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## **Chest Infections** Original Research

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# Characteristics and Prognosis Factors of Pneumocystis jirovecii Pneumonia According to Underlying Disease A Retrospective Multicenter Study

Romain Lécuyer, MD, PharmD; Nahéma Issa, MD; Fabrice Camou, MD; Rose-anne Lavergne, PharmD, PhD; Frederic Gabriel, MD, PhD; Florent Morio, PharmD, PhD; Emmanuel Canet, MD, PhD; François Raffi, MD, PhD; David Boutoille, MD, PhD; Anne Cady, PharmD; Marie Gousseff, MD; Yoann Crabol, MD; Antoine Néel, MD, PhD; Benoît Tessoulin, MD, PhD; and Benjamin Gaborit, MD, PhD; and the PRONOCYSTIS Study Group\*

> BACKGROUND: Pneumocystis jirovecii pneumonia (PcP) remains associated with high rates of 76 mortality, and the impact of immunocompromising underlying disease on the clinical pre-77 sentation, severity, and mortality of PcP has not been adequately evaluated.

> **RESEARCH QUESTION:** Does the underlying disease and immunosuppression causing PCP impact the outcome and clinical presentation of the disease?

> STUDY DESIGN AND METHODS: In this multicenter retrospective observational study, con- 82 ducted from January 2011 to December 2021, all consecutive patients admitted with a proven 83 or probable diagnosis of PcP according to The European Organisation for Research and <sup>84</sup> Treatment of Cancer consensus definitions were included to assess the epidemiology and <sup>85</sup> impact of underlying immunosuppressive diseases on overall and 90-day mortality.

> **RESULTS**: Overall, 481 patients were included in the study; 180 (37.4%) were defined as 88 proven PcP and 301 (62.6%) were defined as probable PcP. Patients with immune-mediated 89 inflammatory diseases (IMIDs) or solid tumors had a statistically poorer prognosis than other 90 patients with PcP at day 90. In multivariate analysis, among the HIV-negative population, 91 solid tumor underlying disease (OR, 5.47; 95% CI, 2.16-14.1; P < .001), IMIDs (OR, 2.19; 92 95% CI, 1.05-4.60; P = .037), long-term corticosteroid exposure (OR, 2.07; 95% CI, 1.03-4.31; 93 P = .045), cysts in sputum/BAL smears (OR, 1.92; 95% CI, 1.02-3.62; P = .043), and SOFA 94 score at admission (OR, 1.58; 95% CI, 1.39-1.82; P < .001) were independently associated 95 with 90-day mortality. Prior corticotherapy was the only immunosuppressant associated with 96 90-day mortality (OR, 1.67; 95% CI, 1.03-2.71; P = .035), especially for a prednisone daily <sup>97</sup> dose  $\geq$  10 mg (OR, 1.80; 95% CI, 1.14-2.85; P = .010).

> INTERPRETATION: Among patients who were HIV-negative, long-term corticosteroid prior to 100 PcP diagnosis was independently associated with increased 90-day mortality, specifically in 101 patients with IMIDs. These results highlight both the needs for PcP prophylaxis in patients 102 with IMIDs and to early consider PcP curative treatment in severe pneumonia among pa- 103 tients with IMIDs. CHEST 2024; ∎(■):■-■ <sup>104</sup>

> KEY WORDS: corticosteroids; immune-mediated inflammatory diseases; Pneumocystis jirovecii 106 pneumonia; outcome; solid tumors

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## Take-home Points

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Study Question: Does the underlying disease and immunosuppression causing Pneumocystis jirovecii pneumonia (PcP) impact the outcome and clinical presentation of the disease?

**Results:** We present the findings of a cohort study involving 481 patients diagnosed with probable or proven PcP to assess the impact of various immunocompromising underlying conditions on the clinical presentation and mortality associated with PcP. This large multicenter study is the first to identify patients with immune-mediated inflammatory diseases (IMIDs), solid tumors, and prolonged corticosteroid therapy as independent factors contributing to 90-day mortality. Notably, patients with IMIDs, particularly those exposed to long-term corticosteroid therapy, exhibit the most unfavorable prognosis compared with other immunocompromised conditions.

**Interpretation:** These results highlight that, across all patient categories, patients with IMID and solid tumors experience the most severe forms of PcP and the highest mortality rates. Additionally, a history of prior long-term corticosteroid therapy was associated with a poor prognosis, especially among patients with IMIDs. These findings emphasize the necessity of considering PcP prophylaxis for patients with IMIDs and promptly initiating PcP treatment in cases of severe pneumonia in this specific population.

