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Short Communication

# *Pneumocystis jirovecii* pneumonia in HIV-negative patients, a frequently overlooked problem. A case series from a large Italian center

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ABSTRACT

*Background and objectives:* *Pneumocystis jirovecii* pneumonia (PCP) still has substantial morbidity and mortality. For non-HIV patients, the course of infection is severe, and management guidelines are relatively recent. We collected all PCP cases (European Organization for Research and Treatment of Cancer criteria) diagnosed in HIV-negative adult inpatients in 2019-2020 at our center in northern Italy.

*Results:* Of 20 cases, nine had microbiologic evidence of probable (real-time polymerase chain reaction, RT-PCR) and 11 proven (immunofluorescence) PCP on respiratory specimens. Half were female; the median age was 71.5 years; 14 of 20 patients had hematologic malignancies, five had autoimmune/hyperinflammatory disorders, and one had a solid tumor. RT-PCR cycle threshold (Ct) was 24-37 for bronchoalveolar lavage (BAL) and 32-39 for sputum; Ct was 24-33 on BAL proven cases. Of 20 cases, four received additional diagnoses on BAL. At PCP diagnosis, all patients were not on anti-pneumocystis prophylaxis. We retrospectively assessed prophylaxis indications: 9/20 patients had a main indication, 5/9 because of prednisone treatment ≥ 20 mg (or equivalents) for ≥4 weeks. All patients underwent antimicrobial treatment according to guidelines; 18/20 with concomitant corticosteroids. A total of 4/20 patients died within 28 days from diagnosis.

*Conclusion:* Despite appropriate treatment, PCP is still associated to high mortality (20%) among non-HIV patients. Strict adherence to prophylaxis guidelines, awareness of gray areas, and prompt diagnosis can help manage this frequently overlooked infection.



## Introduction

A classic AIDS-defining condition, *Pneumocystis jirovecii* pneumonia (PCP) is still associated with substantial morbidity and mortality among immunocompromised individuals. For patients with hematologic malignancies and stem cell transplant recipients, a diagnosis might be difficult or delayed, the course of infection is often severe, and management guidelines are relatively recent (Avino et al., 2016; Liu et al., 2019; Wang et al., 2021).

The European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group Education and Research Consortium (MSGERC) have recently elaborated consensus definitions for *Pneumocystis* disease for research purposes (Lagrou et al., 2021). Diagnosis of proven PCP is based on compatible host factors and clinical/radiologic criteria, plus a demonstration of *P. jirovecii* in tissue or respiratory tract specimens by microscopy using conventional or immunofluorescence staining. Probable PCP is defined by the presence of host factors and clinical-radiologic criteria, plus amplification of *P. jirovecii* DNA by real-time polymerase chain re-

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action (RT-PCR) in respiratory specimens (and/or detection of (1,3)-$\beta$-D-glucan under certain conditions).

RT-PCR thresholds to differentiate between *Pneumocystis* colonization and infection have not been univocally established yet, especially because the pathogenic fungal load may vary according to underlying conditions and respiratory specimen used (Damiani et al., 2021; Fan et al., 2013; Limper et al., 1989; Senécal et al., 2022). Therefore, if positive RT-PCR with negative direct demonstration occurs, the decision whether to institute anti-pneumocystis therapy still relies on clinical judgment (Grønseth et al., 2021).

Perceived risk for immunocompromised patients varies, and audits should be held in centers, as anti-pneumocystis prophylaxis is critical in high-risk conditions (Stern et al., 2014).

We retrospectively collected all PCP cases diagnosed in HIV-negative inpatients throughout two years at our center, aiming to assess patients' characteristics and evaluate overlooked risk factors and management issues.

## Materials and methods

We present a case series of all proven and probable PCP diagnosed in adult HIV-negative patients in 2019-2020 at our institution in Milan, Italy, a 900-bed tertiary hospital including rheumatology, hematology, bone marrow, and solid organ transplant wards.

