



Risk Factors and Prevention of *Pneumocystis jirovecii* Pneumonia in Patients With Autoimmune and Inflammatory Diseases

Amine Ghembaza, Mathieu Vautier, Patrice Cacoub, Valérie Pourcher, David Saadoun

► To cite this version:

Amine Ghembaza, Mathieu Vautier, Patrice Cacoub, Valérie Pourcher, David Saadoun. Risk Factors and Prevention of *Pneumocystis jirovecii* Pneumonia in Patients With Autoimmune and Inflammatory Diseases. *Chest*, 2020, 158, pp.2323 - 2332. 10.1016/j.chest.2020.05.558 . hal-03493466

HAL Id: hal-03493466

<https://hal.science/hal-03493466>

Submitted on 15 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Word Count: 3107

References Count: 74

Submitted for: CHEST Reviews

“Risk factors and prevention of *Pneumocystis jirovecii* pneumonia in patients with autoimmune and inflammatory diseases”

Running head : Pneumocystis jirovecii pneumonia in patients with autoimmune diseases

Amine Ghembaza^{1,2,3}, MD

Email: amineghembaza@gmail.com

Address: 47-83 Boulevard de l'Hôpital, 75013 Paris

Conflict of Interest statement: the author has no conflict of interest to disclose.

Mahtieu Vautier^{1,2,3}, MD

Email: mathieu.vautier@aphp.fr

Conflict of Interest statement: the author has no conflict of interest to disclose.

Patrice Cacoub^{1,2,3}, MD

Email: patrice.cacoub@aphp.fr

Conflict of Interest statement: the author has no conflict of interest to disclose.

Valérie Pourcher^{4,5}, MD PhD

Email: valerie.martinez@aphp.fr

Conflict of Interest statement: the author has no conflict of interest to disclose.

David Saadoun^{1,2,3}, MD PhD

Email: david.saadoun@aphp.fr

Conflict of Interest statement: the author has no conflict of interest to disclose.

Institutional affiliations:

1- AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France.

2- Centre national de références Maladies Autoimmunes systémiques rares et Centre national de références Maladies Autoinflammatoires et amylose inflammatoire.

3- Sorbonne Universités, UPMC Université Paris 6, INSERM, UMR S 959, Immunology-Immunopathology- Immunotherapy (I3); F-75005, Paris, France.

4-Service des maladies infectieuses et tropicales, hôpital Pitié-Salpêtrière, AP-HP, 75013, Paris, France.

5- INSERM UMR-S 1136, Pierre Louis Institute of Epidemiology and Public Health, Sorbonne Université, Paris, France.

Address correspondence to: Pr David Saadoun, MD, PhD, Sorbonne Universités, UPMC Université Paris 6, INSERM, UMR S 959, Immunology-Immunopathology-Immunotherapy (I3), Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.

E-mail : david.saadoun@aphp.fr, Phone : +33(0)142178042, Fax : +33(0)142178080.

Conflict of Interest statement: the authors has no conflict of interest to disclose.

Risk factors and prevention of *Pneumocystis jirovecii* pneumonia in patients with autoimmune and inflammatory diseases

Amine Ghembaza^{1,2,3} MD, Mathieu Vautier^{1,2,3} MD, Patrice Cacoub^{1,2,3} MD, Valérie Pourcher^{4,5} MD PhD and David Saadoun^{1,2,3} MD PhD

1- AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France.

2- Centre national de références Maladies Autoimmunes systémiques rares et Centre national de références Maladies Autoinflammatoires et amylose inflammatoire.

3- Sorbonne Universités, UPMC Université Paris 6, INSERM, UMR S 959, Immunology-Immunopathology- Immunotherapy (I3); F-75005, Paris, France.

4-Service des maladies infectieuses et tropicales, hôpital Pitié-Salpêtrière, AP-HP, 75013, Paris, France.

5- INSERM UMR-S 1136, Pierre Louis Institute of Epidemiology and Public Health, Sorbonne Université, Paris, France

Address correspondence to: Pr David Saadoun, MD, PhD, Sorbonne Universités, UPMC Université Paris 6, INSERM, UMR S 959, Immunology-Immunopathology-Immunotherapy (I3), Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.

E-mail : david.saadoun@aphp.fr Phone : +33(0)142178042, Fax : +33(0)142178080.

Abbreviation list:

AID= autoimmune and inflammatory diseases; GPA= granulomatosis with polyangiitis ; HIV= human immunodeficiency virus; MMF= mycophenolate mofetil; PAN= periarthritis nodosa; PJP= *Pneumocystis Jirovecii* pneumonia; PM/DM= polymyositis/dermatomyositis ; RA= rheumatoid arthritis ; SLE= systemic lupus erythematosus; TMP-SMX= trimethoprim-sulfamethoxazole.

Abstract:

Patients with autoimmune and/or inflammatory diseases (AID) are prone to serious infectious complications such as *Pneumocystis Jirovecii* pneumonia (PJP). In non-HIV patients, the prognosis is poorer and diagnosis tests are of lower sensitivity. Given the low incidence of PJP in AID, with the exception of granulomatosis with polyangiitis, and the non-negligible side effects of chemoprophylaxis, routine prescription of primary prophylaxis is still debated. Absolute peripheral lymphopenia, high doses of corticosteroids, combination with other immunosuppressive agents, and concomitant lung disease are strong predictors for the development of PJP, and thus should warrant primary prophylaxis. Trimethoprim-sulfamethoxazole is considered as the first line therapy and the most extensively used drug for PJP prophylaxis. Nevertheless, it may expose patients to side effects. Effective alternative drugs could be used when trimethoprim-sulfamethoxazole is not tolerated or contraindicated such as atovaquone, or aerosolized pentamidine. No standard guidelines are available to guide PJP prophylaxis in patients with AID. This review covers the epidemiology, risk factors and prevention of pneumocystis in the context of AID.