145 The growing number of patients undergoing 146 immunosuppressive treatments and the development 147 of new biotherapies for hematologic malignancies, 148 solid organ transplantations, or immune-mediated 149 150 inflammatory diseases (IMIDs) has led to the 151 emergence of new conditions for opportunistic

ABBREVIATIONS: CMV = cytomegalovirus; IMID = immune-mediated inflammatory disease; PcP = Pneumocystis jirovecii pneumonia; SOFA = Sequential Organ Failure Assessment

155 AFFILIATIONS: From Internal Medicine and Infectious Diseases (R. L., 156 M. G., and Y. C.), Centre Hospitalier Bretagne-Atlantique, Vannes; Nantes Université (R. L., R.-a. L., and F. M.), CHU Nantes, Cibles et 157 médicaments des infections et de l'immunité, IICiMed, UR1155, 158 Nantes; the Intensive Care and Infectious Disease Unit (N. I. and F. 159 C.), Groupe Saint-André, University Hospital, Bordeaux; the Centre 160 Hospitalier Universitaire de Bordeaux (F. G.), Service de Parasitologie Mycologie, Bordeaux; the Laboratoire de Parasitologie-Mycologie (F. 161 M.), Institut de Biologie, University Hospital, Nantes; the Medical 162 Intensive Care (E. C.), University Hospital, Nantes; the Department of 163 Infectious Diseases (F. R., D. B., and B. G.), University Hospital of Nantes and Centre d'Investigation Clinique 1413, INSERM, Nantes; 164 the Nantes Université (D. B. and B. G.), CHU Nantes, INSERM, Center 165 for Research in Transplantation and Translational Immunology, UMR

166 pulmonary fungal infections. Currently, around three-167 quarters of *Pneumocystis jirovecii* pneumonia (PcP) 168 cases are diagnosed in patients who are HIV-negative 169 in high-income countries.<sup>1,2</sup> HIV-negative PcP is 170 associated with a higher morbidity and mortality rate, 171 and may be more challenging to diagnose than in 172 patients who are HIV-positive; therefore, it is 173 necessary to further improve risk reduction, diagnosis, Q8 174 and treatment procedures. In the HIV-negative 175 population, the prognosis of PcP is highly variable, 176 suggesting that the underlying disease and 177 178 immunosuppressive therapies both have an impact on 179 the severity and outcome of this infection.<sup>3</sup> Prior 180 corticosteroid therapy has been identified as a risk 181 factor for PcP<sup>4-6</sup> and has been associated with 182 mortality.<sup>7</sup> The advent of new immunosuppressive 183 treatments raise the question of the appropriate 184 criteria to introduce primary prophylaxis.<sup>8</sup> We 185 previously reported that the pattern of immune 186 responses,<sup>9</sup> and respiratory coinfection by 187 cytomegalovirus (CMV)<sup>10</sup> as a probable marker of 188 profound immunosuppression, were associated with a 189 190 worse prognosis. However, the impact of underlying 191 disease and of specific immunologic disorders on the 192 clinical presentation, severity, and mortality of PcP is 193 poorly studied in the contemporary cohorts of 194 patients. Investigating the features and the prognosis 195 of PcP subpopulations according to the underlying 196 disease and immunosuppressive therapies may allow 197 an earlier diagnosis of PcP and a faster initiation of 198 anti-Pneumocystis treatment. Q9 199

In this study, we took a large multicenter cohort of patients with probable or proven PcP from three French hospitals over 10 years of follow-up and studied the impact of the immunocompromising underlying disease and of the type of immunosuppressive treatment on the clinical presentation and mortality of PcP.

1064, Nantes; the Department of Microbiology (A. C.), Centre Hospitalier Bretagne-Atlantique, Vannes; the CRTI UMR 1064 (A. N.), INSERM, Université de Nantes, Nantes; the Department of Internal Medicine (A. N.), University Hospital, Nantes; and the INSERM (B. T.), U1232, Hematology Department, Nantes University Hospital, CRCI<sup>2</sup>NA, Nantes University, Nantes, France. \*Collaborators from the PRONOCYSTIS Study Group are listed in the Acknowledgments. Drs Lécuyer and Issa contributed equally to this manuscript. CORRESPONDENCE TO: Benjamin Gaborit, MD, PhD; email: Q4 216

benjamin.gaborit@chu-nantes.fr 217 Copyright © 2024 The Author(s). Published by Elsevier Inc under li-218 cense from the American College of Chest Physicians. This is an open 219 access article under the CC BY-NC-ND license (http:// creativecommons.org/licenses/by-nc-nd/4.0/). 220 DOI: https://doi.org/10.1016/j.chest.2024.01.015

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## 222 Study Design and Methods

## 223 Study Design and Population

224Q10This study is a substudy from the PRONOCYSTIS cohort,10 a225retrospective multicenter network involving three French hospitals.226All consecutive patients admitted with a proven or probable227diagnosis of PcP according to The European Organisation for228consensus definitions of invasive fungal diseases from January 2011229to December 2021 were retrospectively included. Patients were230followed-up for at least a year.