Positive *P. jirovecii* PCR and/or immunofluorescence staining on respiratory specimens were selected through the microbiology database, and patient clinical history was retrieved.

To qualify, cases had to test negative for HIV upon PCP diagnosis and fulfill the criteria employed by EORTC (Lagrou et al., 2021). (1,3)-$\beta$-D-glucan was not available at our facility throughout the study period; therefore, it was not used as an alternative method to diagnose probable PCP.

Direct immunofluorescence was performed through the Merifluor Pneumocystis kit (Meridian Bioscience, United States); DNA extraction through EXTRAcell kit (ELITech group, United Kingdom); And RT-PCR through Real Cycler PJIR-UX/PJIR-GX (Progenie Molecular-Valencia, Spain), a commercial qualitative real-time PCR kit targeting the mitochondrial large subunit ribosomal rRNA gene of *P. jirovecii* (Guillaud-Saumur et al., 2017).

Indication for prophylaxis was retrospectively assessed according to the European Conference on Infections in Leukaemia (ECIL-5) 2016 guidelines and the 2019 Sanford Guide (Maertens et al., 2016, The Sanford Guide to Antimicrobial Therapy. Dallas, 2019).

The study was registered by the Milan Area 2 Institutional Review Board, approval number 1082_2021.

## Results

Overall, 20 adult inpatients were diagnosed with PCP throughout 2019 and 2020. Of them, 10 were female (50%), and the median age was 71.5 years (interquartile range, IQR, 51.5 – 81). Host factors and clinical/radiology findings are listed in Table 1 . All patients had a fever and respiratory symptoms; all had respiratory failure, requiring low to high flow oxygen support. Four patients received additional respiratory diagnoses and subsequent treatments based on bronchoalveolar lavage (BAL) analysis: Herpes simplexvirus (HSV)-1 pneumonia, cytomegalovirus (CMV) pneumonia (two cases), and invasive aspergillosis. Of note, 3/4 had autoimmune disorders as host factors.

In regard to PCP diagnosis, all patients had positive RT-PCR BAL, 18/20, or sputum, 2/20. RT-PCR cycle threshold (Ct) was between 24 and 37 for BAL and 32 and 39 for sputum. Furthermore, 11 patients also had positive immunofluorescence staining, qualifying as proven PCP cases. When immunofluorescence was positive on BAL, RT-PCR Ct was between 24 and 33 (median 29, IQR 26-31.25).

At the time of PCP diagnosis, all patients were not on primary PCP prophylaxis.

Nine patients had a main indication to prophylaxis: five were on steroid treatment with prednisone $\geq$ 20 mg (or equivalents) from $\geq$4 weeks; two had acute lymphoblastic leukemia and had not reached the end of maintenance; two had received allogeneic human stem cell transplant and were still undergoing immunosuppressant treatment. Most patients without a main indication still had a recognized "host factor" for PCP diagnosis.

Once they had received a PCP diagnosis, all patients were treated in accordance with guidelines (21 days, 19/20 with trimethoprim/sulfamethoxazole (TMP/SMX), 1/20 with intravenous pentamidine, 18/20 with concomitant methylprednisolone/prednisone). Of 19 patients, 12 were switched from intravenous to oral TMP/SMX upon clinical improvement.

Four patients died within 28 days from diagnosis, all due to respiratory failure. Three had a proven PCP (the fourth had unavailable immunofluorescence results), and three also had a concomitant diagnosis (CMV pneumonia or invasive aspergillosis). One was the only patient treated with pentamidine. Of the 16 patients who had survived on day 28, 15 progressed to TMP/SMX secondary prophylaxis.

## Discussion

This series describes the HIV-negative population diagnosed with *Pneumocystis* pneumonia across two years in a tertiary hospital in northern Italy and confirms that, despite appropriate treatment, PCP is still associated with high mortality (20% within 28 days from diagnosis) among HIV-negative patients.

