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Pneumocystis jirovecii pneumonia in patients with inflammatory bowel disease – A case series

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Abbreviations: CD: Crohn's disease; ECCO: European Crohn's and Colitis Organisation; HIV: Human immunodeficiency virus; IBD: Inflammatory bowel disease; PJP: Pneumocystis *jirovecii* pneumonia; TMP-SMX: Trimethoprim-sulfamethoxazole; UC: Ulcerative colitis

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Abstract

Background and Aim: *Pneumocystis jirovecii* pneumonia (PJP) is a very rare, potentially life-threatening pulmonary fungal infection that occurs in immunocompromised individuals including patients with inflammatory bowel disease (IBD). Our aim was to describe immunosuppressive treatment exposure as well as the outcome in IBD patients with PJP.

Methods: PJP cases were retrospectively collected through the COllaborative Network For Exceptionally Rare case reports of the European Crohn's and Colitis Organization. Clinical data were provided through a case report form.

Results: 18 PJP episodes were reported in 17 IBD patients (10 ulcerative colitis and 7 Crohn's disease). The median age on PJP diagnosis was 55 years (IQR, 40-68 years). Two PJP (11.1%) occurred in patients on triple immunosuppression, 10 patients (55.6%) had double immunosuppressive treatment, 4 patients (22.2%) had monotherapy and 2 PJP occurred in absence of immunosuppressive treatment (one in a human immunodeficiency virus patient and one in a patient with a history of autologous stem cell transplantation). Immunosuppressive therapies included steroids (n=12), thiopurines (n=10), infliximab (n=4), ciclosporin (n=2), methotrexate (n=1) and tacrolimus (n=1). None of the patients diagnosed with PJP had received prophylaxis. All patients were treated by trimethoprim/sulfamethoxazole or atovaquone and an ICU stay was required in 7 cases. Two patients (aged 71 and 32 years) died, and one patient had a recurrent episode 16 months after initial treatment. Evolution was favourable for the others.

Conclusion: This case series reporting potentially fatal PJP highlights the need for adjusted prophylactic therapy in patients with IBD on immunosuppressive therapy.

Keywords: *Pneumocystis jirovecii* pneumonia, Inflammatory bowel disease

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Introduction

Pneumocystis jirovecii is a ubiquitous unicellular fungus which causes pneumonia in immunosuppressed patients. There is growing evidence that patients with inflammatory bowel disease (IBD) are at increased risk of *Pneumocystis jirovecii* pneumonia (PJP) as a probable consequence of the increased and earlier use of immunosuppressive treatment.[1] In different ways, immunomodulators dysregulate cellular immunity, an innate mechanism in the eradication of disease-causing intracellular germs, including *Pneumocystis jirovecii.*[2] Although the absolute risk is low, IBD patients have an increased risk of PJP (10.6 per 100,000 person-years) compared with non-IBD patients (3 per 100,000 person-years), and this risk is higher in patients on immunosuppression (32 per 100,000 person-years).[3]

Clear guidelines for PJP chemoprophylaxis do exist for patients infected with human immunodeficiency virus (HIV) with low $CD4^+$ lymphocyte counts,[4] patients undergoing chemotherapy owing to solid or haematological malignancies, and recipients of solid organ or haematopoietic stem cell transplantation.[5–8] However, there is a lack of consensus on the need for primary PJP prophylaxis in other disease conditions such as IBD. In 2021, the European Crohn's and Colitis Organisation (ECCO) recommended primary PJP prophylaxis for IBD patients on triple immunosuppression (including steroids, methotrexate, thiopurines, biologics), for those on double immuno-suppressive therapy, especially if one is a calcineurin inhibitor as well as for any combination of high-dose corticosteroids, low lymphocyte count, or JAK inhibitors.[9] There is a dearth of robust information on patients on single or double immunosuppression which makes it challenging to provide guidance in these frequent situations. For this reason and despite the disease severity and the efficacy of chemoprophylaxis,[10] there has been no consistency in preventive approaches in patients with double or single immunosuppression outside the use of calcineurin inhibitors.[9] Our aim is to

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describe the profile of IBD patients diagnosed with PJP, the course of infection and its outcome.