Key words: *Pneumocystis jirovecii* Pneumonia; Trimethoprim-Sulfamethoxazole; inflammatory diseases; autoimmune diseases; prophylaxis.

1.Introduction:

Infection is a major leading cause of morbidity and mortality in patients with autoimmune and inflammatory diseases (AID). Relevant studies showed that the incidence of mortality related to infections in patients with AID ranged between 1.2% and 36% .¹ Pneumocystis Jirovecii pneumonia (PJP) is an emerging threat to immunocompromised patients without HIV infection, such as those receiving immunosuppressive therapeutics for AID.² Clinical manifestations of PJP are quite different between patients with and without HIV infections. In patients without HIV infection, PJP rapidly progresses, is difficult to diagnose correctly, and can causes severe respiratory failure with a poor prognosis.² Several mechanisms have been outlined to explain the susceptibility to PJP in patients with AID. They could be categorized as intrinsic and extrinsic factors.

Intrinsic factors are mainly represented by lymphopenia. Lymphopenia is a frequent feature in many AID such as systemic lupus erythematosus (SLE) and sarcoidosis or secondary to immunosuppressive drugs. It is considered as an independent risk factor for infections, especially opportunistic infections.³ It was postulated that CD4 cells play a pivotal role in controlling PJP, as evidenced by the inverse relationship that exists between CD4 count level and the incidence of PJP in HIV patients .⁴

Extrinsic factors are mainly represented by steroids and immunosuppressants. Corticosteroids exert several complex quantitative and qualitative immune dysregulations such as reversible lymphopenia and monocytopenia, CD4+ depletion, decreased lymphocytes proliferation and migration, Th1/Th2 dysregulation, and impaired neutrophils phagocytosis .⁵

2.Epidemiology of PJP in AID patients

Pneumocystis jirovecii pneumonia is a potentially life-threatening opportunistic fungal infection that occurs predominantly in immunocompromised hosts including particularly patients with Human Immunodeficiency Virus (HIV) but also those with malignancies, organ or bone marrow transplantation and AID. In developed countries, prompt prescription of highly active antiretroviral therapy, the routine use of trimethoprim-sulfamethoxazole (TMP-SMX) as PJP primary prophylaxis and the development of new diagnostic tools for PJP are all factors that have dramatically contributed to a substantial decline in the incidence of PJP among HIV patients. Conversely, the number of PJP in non-HIV patients have dramatically increased in the current era because of the widespread use of antitumor chemotherapy and immunosuppressive drugs, the broader application of solid organ and bone marrow transplantation and the improving life expectancy of patients with AID, thereby increasing the importance of prophylaxis .⁶ In a meta-analysis including 867 patients

with non-HIV related PJP, the most common predisposing conditions were hematologic malignancies (29.1%), AID (20.1%), solid organ or bone marrow transplantation (14%) and solid tumors (6%) .⁷ In the setting of AID (**Table 1**), the most common underlying condition for the development of PJP is GPA (8-12%), followed by periarteritis nodosa (PAN) (6.5%), polymyositis/dermatomyositis (PM/DM) (2.7%), SLE (2%) and rheumatoid arthritis (RA) (0.1-0.3%).⁸

While PJP in HIV patients tends to be subacute, evolving over one to two weeks. PJP in non-HIV patients presents typically more abruptly, with marked severe respiratory symptoms and requires more frequently intensive care admission and mechanical ventilation .⁹ Furthermore, the reported PJP-related mortality rate in those patients is estimated to be as high as 30% to 60% ,¹⁰ which is significantly much higher than the 6.7% in HIV patients .¹¹ PJP-related prognosis varies according to the underlying condition with the highest mortality rate observed in patients with GPA (62.5%) .¹² In a postmarketing Japanese study carried out in 5000 RA patients treated with infliximab, the reported incidence of PJP was 0.4%. All patients received methotrexate concomitantly at a mean dose of 7.3 ± 2 mg per week. It is worth mentioning that almost 90% of patients were treated with corticosteroids.¹³ Conversely, in a randomized controlled trial including 1.050 RA patients who were assigned to receive either methotrexate alone or in combination with infliximab, none of the patients developed PJP. However, in this study, corticosteroid users (36%) were much lower than that in the former study.¹⁴ In North America, RA patients treated with TNF alpha antagonists experienced lower incidence rate (0.01%) of PJP.¹⁵

2.1.PJP Risk factors

Several risk factors have been described in patients with AID including mainly corticosteroid use and lymphopenia. The underlying AID is also an independent risk factor for PJP. PJP in AID develops in patients with immunosuppression or immunomodulation due to the underlying disease or its treatment. Risk assessments for PJP in this population are somewhat complex and cannot be clearly determined by CD4+ lymphocyte counts as in patients with HIV infection. These differences in the risk of PJP are thought to be owing to the differences in the immune response of the host and the underlying AID. Although lymphopenia is common in SLE and sarcoidosis, the incidence of PJP remains low in these conditions compared to others AID. In addition, corticosteroids do not seem to increase the susceptibility to PJP in patients with giant cell arteritis, although they require long-term use of high-dose corticosteroids. In contrast, GPA is by far the most common AID associated with PJP. Determining specific risk factors for the development of PJP may identify the subgroup of patients at greatest risk of PJP and thus those who are eligible to receive chemoprophylaxis.

