoses[49–51] and of the 37 patients with reported PJP diagnoses, nine patients died (24.3%).[53–55] These patients were also older than patients who did not die from PJP (mean age 66.3 years versus 34.5 years). In one case series, the mean total daily dose of corticosteroids (in prednisone equivalents) was 26.7 mg (median 12.5 mg)[50]; similar results were found in a second case series, where the mean and median dose was 27.5 mg.[51]

Five retrospective cohort studies reported 85 patients with PJP of 120,897 patients (0.07%). The majority of these patients was diagnosed with UC (n = 52, 61.1%). Of the four studies that presented mortality data, nine of 47 patients died (24.3%).[4,53–55] Only three studies[4,53,54] reported time from IBD diagnosis to PJP diagnosis, ranging from 2 years to almost 7 years. The majority of patients (n = 61, 71.2%) were receiving corticosteroids at time of PJP diagnosis[53–56]; other common medications included thiopurines (n = 27, 31.8%)[4,53–55] and anti-TNFs (n = 17, 20%).[4,53–55] Most patients were receiving two immunosuppressive medications at time of PJP diagnosis (n = 25, 29%),[4,53–55] although some were receiving one or three immunosuppressive agents concomitantly (n = 18, 21.2% and n = 18, 21.2%, respectively).[4,53–55]

A retrospective cohort study concluded that patients who were diagnosed with PJP had a significantly higher C-reactive protein (CRP) (6.5 mg/dl vs. 0.1 mg/dl, p = 0.006) and were more likely to be receiving corticosteroids (100% vs. 37.5%, p = 0.017) than those who were not diagnosed with PJP.[54] The study found that a higher CRP at time of diagnosis of IBD was a significant risk factor for development of PJP (OR 1.855, 95% confidence interval [CI] 1.065–2.30).[54] Another study found that patients who died from PJP were significantly older than patients who did not die from PCP (69.0 ± 5.4 vs. 58.0 ± 14.0 years, respectively, p = 0.011) and that low serum albumin was a significant risk factor for mortality (OR 0.09, 95% CI 0.01–0.52, p = 0.027).[55] Similarly, patients who received a higher steroid dose over the 2 months prior to PJP diagnosis were more likely to die from PJP infection (OR 7.45, 95% CI 1.42–76.48).[55] Another study found that, of the 38 patients with IBD who were documented to have PJP, five of them were receiving no immunosuppressive medications at all.[56]

4 | DISCUSSION

Compilation of the data examining PJP incidence in patients with IBD confirms that the incidence itself is extremely low. Indeed, the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) cites data indicating that the lifetime risk of any patient with IBD developing PJP is extremely low (10.6 in 100,000).[2,57] Similarly, a study examining risk factors for development of PJP found that a diagnosis of IBD carried an OR of 2.6 (95% CI 3.9–4.3) in comparison with an OR of 270.2 (95% CI 264.5–276) in patients with HIV infection.[58] This study also found the overall incidence of PJP in patients without HIV to be 0.12%,[58] indicating that despite the increased relative risk of PJP development in patients with IBD, the overall absolute risk is extremely low. These results

are corroborated by this review, finding that the absolute risk of developing PJP in patients with IBD is 0.07%. This low incidence of PJP in patients with IBD makes it difficult to heavily weigh the results of any studies examining the potential risk factors for PJP development in this patient population.

Partially due the low incidence of PJP development, most guidelines and recommendations do not have a definitive call for prophylaxis in pediatric or adult patients with UC or CD. Many studies cite Part 2 of the ECCO guidelines to support their recommendation to consider PJP prophylaxis in patients with triple immunosuppressive therapy but do not provide their own evidence for this recommendation.[21] This recommendation was based upon expert opinion, but the guidelines do not take a stance outside of patients receiving triple immunosuppression, one medication of which must be a CNI or anti-TNF. Another portion of the ECCO guidelines cites that, despite the low absolute risk of development of PJP, the disease can be fatal, in particular to patients receiving CNI. Ferretti and colleagues similarly acknowledge the increased risk of PJP development while on CNIs but do not propose that PJP prophylaxis is indicated in patients receiving these therapies.[59] Although the ECCO guidelines acknowledge that chemoprophylaxis for PJP cannot be recommended to all patients with IBD, they do suggest that several underlying risk factors may warrant the need for prophylaxis, including high-dose corticosteroids (at least 15 mg/day of prednisone) and advanced age.[21] Indeed, patients in the studies examined in this review who were diagnosed with PJP were frequently receiving higher doses of prednisone and of advanced age, though this was not universally true.