Materials and Methods

Study design

This European Crohn's and Colitis Organisation (ECCO) observational multicentre study retrospectively collected cases of PJP through the CONFER (COllaborative Network For Exceptionally Rare case reports) project. The CONFER project was initiated by ECCO in order to identify and report rare IBD associations. Once a specific topic is selected by the Steering Committee as a CONFER project (PJP in IBD patients in the case of the present manuscript), ECCO launches a call to identify similar cases encountered by IBD physicians worldwide. The call to physicians is made through announcements at the annual ECCO Congress and at national and international IBD meetings across Europe. Moreover, the call for similar cases has been spread by direct emails to all ECCO members and affiliated physicians, on the ECCO website and eNews. Physicians have been asked to report their cases to the CONFER database using pre-determined standardised Case Report Forms (CRF).

Patients and procedures

All IBD patients with PJP were eligible for inclusion. The CRF included patient (epidemiological data, past medical history, smoking, family history) and IBD (IBD subtype, date of diagnosis, Montreal classification, extraintestinal manifestations and IBD treatment) characteristics, and the description of the infectious disease course (IBD treatment at the time of PJP diagnosis, PJP-related symptoms, diagnosis methods, treatments and outcome).

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Ethics

The ECCO CONFER Cases project was centrally approved by the Institutional Review Board (IRB) of the Sheba Medical Center (Israel). All of the included cases have been anonymised to protect confidentiality and respect patient privacy.

Statistical analyses

Demographic and disease specific data are given descriptively or tabulated. Results are presented as medians and quartiles (IQR) for continuous parameters or as frequency tables for qualitative parameters. Calculations were performed with SAS version 9.4.

Results

Patient and disease characteristics

We identified a total of 18 PJP episodes in 17 IBD patients from 7 medical centres across Europe (5 university centres and 2 non-university centres). None of these cases had previously been reported. Seven patients had Crohn's disease (CD) and 10 patients had ulcerative colitis (UC). The median age at the time of IBD diagnosis was 48 (26-57) years, and the median disease duration at PJP diagnosis was 7.5 (0-13.5) years. A total of 68.8% of patients had comorbidities and 2 patients (11.8%) had a history of lung disease (pulmonary embolism in one patient and tuberculosis in childhood in another). Two patients were current smokers and one was a former smoker. Patient clinical characteristics are shown in Table 1.

PJP and IBD

The median age of patients at the time of PJP diagnosis was 55 (40-68) years and 11 patients (64.7%) had active inflammatory disease at the time of PJP diagnosis. PJP symptoms, biological and radiological data are summarized in Table 2. The mean time between pulmonary symptoms and diagnosis was 14.7 days (range 2-46) and the latter was confirmed by PJ polymerase chain reaction (PCR) on bronchoalveolar lavage fluid in 14 cases (77.8%), by PJ PCR on induced sputum sample in one patient and by microscopic direct fluorescent

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antibody staining in two patients (method unreported in one patient with clinical and radiological findings of PJP).

A total of 15 patients were on immunosuppressive therapies at the time of diagnosis including systemic corticosteroids (n=12), thiopurines (n=10), infliximab (n=4), ciclosporin (n=2), methotrexate (n=1) and tacrolimus (n=1). The treatment combinations and doses of systemic corticosteroids are detailed in Table 3 for each patient. A minority of pneumonias occurred in patients on triple immunosuppression (11.1%), 10 patients (55.5%) had double immunosuppressive treatment and 4 patients (22.2%) were on monotherapy. The time between the initiation of immunosuppressive treatment and PJP diagnosis was very heterogeneous and ranged from 30 to 150 days. The lymphocyte count at the time of PJP infection was reported for 15 of the 17 patients. Of these 15 patients, 10 (66.7%) had a total lymphocyte count below 600/mm³.

Two PJP episodes occurred in the absence of any immunosuppressive treatment: one in a HIV patient (with $CD4^+$ counts of 172 cells/mm³; lymphocytes > 600/mm³) and one in a patient with a history of autologous stem cell transplantation for CD (with a $CD4^+$ count of 47 cells/mm³; lymphocytes < 600/mm³) the year before PJP diagnosis. A third patient had a low $CD4^+$ count (300 cells/mm³; lymphocytes > 600/mm³) at the time of PJP infection related to a recent history of B-cell lymphoma in the splenic marginal zone. $CD4^+$ counts at the time of PJP were not available for the other patients. Nine out of 17 patients (52.9%) had hypoalbuminemia. None of the patients had received primary prophylaxis.