The cases were diverse in terms of age, gender, and clinical history; however, almost three out of four cases had a hematologic malignancy, and almost 1/3 were on high-dose steroid treatment as per the EORTC definition. Few cases had known CD4+ T-cell counts, and when available, counts were >200 cells/mcL. This both highlights limited awareness of CD4+ T-cell count as an independent risk factor for PCP in HIV-negative patients and the need for considering different risk factors in this population. The only common element between all cases was the lack of antimicrobial prophylaxis. This finding indirectly confirms the effectiveness of this measure in preventing PCP and the need to raise awareness on indications for prophylaxis.

Concomitant viral or fungal preventable lung opportunisms were present in 4/20 patients, highlighting a need for awareness on chemoprophylaxis not limited to *Pneumocystis*, especially in the immune-rheumatologic setting.

If indications of prophylaxis from ECIL and/or the Sanford Guide were strictly applied, approximately half of the cases might have been prevented. The other half did not fall within the main indications. Further studies might help investigate additional risk factors, especially in light of the growing number of chronically immunosuppressed/immunomodulated patients.

In regard to invasive diagnostic procedures, more than half of PCP cases were defined as proven because of positive immunofluorescence. Of note, immunofluorescence was consistently positive when RT-PCR Ct was lower than 30, with one exception, and 3/6 negative immunofluorescence cases had a Ct >35; despite the latter case being compatible with colonization, all patients were treated as PCP because of clinical judgment. Further studies correlating RT-PCR findings with proven infection for the HIV-negative population, validating optimal cutoff values for conditions with lower expected fungal load, are needed (Robert-Gangneux et al., 2014). Consistent with our findings, a recent study (using in-house RT-PCR) found that a Ct value < 31 confirmed PCP,

**Table 1**
Characteristics of the 20 cases included in the case series. Treatments are listed if undertaken within the last six months.