The study was designed in accordance with the Declaration of Helsinki
and conducted in accordance with French legislation with approval
obtained from the local ethics committee (groupe nantais d'éthique
dans le domaine de la santé [GNEDS] No. 23-34-03-091).

## 235 Data Collection

236 For each case, data were collected for patient demographic 237 characteristics, underlying disease, immunosuppressive treatment 238 exposition during the year prior to PcP onset, use of PcP prophylaxis, nature of symptoms and time from symptoms onset to 239 PcP diagnosis and hospital admission, laboratory findings, presence 240 of other pathogenic microorganisms (bacteria, virus, or fungi) on 241 diagnostic respiratory samples, use of corticosteroid therapy and its 242 duration, oxygen requirement, and ventilatory support at admission. The Sequential Organ Failure Assessment (SOFA) and Simplified 243 Acute Physiology Score II were retrospectively determined for each 244 patient at the time of PcP diagnosis based on the medical records. If 245 any parameters required were missing, the score values were treated 246 as missing data. The retrospective assessments of FIO2 in non-ICU 247 patients were approximated using a concordance table (with 248 estimated  $Fio_2$  values for nasal oxygen = 0.3, mask oxygen = 0.4, and reservoir mask = 0.6).<sup>12</sup> Finally, final outcome with 90-day 249 mortality was registered in the study database. 250

#### Definitions

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252 Criteria for PcP diagnosis involved compatible clinical presentation 253 (fever, respiratory symptoms, cough, dyspnea, and hypoxemia) and 254 an interstitial syndrome on chest radiograph or CT scan, along with mycologic evidence for P jirovecii in respiratory samples, induced 255 sputum, bronchial aspiration fluid, or BAL. PcP was proven when P 256 jirovecii asci (cysts) were found at direct microscopic examination. 257 Probable PcP was determined by a negative direct mycologic 258q11 examination but a positive P jirovecii qPCR (laboratory-defined threshold) in respiratory sample,11 associated with a compatible 259 clinico-radiologic presentation. Colonization was defined as the 260 presence of a positive real-time polymerase chain reaction without 261 meeting the clinical and/or radiologic criteria for a proven or 262

## Results

## Patient Characteristics

267 Over the 10-year study period, a total of 8,508 268 respiratory samples were tested for P jirovecii across 269 the three hospitals, with 1,238 patients having a 270 positive P jirovecii qPCR. After assessment of clinical 271 and radiologic data, 508 patients were categorized as 272 273 probable or proven PcP (730 colonized patients were 274 excluded). Of these, nine patients < 18 years of age 275 and 18 patients with missing data during follow-up

probable diagnosis of PcP. PcP cases involving patients < 18 years of age or with mortality missing data were excluded from the study. Date of PcP diagnosis was the day of confirmation by mycologic investigation (direct examination or qPCR). 280

Several predisposing clinical conditions were considered, including 281 HIV infection, hematologic malignancies, progressive cancer, solid 282 organ transplantation, and IMIDs. Ongoing immunosuppressive or immunomodulatory treatment did not constitute an independent 283 subgroup of predisposing condition but was an analysis parameter. 284 Patients undergoing corticosteroid treatment were considered to be 285 immunosuppressed if they had been receiving > 7 days at a dose  $\ge$ 286 1 mg/kg/d (prednisone equivalent) or for > 3 months at a lower 287 dose. When a patient had several predisposing conditions (n = 30), the underlying disease chronologically associated with the onset of <sup>288</sup> PcP was considered (eg, an immuno-virologically controlled patient 289 who was HIV-positive receiving secondary chemotherapy for lung 290 cancer would be classified in the solid oncology group). 291

Adjuvant corticosteroid therapy was defined as any current or initiated 292 high-dose steroid treatment justified by a PcP severe form, with a 293 regimen similar to that used for patients with HIV with severe PcP.<sup>13</sup> 294