All of the patients were treated with trimethoprim/sulfamethoxazole (TMP-SMX) except one who received atovaquone. Concomitant treatment with corticosteroids was administrated in 8 cases with variable doses (30 to 80 mg/day). Mean hospital stay was 21.6 days (range 7-81). Eight patients (44%) were hospitalized in an intensive care unit (mean stay: 7.6 days) of whom three required mechanical ventilation. Two patients (14%) aged 32 and 71 died (one

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patient on triple immunosuppression and one patient on double immunosuppression with systemic steroid and tacrolimus). One patient had a recurrent episode 16 months after initial treatment. Evolution was favourable for the other patients. Regarding IBD treatment at the time of PJ infection, immunosuppression was stopped in almost all patients (except one on thiopurine and one on anti-TNF). Corticosteroid treatment was less homogeneous with continuation of the same dose for two patients, reduced dose for four patients, increased dose for two patients and withdrawal in one patient (unreported for two patients and one patient died before IBD adaptation treatment). After recovery, all patients except six patients were started on PJP secondary prophylaxis. For two of them, this can be explained by discontinuation of immunosuppressive therapy, but this was not the case for the other four patients. The IBD treatment ‘s outcomes after the infection were variable and based on the IBD medical history.

Discussion

We report here the first European case series of PJP in IBD patients. This case series confirms

what was reported by previous cohorts (Table 4) namely that PJP can occur at any age but with a risk that increases with age (as 58.8% of patients ≥ 55 years in our cohort)[3,11–13], at any time during the IBD course as well as at any time after initiation of IBD treatment (as a substantial proportion of patients were on stable dose of treatment since several months before PJP onset).[12,14] While some studies reported a higher rate of PJP in patients with CD[3] or UC[11,14,15], a similar proportion of patients with UC and CD with PJP has been reported here. These variations are probably related to the small number of patients in these cohorts and no clear gender predisposition has been found.[11,14,15] A total of 68.8% of our patients had comorbidities and none had received primary prophylaxis, similarly to other reported case

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series.[11,12,14,15] We found 64.4% of patients with active disease at the time of PJP diagnosis, similar to the cohort of Yoshida et al. who reported that PJP occurred in patients with moderate severity disease.[15] Only 11.1% of PJP occurred in patients on triple immunosuppression, which is less than what is reported in Asian cohorts (ranging from 25 to 55.6%)[11,12,15], possibly due to the European ECCO guidelines which suggest primary prophylaxis for triple immunosuppression.[16] A significant proportion of our patients were on corticosteroids at the time of infection (12/17 patients; 70.5%), similar to what was found in previous reports (ranging from 33.3 to 100%).[3,11,12,14,15] Finally, the mortality rate of 14% found in our case series was consistent with those reported in the other studies, as high as 30%.[15,17,18] Some data suggest that PJP mortality is higher in the non-HIV population owing to a more hyperinflammatory response in non-HIV patients.[18,19] For this reason, opportunistic infections and especially PJP should be primarily considered in the differential diagnosis of respiratory symptoms in immunosuppressed IBD patients since early detection reduces the mortality rate[20] and further introduction of a prophylaxis appears to be the most appropriate strategy.[21]

In 2021, ECCO strongly recommended primary PJP prophylaxis with TMP-SMX for IBD patients on triple immunosuppressive therapy (including steroids, methotrexate, thiopurines, biologics). Prophylactic TMP-SMX may also be considered for those on double immuno-suppressive therapy, especially if there is a calcineurin inhibitor as well as for any combination of high-dose corticosteroids, low lymphocyte count, or JAK inhibitors.[9] However, Cotter et al. reported that the incidence of PJP was not higher in patients with triple immunosuppression than those with single or double immunosuppression.[14] Accordingly, in a recent case-control analysis by Nam et al., exposure to more than one multiple immunosuppressive therapy did not create a significantly increased risk factor for PJP compared with patients on monotherapy.[11] Consistent with previous studies,[15,22] our case

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series reports PJP in IBD patients on single or double immunosuppression highlighting the risk in this population. ECCO recommendations do not reflect individual patient risk of developing PJP and a personalised case-by-case approach to manage these patients based on each patient's immune status and/or comorbidities may help to prevent opportunistic infections due to IBD therapy and should be cost-effective.[2,23]