2.1.1. Corticosteroids and immunosuppressive agents

Corticosteroids are the most common drug implicated as a risk factor for the development of PJP. In a retrospective study including 116 non-HIV immunocompromised patients with PJP, up to 90% had received corticosteroids within one month prior to PJP diagnosis.¹⁶ Nevertheless, data regarding the threshold daily dose, the cumulative dose, and the administration route associated with the risk of PJP are still conflicting. Some authors considered corticosteroids given at a daily dose ≥ 20 mg of prednisone equivalent during at least 4 weeks as a risk factor for PJP.¹⁷ In the study by Yale and Limper, the median daily dose of corticosteroids was 30 mg, but one quarter of patients received a daily dose ≤ 16 mg of prednisone. Of note, in the subgroup of patients with inflammatory disorders, 23 out of 26 patients were receiving corticosteroids at PJP diagnosis; moreover, the median daily dose of prednisone equivalent and the treatment duration were 40 mg and 16 weeks, respectively.¹⁶

Corticosteroids do not seem to increase the susceptibility to PJP in patients with giant cell arteritis, although they require long-term use of high-dose corticosteroids. In fact, in a study including 7,543 patients with giant cell arteritis, only seven developed PJP. The median daily dose of prednisone at the time of PJP diagnosis was 50 mg, and 5 out of 7 patients received only prednisone without any other cytotoxic agent.¹⁸ Similarly, although patients with SLE and sarcoidosis require high and prolonged corticosteroid dose, the incidence of PJP in these conditions remains low. In an analysis from a retrospective cohort study, Kapoor et al. reported a low incidence of PJP (0.17%) in patients with SLE. In this study, the median daily dose of prednisone was 15 mg, and five out of nine patients with PJP were on immunosuppressants.¹⁹ More recently, a retrospective cohort study including 585 patients with sarcoidosis, only three patients developed PJP.²⁰ These findings indicate that corticosteroids per se may not be sufficient to induce PJP in the setting of AID. PJP might be related to the underlying pathophysiology of the inflammatory disorder itself as well as other associated risk factors.

Additionally, other immunosuppressant agents and biologic medication have been associated with PJP in immunocompromised individuals. Rekhtman et al. reported that the overall incidence of PJP in non-HIV immunocompromised hosts was much higher when corticosteroids and immunosuppressive drugs were used in combination. The PJP incidence was of 0.199%, 0.012%, 0.008, and 0.001% in the subgroup of patients exposed to corticosteroids and immunosuppressants, immunosuppressants alone, corticosteroids alone, and untreated, respectively.²¹ In a retrospective study including 100 patients with SLE treated with cyclophosphamide, 3% developed PJP. The high incidence of PJP in

that study population might be related to disease severity and the fact that cyclophosphamide was prescribed in combination with high-dose corticosteroids.²² In contrast to other immunosuppressive drugs, mycophenolate mofetil may exert a protective action against PJ. This finding has been reported in both animal studies and renal transplant trials.^{23,24} This antimicrobial activity might be explained by the fact that mycophenolate mofetil inhibits inosine monophosphate dehydrogenase of PJ.²⁵ **Table 2** summarizes the incidence of PJP in AID patients treated with biologics.

2.1.2. Lymphopenia

Many authors have considered low lymphocyte count as a predictor of PJP in patients with AID.^{26,27} Porges et al. proposed a cut-off of total lymphocyte count of 350 cells/mm³ as a strong predictor for PJP in patients with SLE.²⁷ In patients with GPA, Godeau et al. pointed out that pre-treatment total lymphocyte count < 800 cells/mm³ and a 3-month treatment lymphopenia less than 600 cells/mm³ were significantly associated with an increased risk of developing PJP.²⁸ Li et al. studied the usefulness of lymphocyte subtyping for predicting PJP in the setting of AID. A CD3+ cell count < 625 cells/mm³ was the strongest predictor of PJP; whereas, CD4+ was the least discriminatory marker of PJP.²⁹ Another study including 90 non-HIV immunocompromized subjects with PJP compared patients with (n=11) and without AID; the formers were significantly more lymphopenic than the second group (170 versus 580 cells/mm³; p=0.034). However, CD4+ counts were not assessed in this study.³⁰ These findings suggest that unlike HIV patients, CD4+ count seems to be less helpful to determine PJP risk in patients with AID. Moreover, the cut-off value of CD4+ that warrant chemoprophylaxis should be much higher than the value recommended in HIV patients.