| ID | GENDER, AGE | CLINICAL HISTORY | EORTC HOST FACTOR: ≥0.3 mg/kg prednisone equivalent for ≥2 weeks in the past 60 days | EORTC HOST FACTOR: medical condition or anticancer, anti-inflammatory, immunosuppressive treatment expected to lower CD4+ lymphocyte counts | T CD4+ count (TOT, %) | RETROSPECTIVE «MAIN» INDICATION TO PROPHYLAXIS ACCORDING TO ECIL | PJP PROPHYLAXIS AT PJP DIAGNOSIS | SYMPTOMS (FEVER, COUGH, DYSPNEA, AND/OR HYPOXEMIA) | COMPATIBLE CT SCAN FINDINGS (Extensive, mostly diffuse GGO on CT scans; consolidations, small nodules less common) | PCR SAMPLE | PJ DNA RT-PCR CYCLE THRESHOLD | IMMUNOFLUORESCENCE | CONCOMITANT DIAGNOSES | ANTIMICROBIAL THERAPY FOR PJP | OUTCOME AT DAY 28 | SECONDARY PROPHYLAXIS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1_19 | F, 43 | Dermatomyositis | no | autoimmune disorder | 441 (66) | no | no | yes | GGO, consolidations | BAL | 31 | positive | | IV TMP/SMX + methylprednisolone | alive | yes |
| 2_19 | M, 72 | DLBCL | no | non-Hodgkin's lymphoma; polatuzumab treatment | n/a | no | no | yes | GGO | BAL | 29 | negative | | IV TMP/SMX + methylprednisolone | alive | yes |
| 3_19 | M, 53 | AML | no | acute leukemia; allo-HSCT (2017); sirolimus treatment | 540 (26) | allogeneic HSCT as long as immunosuppression is ongoing (sirolimus) | stopped because of clinical judgment (CD4 count) | yes | GGO, nodules, cavities | BAL | 33 | n/a | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 4_19 | F, 82 | AML | no | acute leukemia | n/a | no | no | yes | GGO, consolidations | BAL | 36 | negative | | oral TMP/SMX | alive | yes |
| 5_19 | F, 61 | PBC | yes | autoimmune disorder | n/a | 20 mg/day prednisone for 4 weeks | no | yes | GGO, consolidations, cavities | BAL | 26 | positive | invasive aspergillosis; pulmonary nocardiosis | IV TMP/SMX + methylprednisolone | deceased (D22 from diagnosis) | n/a |
| 6_19 | F, 44 | Sezary syndrome | no | T-cell lymphoma; allo-HSCT (2018); alemtuzumab treatment (2018) | 347 (21) | no | no | yes | GGO | BAL | 27 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 7_19 | F, 75 | Follicular lymphoma | no | non-Hodgkin's lymphoma; high-dose intramuscular betamethasone treatment < 2 weeks | 283 (40) | no | no | yes | GGO | BAL | 29 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 8_19 | F, 90 | DLBCL | no | non-Hodgkin's lymphoma; rituximab treatment | n/a | no | stopped because of clinical judgment (hepatic toxicity) | yes | GGO | sputum | 39 | positive | | IV pentamidine (TMP/SMX allergy) + methylprednisolone | deceased (D11) | n/a |
| 9_20 | M, 59 | AML | no | acute leukemia; midostaurin treatment | n/a | no | no | yes | GGO, consolidations | BAL | 24 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 10_20 | F, 51 | ALL | no | acute leukemia; allo-HSCT (2018); potatinib treatment | 267 (14) | allogeneic HSCT as long as immunosuppression is ongoing (potatinib) | no | yes | GGO | BAL | 33 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 11_20 | M, 78 | Follicular lymphoma | yes | non-Hodgkin's lymphoma; R-COMP treatment protocol | n/a | 20 mg/day prednisone for 4 weeks | no | yes | GGO | BAL | 32 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 12_20 | F, 28 | ALL | no | acute leukemia; cyclophosphamide, dexamethasone, mercaptopurine, idarubicin treatment | n/a | ALL from induction to end of maintenance | no | yes | GGO | BAL | 31 | positive | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 13_20 | F, 57 | AML | no | acute leukemia; daunorubicin, midostaurin, cytarabine treatment | n/a | no | no | yes | GGO | BAL | 29 | positive | | IV TMP/SMX + methylprednisolone | alive | yes |

(*continued on next page*)