The risk factors for developing PJP appear to be comparable to all diseases requiring immunosuppressive treatment.[2] Paradoxically, As previously discussed, corticosteroids improve clinical outcomes in severe PJP when introduced early[2] and have emerged as a major risk factor to PJP in the non-HIV immunosuppressed population (accounting for 57% to 97%).[24–26] The risk is greater with a daily dose of 16 mg or more of prednisolone for at least 8 weeks or when given in combination with other immunosuppressive medications.[2,21,24,27–29] The majority of IBD patients with PJP in this case series were on corticosteroid treatment (66.7%) which is consistent with the results of other series.[3,11] Lymphopenia, especially with a total lymphocyte count < 600 cells/mm³ and $CD4^+$ count < 300 cells/mm³, is often caused by medications that treat IBD such as corticosteroids or thiopurines and has also been associated with increased risk of PJP.[27,30] In another series of immunosuppressed patients with PJP, 100% of the cases occurred in patients with $CD4^+$ count < 200 cells/mm³ at the time of diagnosis. Some authors suggest that monitoring $CD4^+$ counts in patients with a total lymphocyte count lower than 600/mm³ may help to identify patients at higher risk for PJP and potentially serve to guide the initiation of chemoprophylaxis.[12,19,22] In our case series, 66.7% of patients had a lymphocyte count below 600/mm³, and in 3 patients, $CD4^+$ count was < 300 cells/mm³ supporting this suggestion. Low serum albumin, identified as a risk factor for PJP mortality, should be considered when starting immunosuppressive treatment and early prophylaxis should be taken into consideration.[15,20] In our cohort, 9 out of 17 patients had low albumin levels. While this can possibly be attributed to disease activity in 6 of these patients,

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3 of them had hypoalbuminemia while their disease was quiescent. Advanced age (≥ 55 years; 8/17 patients in this case series) was found to be an additional risk factor for PJP and the initiation of immunosuppressive drugs should be undertaken with caution in this population.[2,3,16] Other additional risk factors for PJP infection have been demonstrated in the literature, including coexisting pulmonary diseases (e.g. bronchiectasis, or chronic obstructive pulmonary disease),[3,31,32] PJP colonisation before initiation of immunosuppressive therapy[33] as well as a higher serum CRP level at the time of IBD diagnosis suggesting severe disease activity requiring corticosteroid treatment.[11]

Based on existing data, recommendations will probably evolve and PJP prophylaxis on a case-by-case basis would be more appropriate. Particular attention should be paid to patients on long-term and high-dose corticosteroids, on triple immunosuppression with corticosteroids, anti-metabolites, biological agent or calcineurin inhibitor. Additionally, patients with lymphopenia (absolute lymphocyte count < 600 cells/mm³ and $CD4^+$ lymphocyte count < 300 cells/mm³), with pulmonary comorbidities and/or older than 55 years should be cautiously evaluated.

Paradoxically, corticosteroids, identified as a major risk factor for PJP, improve clinical outcomes in severe PJP and has shown mortality benefit when introduced early[2,34]. The addition of corticosteroids could control the self-sustaining host inflammatory response as a reaction to pneumocystis particles from killed organisms, which is generally responsible for the severity of lung injury.[34] While it is generally accepted that corticosteroids should be started within 72 hours after the initiation of anti-PJP therapy, there is no clear consensus on the recommended duration and doses.[34] However, a 21-day regimen of oral prednisolone has been proposed with 5 days of 40 mg twice daily, 5 days of 40 mg once daily and 20 mg once daily the remaining 11 days.[34,35] Only 2 patients in our cohort appear to have benefited from these starting doses.

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Surprisingly, secondary PJP prophylaxis was applied in only 55.6% of the cases which was probably related to the lack of knowledge about the need for secondary prophylaxis and the absence of guidelines in this situation.[36] While some authors advocate discontinuation one month after stopping immunosuppressive drugs,[37] others prefer to maintain prophylaxis for up to three months since there is a remaining risk of PJP during the immune reconstitution phase. ECCO guidelines do not explicitly indicate the best moment to discontinue prophylaxis. Question is raised regarding the choice of IBD treatment in patients recovering from infection. Kojima K et al. reported no new incident cases of PJP among UC patients aged ≥ 50 years who were prescribed three or more immunosuppressive agents given prophylactic TPM-SMX, suggesting that prophylaxis may be effective and could possibly allow continuation of IBD treatment as prescribed prior to the onset of infection (especially if effective).[12] In the cohort of Yoshida et al, which is the only one to have evaluated IBD treatment outcomes, 78% of patients were able to continue their IBD treatment with the addition of a TPM-SMX prophylaxis[15]. Others propose the avoidance of therapy associated with lymphopenia (such as corticosteroid or thiopurine) and promote the prescription of newer biologics (such as vedolizumab and ustekinumab), which appears to be less frequently associated with PJP than older therapies such as anti-TNFα[13,38,39] There is no clear recommendation on the subject to date and we believe that a case by case discussion is needed based on the medical history of the patient and disease.