#### Statistical Analysis

296 Patient characteristics were described using mean  $\pm$  SD for continuous variables (or 95% CI when appropriate) and proportions for qualitative <sup>297</sup> variables. Overall survival estimates were assessed using the Kaplan- 298 Meier method. To remove potential biases associated with 299 underlying condition impact on overall outcome in the long term, 300 90-day all-cause mortality was used (as previously described<sup>10</sup>). 301 Preanalysis of the dataset did not show discrepancies across centers (n = 3) for the results, and we decided to carry on with a fixed- 302effect logistic regression model. All regression tests (OR estimates 303 and CIs) for 90-day mortality were performed on variables involving 304 > 10 events. The multivariate analysis was primarily performed to  $_{305}$ assess the respective weights of each variable, taking into account the 306 other variables as fixed. Factors associated with 90-day mortality were identified by logistic regression analysis. Only factors reaching 307 statistical significance (P < .05), with no more than 10% missing 308 data, were included in the multivariate model. For subcategory 309 comparisons with a low number of occurrences, numbers and 310 percentages are given. When colinearity between covariates was 311 detected, only the variable with the highest OR was kept in the 312 multivariate regression model. Results were reported as logtransformed coefficients with their 95% CIs. Missing data were not 313 interpolated. Analyses were performed on the overall population and 314 then on the HIV-negative and IMIDs subgroups, taking into account 315 respective missing data percentages. All analyses were conducted in 316 R (4.3.1), using the finalfit and survminer packages. 317

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319 were excluded (Fig 1). A total of 481 patients were 320 therefore included, of which 180 (37.4%) were defined 321 as having proven PcP and 301 (62.6%) as having 322 probable PcP. The baseline characteristics of the 323 included patients are shown in Table 1 (comparison 324 according to HIV status in e-Table 1 or to other 325 underlying diseases in e-Table 2). All patients from 326 this cohort were immunocompromised with 327 hematologic malignancy ranking first (n = 118, 328 24.5%), followed by HIV infection (n = 114, 23.7%), 329 330 solid organ transplantation (n = 103, 21.4%), IMIDs



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jirovecii pneumonia.

348 (n = 87, 18.1%), solid tumor (n = 56, 11.6%), and 349 other immunodeficiency (n = 3, 0.6%). The mean 350 CD4 T lymphocyte count at the time of PcP diagnosis 351 352 was significantly higher in the HIV-negative group 353 than in the HIV-positive group (292  $\pm$  360 vs 64  $\pm$ 354  $129/\text{mm}^3$ , respectively; P < .001). Only 50 of 481 355 patients (10.4%) were given PcP prophylaxis prior to 356 their PcP episode. Trimethoprim-sulfamethoxazole 357 was used as first-line therapy for 443 patients (92.1%), 358 and adjuvant corticosteroid therapy was administered 359 to 226 patients (47.0%). The average SOFA score was 360  $3.3 \pm 3.0$ . The 90-day mortality rate was 25.6% (n = 361 123). BAL was conducted at PcP diagnosis in 342 362 patients (71.1%). The detailed characteristics of BAL 363 364 according to patient groups are presented in e-Table 3.

#### 366 Previous Immunosuppressive Treatments

367 Among the overall population, 330 patients (89.9%) who 368 were HIV-negative had received immunosuppressive 369 treatment prior to PcP diagnosis (e-Table 4). The most 370 common immunosuppressants were corticosteroids 371 372 (n = 232, 63.2%), with an average dose of 29.2 mg/ 373 d prednisone equivalent. Prior corticosteroid therapy 374 was more frequent in patients with IMIDs (79 of 87 375 [90.8%] vs 152 of 280 [54.3%]; OR, 8.25; 95% CI, 3.84-376 17.7; P < .001) and given at higher doses (31.0 377 vs 19.5 mg/d; P = .008) (e-Table 4). 378

#### 379 Outcomes and Predictors of 90-Day Mortality 380

Patients with IMIDs and solid tumors had a statistically 381 382 significant worse outcome at 90 days (e-Figs 1, 2; Fig 2), 383 whereas patients who were HIV-positive had the best 384 survival rate at 90 days (Fig 2, Table 2). Of the 56 385 patients with solid tumors, 36 (64.3%) had metastatic

8,508 respiratory samples (induced sputum, bronchial aspiration or BAL) screened for P jirovecii between January 2011 and December 2021 ၀ု388 ġ 1,238 patients tested positive for P jirovecii (qPCR or direct examination) ອງ 391 730 patients with P jirovecii airway colonisation 1<u>1</u>392 508 patients with P jirovecii pneumonia (PcP, proven/probable) 9 patients < 18 years 18 patients with missing data 481 patients with proven or probable PcP 114 HIV-positive patients 367 HIV-negative patients

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disease, which was associated with 90-day mortality in the univariate analysis (OR, 4.71; 95% CI, 1.40-15.9; P =.010). Subtype of hematologic disease was not associated with 90-day mortality, as indicated in e-Table 5.

Among the overall population in multivariate analysis, solid tumor underlying disease (OR, 5.73; 95% CI, 2.25-14.84; P < .01), long-term corticosteroid use (OR, 2.25; 95% CI, 1.12-4.71; P = .026), and SOFA score at admission (OR, 1.63; 95% CI, 1.44-1.87; P < .001) were independently associated with 90-day mortality.