**Table 1** (*continued*)

| ID | GENDER, AGE | CLINICAL HISTORY | EORTC HOST FACTOR: ≥0.3 mg/kg prednisone equivalent for ≥2 weeks in the past 60 days | EORTC HOST FACTOR: medical condition or anticancer, anti-inflammatory, immunosuppressive treatment expected to lower CD4+ lymphocyte counts | T CD4+ count (TOT, %) | RETROSPECTIVE «MAIN» INDICATION TO PROPHYLAXIS ACCORDING TO ECIL | PJP PROPHYLAXIS AT PJP DIAGNOSIS | SYMPTOMS (FEVER, COUGH, DYSPNEA, AND/OR HYPOXEMIA) | COMPATIBLE CT SCAN FINDINGS (Extensive, mostly diffuse GGO on CT scans; consolidations, small nodules less common) | PCR SAMPLE | PJ DNA RT-PCR CYCLE THRESHOLD | IMMUNO-FLUORESCENCE | CONCOMITANT DIAGNOSES | ANTIMICROBIAL THERAPY FOR PJP | OUTCOME AT DAY 28 | SECONDARY PROPHYLAXIS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14_20 | M, 83 | T cell leukemia | yes | T cell leukemia; cyclosporin treatment | n/a | 20 mg/day prednisone for 4 weeks | no | yes | GGO | BAL | 26 | positive | CMV pneumonia | IV TMP/SMX + methylprednisolone | deceased (D22) | n/a |
| 15_20 | M, 83 | AML | yes | acute leukemia; azacytidine, hydroxyurea treatment | n/a | no | no | yes | GGO | BAL | 37 | negative | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 16_20 | M, 71 | ALL | no | acute leukemia; cyclophosphamide, methotrexate, mercaptopurine treatment | n/a | ALL from induction to end of maintenance | stopped because of clinical judgment | yes | GGO | sputum | 32 | negative | | IV TMP/SMX (switch to oral) | alive | yes |
| 17_20 | M, 85 | Giant cell arteritis | yes | autoimmune disorder; methotrexate treatment | n/a | 20 mg/day prednisone for 4 weeks | no | yes | GGO | BAL | 26 | n/a | CMV pneumonia | IV TMP/SMX (switch to oral) + prednisone | deceased (D03) | n/a |
| 18_20 | M, 77 | Leiomyosarcoma | no | solid tumor | n/a | no | no | yes | GGO | BAL | 31 | negative | | IV TMP/SMX (switch to oral) + methylprednisolone | alive | yes |
| 19_20 | F, 72 | Autoimmune hepatitis, autoimmune thyroiditis | yes | autoimmune disorder; azathioprine treatment | n/a | 20 mg/day prednisone for 4 weeks | no | yes | GGO, consolidations | BAL | 27 | n/a | HSV-1 pneumonia | IV TMP/SMX + prednisone | alive | yes |
| 20_20 | M, 44 | Diabetes with terminal renal failure, COVID-19 | yes | hyperinflammatory disorder | 233 (22) | no | no | yes | GGO, consolidations | BAL | 36 | negative | | IV TMP/SMX (switch to oral) + prednisone | alive | no |

M = male; F = female; DLBCL = diffuse large B cell lymphoma; AML = acute myeloid leukemia; PBC = primary biliary cholangitis; ALL = acute lymphoblastic leukemia; Allo-HSCT = allogeneic human stem cell transplant; GGO = ground-glass opacities; IV = intravenous; TMP/SMX = trimethoprim/sulfamethoxazole; n/a = not available.

whereas no Ct permitted exclusion. However, when stratifying according to underlying conditions, a higher cutoff was needed to achieve a 75% sensitivity for patients with hematological malignancies (Grønseth et al., 2021).

A Ct as high as 39 was observed on sputum in a proven PCP case. This is likely explained by the lower fungal burden in minimally invasive samples than in BAL (Desoubeaux et al., 2019).

Evidence supporting corticosteroid adjunctive treatment for PCP in non-HIV patients is controversial and still debated. However, in a recent systematic review and meta-analysis, adjunctive corticosteroids showed a probable benefit in decreasing mortality in hypoxemic non-HIV patients with PCP (Ding et al., 2020).

The limitation of the present study lies in its monocentric, retrospective nature, with a small sample size not allowing comparisons between patient subsets.

In conclusion, strict adherence to prophylaxis guidelines, awareness of gray areas (minor risk factors not included among prophylaxis indications), and prompt diagnosis can help manage this frequently overlooked infection.

## Competing interests

The authors have no competing interests to declare.

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## Author contributions

GB, together with AG and AB, conceived the present work. GB, AMP, LT, RU, and AL were involved in clinical care and drafted the manuscript. PS, MM, VM, and VC were involved in data collection, categorization, and entry under the supervision of AB and AM. All the aforementioned authors also revised existing literature to help draft the manuscript's discussion. PB, AG, AM, and CM performed all microbiology tests, extracted laboratory results, and were involved in laboratory data interpretation. All authors revised the manuscript critically and approved the final version of the manuscript. All the authors listed have substantially contributed to the study's conception, design, and/or performance.

## Ethics statement

The study was conducted according to the Declaration of Helsinki and approved by the Milan Area 2 Institutional Review Board under approval number 1082_2021 on November 9, 2021.

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