This study has some limitations. First, owing the retrospective nature of this investigation, a number of data are missing. Second, the relatively small number of PJP cases and the absence of control cases did not allow us to definitively determine the risk factors associated with PJP and its outcome. Finally, this case series does not allow to presume the incidence or prevalence of PJP in IBD patients. Population-based study or ad hoc registry would be needed to answer this question but are not yet available for Europe at this time.

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In conclusion, the present case series reports PJP cases in IBD patients on single or double immunosuppression highlighting the risk in this population. Identifying risk factors for PJP infection in IBD patients is essential to provide case-by-case prophylaxis.

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Data Availability Statement

No supplementary data.

Author Contributions: SV and JFR conceived the study and were responsible for analysis and interpretation of data and drafting the manuscript; AM, DH, KR, ES, SV, CR, BJ, MA and MF contributed to the cases and were responsible for revision of the manuscript as well as for the treatment of the patients.

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Table 1. Clinical characteristics of inflammatory bowel disease [IBD] patients presenting PJP [n=17].

Characteristics	Value (n=17)
Age on PJP diagnosis (years), median (IQR)	55 (40-68)
Sex, n (%)	
Male	11 (64.7)
Female	6 (35.3)
IBD subtype, n (%)	
UC/CD	10 (58.8)/7 (41.2)
Smoking, n (%)	
Current/past/never/unknown	2 (11.8)/1 (5.9)/9 (52.9)/5 (29.4)
Race, n (%)	
Caucasian/Eurasian/Asian	15 (88.2)/1 (5.9)/1 (5.9)
Age on IBD diagnosis (years), median (IQR)	48 (26-57)
Age on diagnosis, n (%)	
CD: A1/A2/A3	1 (14.3)/2 (28.6)/4 (57.1)
Current disease location, n (%)	
CD: L1/L2/L3/unknown	2 (28.6) /0 (0.0) /4 (57.1)/1 (14.3)
UC: E1/E2/E3	1 (10.0)/4 (40.0)/5 (50.0)
Current disease behaviour, n (%)	
CD: B1/B2/B3/Unknown	2 (28.6)/3 (42.9)/1 (14.3)/1 (14.3)
CD perianal disease, n (%)	2 (28.6)
Comorbidities, n (%)	11 (68.8)
Hypoalbuminemia	9 (52.9)
Atrial fibrillation	3 (42.9)
Hypertension	2 (28.6)
Sleep apnoea syndrome	1 (14.3)
Pulmonary embolism	1 (14.3)
Tuberculosis in childhood	1 (14.3)
Chronic kidney failure	1 (14.3)
HIV	1 (14.3)
B-cell lymphoma in the splenic marginal zone	1 (14.3)
Extraintestinal manifestations, n (%)	3 (17.6)
IBD treatment exposure at time of PJP n (%)	
Monotherapy	3 (17.6)
Steroid monotherapy	1 (5.9)
Thiopurine monotherapy	2 (11.8)
Double immunosuppression	10 (58.8)
Steroid + thiopurine	4 (23.5)
Steroid + infliximab	2 (11.8)

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Steroid + methotrexate	1 (5.9)
Steroid + tacrolimus	1 (5.9)
Infliximab + thiopurine	2 (11.8)
Triple immunosuppression	2 (11.8)
Steroid + thiopurine + ciclosporin	2 (11.8)
None	2 (11.8)

Values are median (IQR) or number of patients (%).
AZA: azathioprine; CD: Crohn's disease; HIV, human immunodeficiency virus; IBD: inflammatory bowel disease, PJP: Pneumocystis *Jirovecii* pneumonia; UC: ulcerative colitis; TNF: tumour necrosis factor; MP: -mercaptopurine.

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Table 2. Clinical, biological and radiological characteristics of 18 *PJ* pneumoniae.