Among patients who were HIV-negative, solid tumor (OR, 416 5.47; 95% CI, 2.16-14.1; *P* < .001), IMIDs (OR, 2.19; 417 95% CI, 1.05-4.60; *P* = .037), long-term corticosteroid 418 exposure (OR, 2.07; 95% CI, 1.03-4.31; P = .045), positive 419 420 direct examination of sputum/BAL smears (OR, 1.92; 421 95% CI, 1.02-3.62; *P* = .043), and SOFA score at admission 422 (OR, 1.58; 95% CI, 1.39-1.82; P < .001) were independently 423 associated with higher 90-day mortality in multivariate 424 analysis (Fig 3, Table 3). Prior corticotherapy was no longer 425 associated with 1-year mortality (Fig 3). Finally, prior 426 corticotherapy was the only immunosuppressive drug 427 associated with 90-day mortality (OR, 1.67; 95% CI, 1.03-428 2.71; P = .035), especially for a daily dose  $\ge 10 \text{ mg}$  (OR, 429 1.80; 95% CI, 1.14-2.85; P = .010) (Table 3). 430

431 In patients who were HIV-positive, 69.3% presented 432 positive direct examination of sputum/BAL smears 433 without significant association with 90-day mortality 434 (n = 74; OR, 0.47; 95% CI, 0.08-2.72; P = .394) nor 435 with a neutrophilic BAL profile (n = 57; OR, 0.41; 436 95% CI, 0.07-2.45; *P* = .317). Conversely, only 27.5% of 437 438 patients who were HIV-negative presented positive 439 direct examination of sputum/BAL smears (e-Table 1), 440 which was associated with high 90-day mortality

4 Original Research

## RTICL

TABLE 1 ] Characteristics of Patients at the Time of Diagnosis of PcP and Follow-up (N $=481)$				
Characteristic	Value			
Age, y	58.2 ± 14.7			
Male	306 (63.6)			
BMI, ka/m <sup>2</sup>	22.94 ± 9.7			
Albumin, a/L	27.7 + 13.9			
Chronic underlying disease				
Chronic kidney disease	166 (34 5)			
Chronic nulmonary disease	101 (21.0)			
Underlying cause of immunodeficiency				
Hemotologic malignancy	118 (24.5)			
	34 (7 1)			
Lymphoma	32 (6 7)			
Chronic lymphoid loukomia	25 (5.2)			
	15 (3.2)			
	15 (3.1)			
	10 (2.1)			
Chronic myelomonocytic leukemia	a 2 (0.4)			
Allogeneic HSCT	32 (6.7)			
Autologous HSCT	9 (1.9)			
HIV infection	114 (23.7)			
Therapeutic rupture	68 (14.1)			
Discovery of HIV-positive status	46 (9.6)			
Solid organ transplantation	103 (21.4)			
Immune-mediated inflammatory disease	87 (18.1)			
Solid tumor	56 (11.6)			
Others <sup>a</sup>	3 (0.6)			
Ongoing immunosuppressive therapy	y 334 (69.4)			
Symptoms				
Dyspnea <sup>b</sup>	396 (82.3)			
Hyperthermia	355 (73.8)			
Cough	309 (64.2)			
Alteration of general condition	290 (60.3)			
Positive sputum/BAL direct examination (cysts in smears)	180 (37.4)			
Prophylaxis prescribed	50 (10.4)			
Aerosolized pentamidine	15 (3.1)			
TMP-SMX	25 (5.2)			
Atovaquone	9 (1.9)			
Prophylaxis observance during the last 2 mo	26 (5.4)			
Aerosolized pentamidine	11 (2.3)			
TMP-SMX	8 (1.7)			
Atovaguone	6 (1.2)			
Time from symptom onset to d	C (112)			
Hospitalization	14 3 ± 27 6			
riospitalization	14.5 ± 27.0			

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#### TABLE 1 (Continued)