2.1.3. Interstitial lung disease

Besides low peripheral lymphocyte count, Kadoya et al. identified interstitial pulmonary involvement as a significant predictor of PJP in patients with SLE and PM/DM.²⁶ In patients with RA treated with TNF alpha antagonists, those who developed PJP were more likely to be older, had more frequent concomitant lung diseases, received higher prednisolone and methotrexate doses and had more advanced structural damage.^{31–33} The association between interstitial lung disease and PJP might be in part explained by PJ colonization.³⁴

2.2. PJP-related mortality

As mentioned earlier, mortality associated with PJP in the setting of AID is consistently reported as high compared with that in HIV infected population.¹⁰ In the study by Ward et al, the highest mortality rate was observed in GPA (62.5%), followed by PM/DM (57.7%), PAN (47.6%), SLE (46.3%), and systemic sclerosis (16.7%).¹² In the meta-analysis by Liu et al. the main risk factors significantly

associated with mortality related to PJP in non-HIV patients were older age, female sex, diagnosis delay, respiratory failure, and mechanical ventilation.⁷ Ward et al. identified GPA, SLE and older age as independent risk factors for mortality related to PJP in patients with AID.¹² In the study by Yale et al. patients who survived after PJP received significantly lower median daily corticosteroids dose than did non survivors (26.5 mg versus 40.5 mg respectively).¹⁶ The high PJP-related mortality rate in the setting of AID underscores the need for a prevention strategy.

3.PJP prophylaxis

Table 3 summarizes the available medications for PJP prophylaxis. In contrast to PJP prophylaxis in HIV patients, there are no guidelines to guide decisions regarding the use of chemoprophylaxis in the setting of AID. Given the paucity of evidence regarding primary prophylaxis in the setting of AID, the initiation of PJP prophylaxis is still based upon expert opinion. We proposed an algorithm for PJP primary prophylaxis in patients with AID (**Table 4**) treated with prednisone ≥ 20 mg/day ≥ 1 month and defined at high, intermediate and low-risk patients. Chemoprophylaxis is usually continued throughout the period of immunosuppression or as long as the risk lasts. Duration of the prophylaxis should be decided in a patient-based manner. Green et al. have proposed the incidence of 3.5% in a given condition as a cut-off value to warrant chemoprophylaxis in non-HIV subjects, which balances the number needed to treat against the number needed to harm.³⁵ TMP-SMX is considered as the first line therapy and the most extensively used drug for PJP prophylaxis in HIV patients with a proven efficacy reaching 89% to 100%.³⁵ In a meta-analysis of randomized controlled trials of bone marrow transplant recipients, hematologic cancer, and AID patients, chemoprophylaxis using TMP-SMX was highly effective by reducing the incidence of PJP by 91% (95% CI, 68%-98%). Mortality specifically attributed to PJP was reduced by 83% (95% CI, 6%-97%). Moreover, no significant differences were shown between TMP-SMX and placebo in terms of severe adverse effects and side effects requiring discontinuation. The dosage usually recommended is one tablet (80 mg of TMP and 400 mg of SMX) daily or two tablets 3 times per week. Although the 3-times-weekly regimen was as effective in the prevention of PJP as the daily regimen, compliance may be enhanced by the daily regimen.^{36,37} The daily dose of TMP-SMX was associated with more adverse reactions and related discontinuation than did thrice-weekly administration in a randomized controlled trial.³⁸ Utsunomiya et al. recently reported a randomized controlled trial that evaluated the effectiveness and safety of a half-strength regimen (40 mg of TMP and 200 mg of SMX daily) in adult patients with AID. No patients developed PJP by week 24, and the discontinuation rate was significantly lower in the half-strength regimen compared to the single-strength regimen ($p=0.007$), suggesting that the daily half-strength regimen might be optimal for prophylaxis of PCP in patients with AID.³⁹ Dose adjustment of

TMP-SMX is required in patients with reduced renal function (creatinine clearance <30 ml/min) to avoid toxicity.⁴⁰

TMP-SMX may expose patients to side effects that can limit its use in such situation. The most commonly reported side effects are thrombocytopenia, hyperkalemia, hypoglycemia, and photosensitivity. Other less frequent but more severe reactions include Steven-Johnson syndrome, agranulocytosis, aplastic anemia, and fulminant hepatic necrosis. All these side effects are reversible after treatment withdrawal.⁴¹ In the meta-analysis by Green et al. adverse events and severe reactions occurred in 15.2% and 3.1% of cases, respectively.³⁵ Alternative prophylaxis [atovaquone (750 mg twice daily), aerosolized pentamidine (300 mg once per month) or dapsone] should be given in case of TMP-SMX intolerance such as cytopenia, hepatitis, renal insufficiency, hyperkalemia, or skin reactions.⁴² However, they are more expensive and were less studied in the setting of AID (**Table 3**). Kitazawa et al. examined the effectiveness and safety of three PJP prophylactic agents in 96 patients with AID. All the patients were initially treated with TMP-SMX or atovaquone or aerosolized pentamidine were given when adverse reactions occurred. At one year of follow-up, drug withdrawal rates were 43%, 15%, and 0% for TMP-SMX, aerosolized pentamidine, and atovaquone, respectively. None of the patients developed PJP during the follow-up study period. Besides the small sample size, a major drawback of this study was its retrospective design.⁴² TMP-SMX is also approved for the treatment and the prevention of toxoplasmosis as well as the treatment of respiratory and urinary tract infections. Furthermore, TMP-SMX has a broad-spectrum antibiotic coverage against many other pathogens such as *listeria monocytogenes*, nocardiosis, shigella, and legionella.⁴³