Symptoms	Symptom frequency
Dyspnoea	82.4%
Cough	66.7%
Desaturation	58.3%
Weakness	53.3%
Fever	52.9%
Tachycardia	50%
Anorexia	13.3%
Bronchospasm	12.5%
Cyanosis	5.9%
Hyperneutrophilia	100%
Increased C-reactive protein	94.1%
Increased LDH	92.3%
Anaemia	55.6%
Leukopenia	27.8%
Thrombopenia	27.8%
Diffuse interstitial infiltrate	58.8%
Pleural effusion	46.7%
Lobar consolidation	20%
Normal chest radiography	5.9%
Bilateral and symmetrical distributions	85.7%
Ground glass	76.9%
Predominance to higher fields	57.1%
Respect of subpleural regions	53.8%
Lymphadenopathy	50%
Pleural effusion	46.7%
Consolidation	40%
Crazy paving	23.1%
Bronchiectasis by traction	7.7%
Nodular lesion	7.1%

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Number of pneumonias (n=18)	Immunosuppressive treatment exposure in IBD patients at time of PJP (duration of immunosuppression in months)	Age on PJP diagnosis (years)	Sex	IBD subtype	Active IBD at the time of PJP diagnosis	Co-morbidities and immunosuppressive factors	PJP prophylaxis	PJP treatment	Stay in ICU	Mechanical ventilation support	Death Yes/No	Secondary prophylaxis
Case 1	None	40	M	CD	Yes	HIV; CD4 count: 172 cells/mm³; Sleep apnoea syndrome, AF, hypoalbuminemia	No	TMP-SMX	Intermediate care station	No	No	Yes
Case 2	None	20	F	CD	No	Autologous stem cell transplantation for CD 6 months before PJP; lymphocytes < 600/mm³, CD4+ count: 47 cells/mm³	No	TMP-SMX	Yes (8 days)	Yes (4 days)	No	Yes
Case 3	18.8 mg prednisolone equivalent monotherapy (for 180 months)	73	M	CD	No	Hypoalbuminemia; lymphocytes < 600/mm³	No	TMP-SMX	Yes (6 days)	No	No	No
Case 4	Thiopurine monotherapy (for 42 months)	65	M	UC	No	AF (lymphocyte or CD4+ count not reported for this patient)	No	TMP-SMX	No	No	No	No
Case 5	Thiopurine monotherapy (for 2.5 months)	68	F	UC	Yes	Recent history of B-cell lymphoma in the splenic marginal zone and splenectomy; CD4+ count: 300 cells/mm³	No	TMP-SMX	No	No	No	Yes
Case 6 1st episod	Decreasing regimen from 50 to 20 mg prednisolone equivalent (for 2 months) + thiopurine (for 2 months)	53	F	CD	Yes	Chronic kidney failure, hypoalbuminemia	No	CS (30 mg/d PO) + TMP-SMX	Yes (1 day)	No	No	Yes
Case 6 2nd episod	5 mg prednisolone equivalent monotherapy (for 2 months)	54			No		No	TMP-SMX	Yes (1 day)	No	No	Yes
Case 7	5 mg prednisolone equivalent (for 4 months) + thiopurine (for 1 month)	26	M	UC	Yes	(Lymphocyte or CD4+ count not reported for this patient)	No	CS (40 mg/d IV) + TMP-SMX	No	No	No	No
Case 8	Systemic steroid, dose unknown (for 3.5 months) + thiopurine (4 months)	58	F	UC	No	Hypoalbuminemia, lymphocytes < 600/mm³	No	CS (40 mg/d IV) + TMP-SMX	Yes (5 days)	No	No	Yes
Case 9	20 mg prednisolone equivalent (for 4.5 months) + thiopurine (3 months)	71	M	UC	Yes	Lymphocytes < 600/mm³	No	CS (8 mg/d PO) + TMP-SMX	No	No	No	Yes
Case 10	62 mg prednisolone equivalent (for 1 month) + infliximab/4 weeks (2 months)	55	M	UC	Yes	None	No	CS (80 mg/d PO) + TMP-SMX	No	No	No	No
Case 11	30 mg prednisolone equivalent (for 1.5 month) + Infliximab (for 10 days)	55	M	CD	Yes	Hypertension, hypoalbuminemia, lymphocytes < 600/mm³	No	TMP-SMX	No	No	No	Yes
Case 12	20 mg prednisolone equivalent (for 4.5 months) + methotrexate (for 4.5 months)	80	M	CD	Yes	Tuberculosis in childhood, hypoalbuminemia, lymphocytes < 600/mm³	No	Atovaquone	No	No	No	Yes
Case 13	20 mg prednisolone equivalent (for 1 month)	71	M	UC	Yes	Pulmonary embolism, AF, hypertension, hypoalbuminemia	No	CS (80 mg/d IV) + TMP-SMX	Yes (11 days)	Yes	Yes	NA