TABLE 1 ] (Continued)		496				
Characteristic	Value	497				
Diagnostic	$\textbf{20.1} \pm \textbf{27.1}$	498				
Anti-Pneumocystis treatment	$19.9 \pm 26.9$	499 500				
SAPS II score	$\textbf{34.4} \pm \textbf{16.2}$	501				
SOFA score	$\textbf{3.3}\pm\textbf{3.0}$	502				
ICU admission	237 (49.3)	503				
ICU length of stay, d	$13.2\pm11.8$	504				
Laboratory findings		505				
WBCs/mm <sup>3</sup>	7,579 ± 5,000	506				
Neutrophils/mm <sup>3</sup>	6,093 ± 4,581	507				
Lymphocytes/mm <sup>3, c</sup>	828 ± 800	500				
CD4/mm <sup>3, d</sup>	$182\pm227$	510				
CRP, mg/L <sup>e</sup>	$109\pm100$	511				
LDH, International Units/L <sup>f</sup>	$460 \pm 250$	<b>61</b> 2				
Time from diagnosis to PcP treatment	-0.2 + 2.4	513				
Anti-Pneumocystis treatment	012 ± 211	514				
TMP-SMX	443 (92 1)	515				
	95 (19.8)	516				
IV pentamidine	12 (2 5)	517				
	206 (92 2)	518				
	100 (22.3)	520				
	109 (22.7)	521				
Exclusive honinvasive ventilation	15 (3.1)	522				
therapy	44 (9.2)	523				
Exclusive simple nasal oxygen	190 (39.5)	524				
therapy	. ,	525				
Adjunctive corticotherapy	226 (47.0)	526				
In-hospital mortality	102 (21.2)	527				
90-d mortality	123 (25.6)	520 529				
Values are mean $+$ SD or No. (%), CRP $=$ C-re	active protein: HSCT =	530				
hematopoietic stem cell transplantation; LDH $=$	lactate dehydrogenase;	531				
PcP = Pneumocystis jirovecii pneumonia; SAPS Physiology Score II: SOEA - Sequential Organ Fa	II = Simplified Acute	532 028				
SMX = trimethoprim-sulfamethoxazole.	nure Assessment, min	533				
<sup>a</sup> Of these three patients, two had Cushing syndrom	ne and one had cirrhosis	534				
<sup>b</sup> Decreased FEV <sub>1</sub> included.	its.	535				
<sup>c</sup> Twenty-four missing values and 10 censored d	ata from patients with	530				
leukemia.						
<sup>e</sup> Thirty-nine missing values.						
<sup>f</sup> Two hundred and thirty-two missing values.						
<sup>9</sup> Eleven missing values.		029 541				
(n = 257; OR, 1.94; 95% CI, 1.13-3.32; $P = .016$ ) and a						
neutrophilic BAL profile (n = 184; OR, 1.83; 95% CI,						
0.97-3.42; P = .059) (Table 3).						
		545				
Characteristics of Patients With IMIDs and Their 5 Prognosis						
						An overview of the diseases of the I
(n = 87) is given in e-Table 6. The most prevalent						

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Figure 2 - Survival analysis according to the underlying cause of immunodeficiency. HEM = hematologic malignancies; IMID = immune*mediated inflammatory diseases;* SOT = *solid organ transplantation;* ST = solid tumor.

disease was rheumatoid arthritis (n = 14, 16.1%), followed by antineutrophil cytoplasmic antibody-associated vasculitis (n = 9, 10.3%) and sarcoidosis (n = 8, 9.2%). Seventy-nine patients with IMIDs (90.8%) received long-term corticosteroid therapy, 37 (42.5%) received antimetabolite drugs, and 17 (19.5%) received anti-CD20 monoclonal antibody therapy 



Figure 3 - Survival analysis according to long-term steroid exposure prior to Pneumocystis jirovecii pneumonia diagnosis in patients who are HIV-negative. D90 = day 90.

(e-Table 4) prior to PcP diagnosis. For 68 patients (78%), immunosuppressive treatment had been introduced or modified in the year prior to PcP diagnosis. The mean time between introduction or change of immunosuppressive therapy and the onset of PcP was 78 days.

Among patients who were HIV-negative, patients with IMIDs were the oldest (P < .001) and presented

		Univariate Analysis			
meter	OR	95% CI	P Value		
Characteristic					
Age	1.04	1.02-1.05	< .001		
Male	0.90	0.52-1.54	.625		
Albuminemia $\leq$ 30 g/L <sup>a</sup>	3.40	1.89-6.10	< .001		
mmunodeficiency					
HIV infection	0.24	0.13-0.47	< .001		
Hematologic malignancy	0.88	0.54-1.43	.597		
Solid tumor	3.19	1.80-5.65	< .001		
Solid organ transplantation	0.86	0.51-1.43	.551		
Immune-mediated inflammatory disease	1.94	1.18-3.18	.008		
mmunosuppressive drug exposure					
Long-term corticosteroid therapy	2.58	1.68-3.96	< .001		

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## TABLE 3 ] Factors Associated With 90-Day Mortality in the HIV-Negative Population