3.1.PJP prophylaxis in GPA

As GPA is by far the most common AID associated with PJP, patients with this condition are more likely to benefit of such prophylaxis. Many clinicians have used TMP-SMX monotherapy as induction treatment in patients with GPA limited to upper and lower airways without systemic involvement.⁴⁴ The mechanism by which TMP-SMX exerts its beneficial action is not clearly understood. However, some authors speculated that GPA relapses are in part triggered by nasal carriage of *Staphylococcus aureus*, thus suppression of this bacterial carriage would protect patients against relapses.⁴⁵ Immunosuppressive property by inhibiting folate metabolism is another mechanism that might explain the efficacy of TMP-SMX to maintain remission in patients with GPA.⁴⁶ In a randomized controlled trial, Stegeman et al. showed that the use of TMP-SMX in patients with GPA in remission reduced significantly relapse rates compared to placebo.⁴⁶ In RITUXVAS trial, 30 out of 44 patients with ANCA-associated vasculitis received chemoprophylaxis with TMP-SMX and no one developed PJP.⁴⁷

3.2.PJP prophylaxis in SLE

In an analysis of data over a 10-year period, Godeau et al. reported an incidence of 8 PJP cases per 10,000 patient-years with SLE, compared to 120 PJP cases per 10,000 patient-years with GPA.⁴⁸ The low incidence of PJP in SLE might be in part explained by the increasing use of hydroxychloroquine in such population. In fact, some studies reported a decreased overall incidence of infection during hydroxychloroquine treatment.⁴⁹ The second possible reason might be the growing use of mycophenolate mofetil and its beneficial effect as discussed earlier.²⁵ In real life, initiation of chemoprophylaxis in patients with SLE varies widely amongst clinicians. In an electronic north American survey, approximately half of rheumatologists reported using primary prophylaxis in SLE patients treated with either oral or intravenous cyclophosphamide.⁵⁰ The higher frequency of adverse drug reactions in SLE patients and anecdotic drug-induced lupus with sulfonamides are the major barriers that limit chemoprophylaxis prescription by clinicians.⁵¹ In the study by Vananuvat et al., five out of 59 patients with AID developed adverse event reactions to TMP-SMX. All were SLE patients; four of whom developed allergic reactions and reversible hepatitis occurred in the remaining patient. However, lupus flares were not statistically different between patients exposed to TMP-SMX than that who did not.⁵² Given the low incidence of PJP in SLE patients and the increased risk of drug adverse reactions, the current evidence does not support the use of routine prophylaxis in all patients.

3.3.PJP prophylaxis in inflammatory myopathies

As discussed above, PM/DM are the second common conditions associated with PJP in the setting of AID after GPA. However, the absolute number of patients with PJP remains low.

3.4.PJP prophylaxis in rheumatoid arthritis

Similarly, the incidence of PJP in RA patients is rare, with the exception of Japanese cohorts where the incidence was much higher.^{13,15} Thus, routine prophylaxis is not recommended in this group of patients.

4.Conclusion:

PJP is a potentially fatal opportunistic infection encountered specifically in immunocompromised patients such as those with AID. Although the incidence of PJP in AID is low, with the exception of GPA, the related mortality rate remains considerably high. Routine chemoprophylaxis in all individuals with AID would not be appropriate; therefore, clinicians should identify patients at risk of developing PJP who warrant chemoprophylaxis. Besides the underlying disease per se, determining risk factors for the development of PJP is crucial when considering chemoprophylaxis. It is clear that

absolute peripheral lymphopenia, high doses of corticosteroids in combination with other immunosuppressive agents, and concomitant lung disease are strong predictors for the development of PJP in the setting of AID. However, none of them individually constitutes such a high risk. While patients with GPA should benefit from chemoprophylaxis during all induction therapy, PJP prophylaxis in other AID should be assessed on a case-by-case basis taking into account the different risk factors of PJP. Although TMP-SMX provides a very effective prophylaxis, patients should be closely monitored to avoid adverse effects.

Declaration of interests

The authors have no conflict of interest to disclose.

5. References:

1. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. *Clin Rheumatol* 2007;26(5):663–670.
2. Roux A, Canet E, Valade S, et al. Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France. *Emerg Infect Dis* 2014;20(9):1490–1497.
3. Ng WL, Chu CM, Wu AKL, Cheng VCC, Yuen KY. Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. *QJM Mon J Assoc Physicians* 2006;99(1):37–47.
4. Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med* 1990;322(3):161–165.
5. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *The Lancet* 2003;362(9398):1828–1838.
6. Sowden E, Carmichael AJ. Autoimmune inflammatory disorders, systemic corticosteroids and pneumocystis pneumonia: A strategy for prevention. *BMC Infect Dis* 2004;4(1):42.
7. Liu Y, Su L, Jiang S-J, Qu H. Risk factors for mortality from pneumocystis carinii pneumonia (PCP) in non-HIV patients: a meta-analysis. *Oncotarget* 2017;8(35):59729–59739.
8. Roux A, Gonzalez F, Roux M, et al. Update on pulmonary Pneumocystis jirovecii infection in non-HIV patients. *Médecine Mal Infect* 2014;44(5):185–198.
9. Roux A, Canet E, Valade S, et al. Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France. *Emerg Infect Dis* 2014;20(9):1490–1497.
10. Thomas CF, Limper AH. Pneumocystis Pneumonia. *N Engl J Med* 2004;350(24):2487–2498.
11. Su Y-S, Lu J-JJ, Perng C-L, Chang F-Y. Pneumocystis jirovecii pneumonia in patients with and without human immunodeficiency virus infection. *J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi* 2008;41(6):478–482.
12. Ward MM, Donald F. Pneumocystis carinii pneumonia in patients with connective tissue diseases: The role of hospital experience in diagnosis and mortality. *Arthritis Rheum* 1999;42(4):780–789.
13. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;67(2):189–194.
14. Clair EWS, Heijde DMFM van der, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: A randomized, controlled trial. *Arthritis Rheum* 2004;50(11):3432–3443.