	+ tacrolimus (11 days)											
Case 14	Infliximab (2 months) + thiopurine (1 month)	48	M	UC	No	Hypoalbuminemia, lymphocytes < 600/mm³	No	TMP-SMX	No	No	No	No
Case 15	Infliximab (2 months) + thiopurine (32 months)	61	F	CD	No	Lymphocytes < 600/mm³	No	CS (40 mg/d IV) + TMP-SMX	No	No	No	No
Case 16	20 mg prednisolone equivalent (for 2 months) + thiopurine (1 month) + ciclosporin (2 months)	29	F	UC	Yes	Lymphocytes < 600/mm³	No	TMP-SMX	No	No	No	Yes
Case 17	20 mg prednisolone equivalent (for 5 months) + thiopurine (4 months) + ciclosporin (4 months)	32	M	UC	Yes	Hypoalbuminemia, lymphocytes < 600/mm³	No	CS (dose unknown) + TMP-SMX	Yes (21 days)	Yes	Yes	NA

Table 3. Demographics and clinical features of the IBD patients with PJP

AF: atrial fibrillation; CD: Crohn's disease; CS: corticosteroids; F: Female; IBD: inflammatory bowel disease; HIV: human immunodeficiency virus; ICU: intensive care unit; IV: intravenous; M: male; NA: non-applicable; PJP: Pneumocystis *jirovecii* pneumonia; PO: per os; TMP-SMX: trimethoprim-sulfamethoxazole; UC: ulcerative colitis.

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Author year	Country Study type period	Incidence or number of pts included in the cohort	Age at the time of PJP diagnosis (years)	F/M	UC/CD/Unknown	Median duration of IBD at the time of PJP diagnosis	Active disease at time of PJP	Patients with comorbidities	Primary PJP prophylaxis	Factors associated or not with PJP compared to the control group	Percentage of patients with PJP who had				Median time between treatment initiation and PJP onset	Patients treated by TMP-SMX/alternative treatment	Mortality rate
											Triple IS Double IS single IS None	CS	Immuno-suppressant	Biologics			
Long MD et al. (2013)[3]	USA Retrospective cohort study 1997-2009	Only patients < 64 years included 38 cases of PJP/108,604 patients with IBD or 10.6/100,000 n=38	Median (IQR) :49 (43–57)	21 (55.3%)/17 (60.7%)	15 (39.5%)/21 (55.3%)/2 (5.3%)	NR	NR	Cardiac (n=4 ; 10.5%), diabetes mellitus (n=6 ; 15.8%), liver disease (n=5 ; 13.2%), renal (n=5 ;13.2%), COPD (n=8 ; 21.1%)	NR	- The risk was somewhat greater for CD as compared to non-IBD - Incidence increase with age (with the highest incidence in the 60+ age strata)	Triple: 4/38 (10.5 %) Double: 5/38 (13.2 %) Single: 12/38 (31.6 %) None: 17/38 (44.7 %)	20/38 (52.6 %)	Uncertain	Uncertain	NR	NR	NR
Cotter at al. (2017)[14]	USA, Olmsted County, Minnesota Population-based cohort study 1970-2011	3 PJP cases/937 patients	63, 74 and 78 years	0 (0%)/3 (100%)	2 (66.7%)/ 1 (33.3%)/ 0 (0%)	9.2 years, 6.2 years and 5.2 years	NR	2/3 (66.7%) COPD (n=1), bronchiectasis (n=1)	None	- The mean total lymphocyte count of these 3 cases was 970 ± 520 mm3, compared to 1430 ± 780 mm3 in a random sample of 30 patients without PJP over the age of 60 years	Triple: 0/3 (0%) Double: 2/3 (66.7 %) Single: 1/3 (33.3 %) None: 0/3 (0%)	1/3 (33.3 %)	2/3 (66.7%)	2/3 (66.7%)	Case 1: 4.2 y. of IFX and MTX Case 2: 1 month of IFX and prednisolone Case 3: 4.7 years of azathioprine	3/3 (100%)	0/3 (0%)
Yoshida A, et al. (2019)[15]	Japan Retrospective observational study of case Multicentric study 2002-2017	n=28	Mean (± SD): 60.1 ± 13.6 y	7 (25%)/21 (75%)	24 (85.8%)/ 4 (14.2%)/0 (0%)	NR	Severity of UC at PJP onset based on the Mayo score was moderate in almost all pts, with a mean score of 7.3 ± 2.1	NR	None	-	Triple: 7/28 (25%) Double: 17/28 (60.7 %) Single: 4/28 (14%) None: 0/0 (0%)	25/28 (89.3 %)	17/28 (60.1%)	10 (36%)	NR	NR	17.9% Mean time to death was 26.6 ± 18.1 d. Pts who died were significantly older (p=0.011) and had lower serum albumin level at the start of IBD treatment (p=0.048) and higher total steroid dose from the start of IBD treatment (p=0.040)