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		Univariate Analysis (n = 367)			Multivariate Analysis (n = 315)		
	Parameter	OR	95% CI	P Value	OR	95% CI	P Value
	Characteristic						
	Age	1.02	1.00-1.04	.023	1.01	0.99-1.03	.401
	Male	0.90	0.52-1.54	.874			
	Albuminemia $<$ 30 g/L <sup>a</sup>	4.36	2.33-8.18	< .001			
	Chronic kidney disease	0.88	0.56-1.39	.594			
	Chronic pulmonary disease	1.10	0.66-1.82	.713			
	Immunodeficiency						
	Hematologic malignancy	0.61	0.37-1.00	.052			
	Solid tumor	2.48	1.39-4.42	.002	5.47	2.16-14.1	< .001
	Solid organ transplantation	0.61	0.36-1.03	.061			
	Immune-mediated inflammatory disease	1.46	0.88-2.42	.146	2,19	1.05-4.60	.037
	Connective tissue diseases	1.57	0.68-3.61	286		1.00	
		1 59	0 70-3 60	0.265			
	Long-term corticosteroid	1.67	1 03-2 71	.035	2 07	1 03-4 31	.045
	Steroid daily dose $> 10 \text{ mg}$	1.07	1 14-2 85	010	2.07	1.05 4.51	
		0.69	0.41-1.12	122			
	Mucanhanalia acid	0.00	0.41 1 22	.152			
		0.71	0.41-1.23	.219			
	Alleheiter	1.10	0.64-1.91	./24			
	Alkylating drug	1.31	0.70-2.45	.395			
	Monoclonal antibodies	1.25	0.73-2.16	.416			
	Anti-CD20	1.22	0.65-2.29	.543			
	Symptomatology						
	Dyspnea	2.51	1.22-5.16	.010	1.08	0.44-2.86	.870
	Hyperthermia	0.86	0.53-1.41	.556			
	Cough	0.79	0.50-1.24	.296			
	AGC	1.89	1.20-2.98	.006	1.31	0.72-2.38	.373
	Sputum/BAL examination <sup>b</sup>						
	Positive direct examinations (cysts in smears) <sup>c</sup>	1.99	1.22-3.24	.005	1.92	1.02-3.62	.043
	Neutrophilic BAL profile <sup>a</sup>	3.23	1.65-6.34	.001			
	Macrophagic BAL profile <sup>a</sup>	1.19	0.63-2.22	.598			
	Lymphocytic BAL profile <sup>a</sup>	0.25	0.11-0.52	< .001			
	CMV respiratory coinfection <sup>a, d</sup>	5.23	2.63-10.4	< .001			
	Laboratory findings						
	Neutrophils $\geq$ 7,500/mm <sup>3</sup>	1.52	0.93-24.48	.092			
	$CD4 \ge 200/mm^{3a}$	1.04	0.46-2.33	.930			
	$CRP \ge 100 \text{ mg/L}^{e}$	1.79	1.11-2.90	.017			
	$LDH \ge 400^{a}$	2.76	1.13-6.76	.024			
	Care						
	Time hospitalization/treatment	1.04	1.02-1.06	.001			
	Adjunctive corticosteroids	1.61	1.02-2.53	.039			
	Exclusive nasal oxygen therapy	0.51	0.32-0.82	.005			
	High-flow oxygen therapy	2.47	1.42-4.31	.932			
	Noninvasive ventilation	2.46	1 48-4 07	.001			
		2.10	1110 1107	1001			

(Continued)

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#### 771 TABLE 3 ] (Continued)

72 72			Univariate Analysis (n $=$ 367)			Multivariate Analysis (n = 315)		
73 74	Parameter	OR	95% CI	P Value	OR	95% CI	P Value	
75	Severity							;
6	SOFA	1.50	1.35-1.70	< .001	1.58	1.39-1.82	< .001	;
7	ICU admission	3.42	2.17-5.51	< .001				
/8				• •			- -	i )

AGC = alteration of general condition; CMV = cytomegalovirus; CRP = C-reactive protein; LDH = lactate dehydrogenase; SOFA = Sequential Organ Failure Q33 Assessment.

780 <sup>a</sup>Item with > 30% missing values.

781 <sup>b</sup>One hundred and seventy-two sputum examinations and 269 BAL examinations; 74 patients had both sputum and BAL examinations.

782 <sup>c</sup>Positive direct examination in BAL only (OR, 1.94; 95% CI, 1.13-3.32; P = .016).

<sup>d</sup>CMV polymerase chain reaction was only performed on BAL samples.

<sup>e</sup>Item with > 10% missing values.

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787 significantly more severe inaugural dyspnea forms of 788 PcP (OR, 4.05; 95% CI, 1.57-10.5; P = .002), increased <u>78</u>9 neutrophilia (P = .002), and more CMV respiratory 790 coinfection (OR, 2.69; 95% CI, 1.65-6.34; P = .007) (e-791 Table 7). Patients with IMIDs reported the worst SOFA 792 score on admission compared with the other HIV-793 negative subgroups (e-Table 7). These patients had less 794 adjuvant corticosteroid therapy (OR, 0.49; 95% CI, 0.30-795 0.81; P = .005) and a higher rate of mechanical 796 ventilation (OR, 2.01; 95% CI, 1.18-3.40; P = .009) to 797 798 treat PcP (e-Table 7).