15. Khanna D, McMahon M, Furst DE. Safety of Tumour Necrosis Factor- α Antagonists. *Drug Saf* 2004;27(5):307–324.
16. Yale SH, Limper AH. Pneumocystis carinii Pneumonia in Patients Without Acquired Immunodeficiency Syndrome: Associated Illnesses and Prior Corticosteroid Therapy. *Mayo Clin Proc* 1996;71(1):5–13.
17. Mecoli CA, Saylor D, Gelber AC, Christopher-Stine L. Pneumocystis jiroveci pneumonia in rheumatic disease: a 20-year single-centre experience. *Clin Exp Rheumatol* 2017;35(4):671–673.
18. Kermani TA, Ytterberg SR, Warrington KJ. Pneumocystis jiroveci pneumonia in giant cell arteritis: A case series. *Arthritis Care Res* 2011;63(5):761–765.
19. Kapoor TM, Mahadeshwar P, Nguyen S, et al. Low prevalence of Pneumocystis pneumonia in hospitalized patients with systemic lupus erythematosus: review of a clinical data warehouse. *Lupus* 2017;26(14):1473–1482.
20. Duréault A, Chapelon C, Biard L, et al. Severe infections in sarcoidosis: Incidence, predictors and long-term outcome in a cohort of 585 patients. *Medicine (Baltimore)* 2017;96(49):e8846.
21. Rekhtman S, Strunk A, Garg A. Incidence of pneumocystosis among patients exposed to immunosuppression. *J Am Acad Dermatol* 2019;80(6):1602–1607.
22. Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. *Arthritis Rheum* 1996;39(9):1475–1482.
23. Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. *Transpl Infect Dis Off J Transplant Soc* 2009;11(4):290–297.
24. Husain S, Singh N. The impact of novel immunosuppressive agents on infections in organ transplant recipients and the interactions of these agents with antimicrobials. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2002;35(1):53–61.
25. O’Gara MJ, Lee CH, Weinberg GA, Nott JM, Queener SF. IMP dehydrogenase from Pneumocystis carinii as a potential drug target. *Antimicrob Agents Chemother* 1997;41(1):40–48.
26. Kadoya A, Okada J, Iikuni Y, Kondo H. Risk factors for Pneumocystis carinii pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. *J Rheumatol* 1996;23(7):1186–1188.
27. Porges AJ, Beattie SL, Ritchlin C, Kimberly RP, Christian CL. Patients with systemic lupus erythematosus at risk for Pneumocystis carinii pneumonia. *J Rheumatol* 1992;19(8):1191–1194.
28. Godeau B, Mainardi JL, Roudot-Thoraval F, et al. Factors associated with Pneumocystis carinii pneumonia in Wegener’s granulomatosis. *Ann Rheum Dis* 1995;54(12):991–994.

29. Li Y, Ghannoum M, Deng C, et al. Pneumocystis pneumonia in patients with inflammatory or autoimmune diseases: Usefulness of lymphocyte subtyping. *Int J Infect Dis* 2017;57:108–115.
30. Teichtahl AJ, Morrisroe K, Ciciriello S, Jennens I, Tadros S, Wicks I. Pneumocystis jirovecii pneumonia in connective tissue diseases: Comparison with other immunocompromised patients. *Semin Arthritis Rheum* 2015;45(1):86–90.
31. Watanabe K, Sakai R, Koike R, et al. Clinical characteristics and risk factors for Pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case–control study of 17 patients. *Mod Rheumatol* 2013;23(6):1085–1093.
32. Komano Y, Harigai M, Koike R, et al. Pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis treated with infliximab: A retrospective review and case–control study of 21 patients. *Arthritis Care Res* 2009;61(3):305–312.
33. Tanaka M, Sakai R, Koike R, et al. Pneumocystis jirovecii pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. *Mod Rheumatol* 2012;22(6):849–858.
34. Morris A, Norris KA. Colonization by Pneumocystis jirovecii and its role in disease. *Clin Microbiol Rev* 2012;25(2):297–317.
35. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis Pneumonia in Immunocompromised Non-HIV-Infected Patients: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Mayo Clin Proc* 2007;82(9):1052–1059.
36. Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med* 2011;183(1):96–128.
37. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. *N Engl J Med* 1987;316(26):1627–1632.
38. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. Terry Bein Community Programs for Clinical Research on AIDS (CPCRA). *Clin Infect Dis Off Publ Infect Dis Soc Am* 1999;29(4):775–783.
39. Utsunomiya M, Dobashi H, Odani T, et al. Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. *Arthritis Res Ther* 2017;19(1):7.
40. Eyler RF, Shvets K. Clinical Pharmacology of Antibiotics. *Clin J Am Soc Nephrol CJASN* 2019;14(7):1080–1090.