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Nam K, et al. (2020)[1] [1]	Korea Case-control cohort study Single tertiary referral center 1989-2016	6/6803 pts (0.09%) 10.4 cases per 100 000 person-years	Median (IQR): 34.5 y (33.0–64.0 y)	2/4	6 (100%)/0 (0%)/0 (0%)	12 m.(IQR 6.5-60 m.)	6/6 (100%)	2/6 (33.3%) Hypertension and hypothyroidism (n=1), asthma (n=1)	None	- Higher CRP at diagnosis of IBD (p= 0.006) - Higher exposure to CS (p= 0.017) - Higher rates of double or triple IS (but not statistically significant) - Significantly more patients underwent colectomy in the IBD-PJP group than in the IBD-only group (p=0.029) Factors not associated with PJP compared to control group: age at the time of IBD diagnosis, sex, history of appendicectomy, exposure to cigarette smoking, the extend and severity of UC at the time of diagnosis and follow-up period	Triple: 2/6 (33.3 %) Double: 3/6 (50%) Single: 1/6 (16.7 %) None: 0%	6/6 (100%)	3/6 (50%)	4/6 (66.7%)	Unknown	100%/ 2 alternative treatment for adverse reaction (pancreatic and liver enzyme elevation)	2/6 (33.3%) but from other causes than PJP
Kojima K, et al. (2020)[1] [2]	Japan Retrospective case-control study Monocentric study 2007-2019	9/4525 UC pts (0.2%)	Median (IQR) :56 y (54–62 y)	NR	Only UC pts studied	38 m. (IQR 24-47 m.)	The median Lichtiger clinical activity index (range) was 13 (8–17) at the initiation of treatment versus 2 (1–8) at PJP onset	NR	None	- Greater median age (p=0.022) - Triple IS were used more frequently than one or double IS in the PJP group than in the non-PJP group (p=0.004) - Lower lymphocyte count during the treatment (p<0.001) No significant differences between the two groups in the UC duration and location at the beginning of immunosuppressive therapy	Triple: 5/9 (55.6 %) Double: 2/9 (22.2 %) Single: 2/9 (22.2 %) None: 0/0 (0%)	9/9 (100%)	7/9 (77.8%)	1/9 (11.1%)	83 days	NR	2/9 (22.2%)
Schwart	USA	235	Mean	44.4%/55.6	NR	NR	NR	48.9% including 20%	NR	- Older patients	NR	NR	NR	NR	NR	NR	Mortality

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z J, et al. (2022)[1] [3]	Retrospective cohort study 2016-2017	**admissions** for PJP/ 641,265 all-cause admissions involving IBD pts (0.035% of the total admissions)	(SD): 58.9 (54.8-63.0)	%				of pts with HIV and one third of pts had an underlying congenital immunodeficiency (including hypogammaglobulinemia, severe combined immunodeficiency, or common variable immunodeficiency)		(p=0.007) - Higher comorbidity burden (p<0.001) - More often exposed to chronic steroids compared to non-PJP IBD patients (15.6% vs 6.4%; p=0.10) and 3.4 times higher odds of chronic steroid use than the overall IBD inpatient population when adjusted in multivariate regression							rate unknown but PJP was associated with a 4.67-fold increase in the odds of inpatient mortality, after controlling for comorbidity burden, hospital characteristics, patient age and inpatient surgery Length of stay: 16.8 days

Table 4. Published case series of PJP in IBD patients.

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CS, corticosteroids; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IFX, infliximab; IS, immunosuppression; m, month; MTX, methotrexate; NR, not reported; PJP, pneumocystis *jirovecii* pneumonia; pts, patients; TMP-SMX, trimethoprim-sulfamethoxazole y, year;