Several recommendations cite studies in which risk factors for development of PJP were determined in patients with IBD.[2,10,21,55] However, these risk factors vary by study, some finding no strong correlation between any underlying risk factor and PJP development, and others making more generalized statements such as receipt of multiple immunosuppressive agents and use of high-dose corticosteroids increasing risk of PJP in patients with IBD.[1] It should be noted, however, that numerous studies have been unable to establish exposure to multiple immunosuppressive therapies as a risk factor for development of PJP.[4,54] Further complicating the picture is the rapid development of new agents for management of IBD; for example, therapy for IBD previously involved use of medications such as cyclosporine, which have been associated with development of PJP but are now used less frequently since the advent of immunomodulator therapies.[60] Data on the risk of immunomodulator therapies and anti-TNF therapies on development of PJP are still in progress.

In support of PJP prophylaxis, the use of sulfamethoxazole-trimethoprim—which was overwhelmingly utilized or recommended in studies examining PJP in patients with IBD—is a cost-effective medication with a manageable adverse event profile. Alternative agents, which may be less effective than sulfamethoxazole-trimethoprim, include dapsone, atovaquone, and aerosolized pentamidine.[61] In a simulation model conducted in patients with CD receiving immunosuppressive medication, the use of PJP prophylaxis with sulfamethoxazole-trimethoprim resulted in an estimated 70%–80% reduction in lifetime PJP risk. The study also found that between 167 and 334 patients needed to be treated with sulfamethoxazole-trimethoprim to prevent one case of PJP over the lifetime of the cohort.[60] While this provides evidence that PJP prophylaxis is feasible, the question that remains is if prophylaxis is necessary. Also, use of sulfamethoxazole-trimethoprim is not without risk, with documented hyperkalemia,[62] hypoglycemia,[63,64] and acute kidney injury,[65] among others.

This review is not without limitations. First, the authors recognize that medications that have been on the market for extended periods of time, or have been approved by the United States Food and Drug Administration for a particular disease state for longer, are more likely to have more reports of adverse events than newly approved medications. As a result, many of the newer medications used to treat IBD may have a falsely low rate of PJP infection reported. Also, many of the studies analyzed were case reports or case series and did not include full information about patient history, medications received, and treatment course of PJP. Similarly, the few cohort studies included provided little data about the patients who were diagnosed with PJP, in particular in regard to medication therapy received prior to development of PJP, making it more challenging to determine potential risk factors. The authors also recognize that many of the medications described in this review are utilized for other autoimmune disorders and that focusing on PJP incidence in patients being treated for IBD results is a narrower scope. Also, although two reviewers independently reviewed the literature and extracted the data, there is the potential for bias in review and reporting of the data.

5 | CONCLUSION

Receipt of immunosuppressive medications for treatment of UC and CD does increase the risk of development of PJP. Prolonged steroid use and older age may be contributing risk factors as well. However, studies included in this review showed significant variability in the number of immunosuppressive medications used, duration of therapy, age, and comorbidities among patients with IBD who developed PJP. Additionally, the absolute risk of PJP development is low in patients with IBD, and the relative risk of PJP in this patient population remains similarly low. Given the lack of conclusive data regarding risk factors for PJP development and the overall low incidence of PJP in patients with IBD, it is recommended to assess the patient's risk on a case-by-case basis to determine if PJP prophylaxis is warranted.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Caroline M. Sierra https://orcid.org/0000-0002-9336-5644

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