41. Ho JM-W, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ Can Med Assoc J J Assoc Medicale Can* 2011;183(16):1851–1858.
42. Kitazawa T, Seo K, Yoshino Y, et al. Efficacies of atovaquone, pentamidine, and trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jirovecii* pneumonia in patients with connective tissue diseases. *J Infect Chemother* 2019;25(5):351–354.
43. Bodro M, Paterson DL. Has the time come for routine trimethoprim-sulfamethoxazole prophylaxis in patients taking biologic therapies? *Clin Infect Dis Off Publ Infect Dis Soc Am* 2013;56(11):1621–1628.
44. Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991;151(8):1649–1652.
45. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, Jong PE de, Kallenberg CG. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med* 1994;120(1):12–17.
46. Stegeman CA, Tervaert JW, Jong PE de, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med* 1996;335(1):16–20.
47. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363(3):211–220.
48. Godeau B, Coutant-Perronne V, Le Thi Huong D, et al. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. *J Rheumatol* 1994;21(2):246–251.
49. Rolain J-M, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents* 2007;30(4):297–308.
50. Cettomai D, Gelber AC, Christopher-Stine L. A Survey of Rheumatologists' Practice for Prescribing *Pneumocystis* Prophylaxis. *J Rheumatol* 2010;37(4):792–799.
51. Lee SL, CHase PH. Drug-induced systemic lupus erythematosus: a critical review. *Semin Arthritis Rheum* 1975;5(1):83–103.
52. Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary Prophylaxis for *Pneumocystis jirovecii* Pneumonia in Patients with Connective Tissue Diseases. *Semin Arthritis Rheum* 2011;41(3):497–502.
53. Ognibene FP, Shelhamer JH, Hoffman GS, et al. *Pneumocystis carinii* pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. *Am J Respir Crit Care Med* 1995;151(3 Pt 1):795–799.
54. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral

- cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997;40(12):2187–2198.
55. Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. *Ann Rheum Dis* 2018;77(5):644–649.
 56. Marie I, Ménard J-F, Hachulla E, et al. Infectious complications in polymyositis and dermatomyositis: a series of 279 patients. *Semin Arthritis Rheum* 2011;41(1):48–60.
 57. Marie I, Hachulla E, Chérin P, et al. Opportunistic infections in polymyositis and dermatomyositis. *Arthritis Rheum* 2005;53(2):155–165.
 58. Redondo-Benito A, Curran A, Villar-Gomez A, et al. Opportunistic infections in patients with idiopathic inflammatory myopathies. *Int J Rheum Dis* 2018;21(2):487–496.
 59. Lertnawapan R, Totemchokchyakarn K, Nantiruj K, Janwityanujit S. Risk factors of Pneumocystis jirovecii pneumonia in patients with systemic lupus erythematosus. *Rheumatol Int* 2008;29(5):491.
 60. Murray SG, Schmajuk G, Trupin L, et al. National Lupus Hospitalization Trends Reveal Rising Rates of Herpes Zoster and Declines in Pneumocystis Pneumonia. *PloS One* 2016;11(1):e0144918.
 61. Yukawa K, Nagamoto Y, Watanabe H, et al. Risk Factors for Pneumocystis jirovecii Pneumonia in Patients With Rheumatoid Arthritis and a Prophylactic Indication of Trimethoprim/Sulfamethoxazole. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2018;24(7):355–360.
 62. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014;371(19):1771–1780.
 63. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. *N Engl J Med* 2010;363(3):221–232.
 64. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus. *Arthritis Rheum* 2010;62(1):222–233.
 65. Furie R, Petri M, Zamani O, et al. A Phase 3, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits BLyS, in Patients With Systemic Lupus Erythematosus. *Arthritis Rheum* 2011;63(12):3918–3930.
 66. Vollenhoven RF van, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet Lond Engl* 2018;392(10155):1330–1339.
 67. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med* 2017;377(4):317–328.

68. Schiff M, Keiserman M, Coddling C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67(8):1096–1103.
69. Taylor PC, Keystone EC, Heijde D van der, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med* 2017;376(7):652–662.
70. Maertens J, Cesaro S, Maschmeyer G, et al. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016;71(9):2397–2404.
71. Nixon GL, Moss DM, Shone AE, et al. Antimalarial pharmacology and therapeutics of atovaquone. *J Antimicrob Chemother* 2013;68(5):977–985.
72. Marras TK, Sanders K, Lipton JH, Messner HA, Conly J, Chan CK. Aerosolized pentamidine prophylaxis for *Pneumocystis carinii* pneumonia after allogeneic marrow transplantation. *Transpl Infect Dis Off J Transplant Soc* 2002;4(2):66–74.
73. Engrav MB, Coodley G, Magnusson AR. Torsade de pointes after inhaled pentamidine. *Ann Emerg Med* 1992;21(11):1403–1405.
74. Wolf R, Matz H, Orion E, Tuzun B, Tuzun Y. Dapsone. *Dermatol Online J* 2002;8(1):2.

Table 1. Incidence, risk factors, PJP-related mortality in patients with AID, and experts opinions for routine prophylaxis.

AID	PJP Incidence (%)	PJP risk factors	Cs daily dose (mg)/ Duration (months)	TLC (cells/mm ³)	PJP mortality (%)	Authors recommendation/ Level of evidence
GPA ^{12,53-55}	6-20	Cs, IS, lymphopenia	≥30/≥1	<800	9-62.5	Routine prophylaxis during induction therapy ¹² /C
PAN ¹²	6.5	NA	NA	NA	47.6	Routine prophylaxis during induction therapy ¹² /C
PM/DM ^{12,56-58}	0.49-10	Lymphopenia, ILD, IS	>20/ >2	<1000	33-57.7	Conditional ^{a56} /C
SLE ^{1,12,19,59,60}	0.04-5	Lymphopenia, ILD, Cs, IS, high disease activity, renal involvement	>20/ NA	<750	20-46.3	No prophylaxis ¹⁹ /C
RA ^{1,12,61}	0.2-1	≥2IS, age≥65 years, Cs≥5 mg/day, MTX≥6 mg/week	≥ 5	NA	30.8	Conditional ^{b61} /C

AID= autoimmune and inflammatory diseases; Cs= corticosteroids; GPA= granulomatosis with polyangiitis ; ILD= interstitial lung disease; IS= immunosuppressants; MTX= methotrexate; NA= not available; PAN= periarteritis nodosa ; PJP= Pneumocystis jirovecii Pneumonia; PM/DM= polymyositis/dermatomyositis; RA= rheumatoid arthritis; SLE= systemic lupus erythematosus; TLC=total lymphocyte count.

Level of evidence C= Consensus of opinion of the experts and/or small studies, retrospective studies.

a: if CD4+< 250 cells/mm³.

b: if patient scores at least five points: Age≥65 years= 1 point, ≥2 immunosuppressants= 1 point, Methotrexate ≥ 6 mg/week= 1 point, Corticosteroids ≥ 5 mg/day= 3 points.

Table 2. Incidence of PJP in patients with AID treated with biologics.

Study design/ reference	Sample size (n=)	AID	Biologic	Daily Cs dose (mg)	Other IS	Follow-up (month)	PJP prophylaxis	PJP incidence (%)
RCT ⁶²	115	AAV	rituximab	18.9	No	28	Yes*	1.75
RCT ⁶³	197	AAV	rituximab	1/kg	No	6	Yes	0
RCT ⁶⁴	257	SLE	rituximab	0.5-1/kg	MMF, AZA, MTX	18	No	0
RCT ⁶⁵	819	SLE	belimumab	8.5**	MMF, AZA, MTX	18	No	0
RCT ⁶⁶	102	SLE	ustekinumab	9.3**	MMF, AZA, MTX	3	No	0
RCT ⁶⁷	251	GCA	tocilizumab	60	No	12	No	0
RCT ⁶⁸	431	RA	Infliximab	≤10	MTX	12	No	0.6
RCT ⁶⁹	1305	RA	Baricitinib	≤10	DMARD S	13	No	0

AAV= anti-neutrophil cytoplasmic antibody-associated vasculitis; AID= autoimmune and inflammatory diseases; AZA=azathioprine; Cs= corticosteroids; DMARDS= disease-modifying anti-rheumatic drugs; GCA= giant cell arteritis; Kg=kilogram; MMF= mycophenolate mofetil; MTX= methotrexate; RA= rheumatoid arthritis; RCT=randomized controlled trial; SLE= systemic lupus erythematosus.

*prophylaxis was required if patients had CD4+<250/mm³

** mean daily dose.

Table 3. Available medications for PJP prophylaxis

Drug	Dose	Cost per month (\$) ^a	Common side effects	Rare side effects	Contra-indications	Drug-Interactions
TMP/SMX 400/80 mg	1/ day	18.6	Nausea, vomiting Skin reactions Elevated serum creatinine Hyperkalemia ⁴¹	Diarrhea Glossitis Hepatitis Cytopenia Agranulocytosis Hypoglycemia Steven-Johnson syndrome, toxic epidermal necrolysis ⁴¹	Known hypersensitivity Pregnancy Liver failure Severe renal insufficiency ⁴¹	Warfarine: anticoagulant effect potentiation Methotrexate: leucopenia ⁴¹
TMP/SMX 800/160 mg	3/ week	13.08				
Atovaquone	1500 mg/ day	1060.92	Nausea, diarrhea Rash Headache ⁷⁰	Marrow toxicity ⁷⁰	Known hypersensitivity ⁷⁰	Rifampicin: reduction in atovaquone concentration ⁷¹
Aerosolized pentamidine	300 mg/month	200.7	Cough, Wheeze, bronchospasm ⁷²	Nausea Mouth burning Anaphylaxis Pancreatitis ⁷²	Known hypersensitivity ⁷²	Drugs-induced QT prolongation ⁷³
Dapsone	100 mg/ day	84.65	Methemoglobinemia Hemolysis ⁷⁴	Hypersensitivity Agranulocytosis Hepatitis ⁷⁴	Glucose-6-phosphate dehydrogenase deficiency ⁷⁴	Other hemolytics ⁷⁴

a: based on Unites States price noted in uptodate.

Table 4. Proposed indications for PJP primary prophylaxis in patients with AID treated with prednisone ≥ 20 mg/day ≥ 1 month

High risk /PJP primary prophylaxis recommended	Intermediate risk/PJP primary prophylaxis discussed	Low risk/ PJP primary prophylaxis not recommended
GPA PM/DM with ILD CTD with ILD	ANCA associated vasculitis (MPA, EGPA) treated with cyclophosphamide or rituximab CTD with renal involvement	GCA and large vessel vasculitis Sarcoidosis*

* without severe ILD

AID= autoimmune and inflammatory diseases; ANCA= antineutrophil cytoplasmic antibody; CTD= connective tissue disease; GCA=giant cell arteritis; GPA= granulomatosis with polyangiitis; ILD= interstitial lung disease; MPA= microscopic polyangiitis; EGPA= eosinophilic granulomatosis with polyangiitis; PJP= Pneumocystis jirovecii Pneumonia; PM/DM= polymyositis/dermatomyositis.