799 Patients with IMIDs with a poor outcome reported a 800 lower albumin level (P < .001), were admitted to 801 hospital earlier from their onset of symptoms (2.8 802 vs 15.8 days, P = .037) with the worst SOFA score on 803 804 admission (6.9 vs 2.8, P < .001), but a had longer time to 805 initiation of anti-Pneumocystis therapy from the time of 806 hospitalization (7.6 vs 3.9 days, P = .027), a higher rate 807 of positive direct examination of respiratory samples 808 (P = .018), and a higher rate of respiratory CMV 809 coinfection (P = .002) (e-Tables 8, 9). Prior prescription 810 of anti-Pneumocystis prophylaxis was rarer among 811 patients with IMIDs (five of 87, 5.7%) and solid tumors 812 (one of 56, 1.8%) (e-Table 2). Among patients with 813 IMIDs, only SOFA score was independently associated 814 with 90-day mortality (OR, 1.50; 95% CI, 1.17-2.10; *P* = 815 816 .007) (e-Table 9).

# <sup>818</sup><sub>819</sub> Discussion

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To our knowledge, our work is the largest study to use a
comprehensive approach of the characteristics and
outcome of PcP as a function of the underlying disease
and the type of immunosuppressive therapies in a large
cohort of patients. We reported that PcP in patients with
IMIDs presented the most severe forms of PcP at

admission, with higher SOFA score and the highest mortality rate attributable to PcP among patients who were HIV-negative. On the other hand, patients with PcP with solid tumors displayed a higher 90-day mortality rate and a poorer long-term outcome, despite a lower SOFA score at PcP diagnosis. These results suggest that these patients (most of whom had metastatic disease) may not have developed the most severe forms of PcP, but that the onset of this opportunistic infection could be a marker of their frailty. 826

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853 Burghi et al<sup>14</sup> reported in an analysis of patients who 854 were HIV-negative (n = 321) that 30-day mortality and 855 presentation of PcP were associated with the underlying 856 disease. However, this study did not include patients 857 who were HIV-positive, and did not provide details of 858 859 patients with IMIDs as a specific subgroup. In our study, prior long-term corticosteroid therapy appeared to be a 860 861 major risk factor and was associated with a poorer 862 prognosis, especially in patients with IMIDs. This higher 863 mortality rate among patients with long-term 864 corticosteroid exposure fades at 1 year, which may be 865 explained by the mortality related to each underlying 866 condition among the HIV-negative group. The longer 867 time to diagnosis and the higher severity of PcP in 868 patients with IMIDs at admission suggest that the 869 delayed diagnosis may be in part responsible for their 870 poor prognosis. 871

872 Almost 90% of the patients had not been prescribed PcP 873 prophylaxis, confirming previous findings<sup>15</sup> which 874 identified the lack of trimethoprim-sulfamethoxazole 875 prophylaxis as a major risk factor for PcP in high-risk 876 patients.<sup>16</sup> To reduce PcP mortality in patients with 877 IMIDs, the first step would be to improve prophylactic 878 879 coverage against this preventable opportunistic 880 infection; however, determining criteria for

881 Pneumocystis prophylaxis in patients with IMIDs is 882 challenging, given the wide range of diseases 883 involved.<sup>17-19</sup> Specific prophylaxis guidelines have been 884 developed for antineutrophil cytoplasmic antibody-885 associated vasculitis, scleroderma, and autoimmune 886 inflammatory myopathies,<sup>20</sup> and for patients receiving 887 prolonged corticosteroid therapy,<sup>21,22</sup> but there are 888 currently insufficient data for rarer IMIDs to allow 889 specific prophylaxis recommendations to be 890 established.<sup>23</sup> This study supports that high-dose 891 corticosteroids are a major issue in patients who are 892 893 HIV-negative because of the risk of PcP, and unlike 894 patients who are HIV-positive, CD4 cell count cannot be 895 used as an indication for prophylaxis in these patients. 896 Rheumatoid arthritis was the most prevalent IMID in 897 this cohort, which is consistent with a recent national 898<sub>Q15</sub> study based on the French RESSIF Network.<sup>17</sup> This 899 highlights the difficulty in identifying the patients who 900 would benefit from Pneumocystis prophylaxis and 901 explains the lack of official recommendations/consensus 902 guidelines for these patients. More than one-half of 903 patients with rheumatoid arthritis in this cohort 904 developed PcP < 6 months after initiation or 905 906 intensifying their immunosuppressive therapy. 907 Atovaquone prophylaxis during the year after the 908 initiation of their immunosuppressive therapy could be 909 an effective alternative<sup>24</sup> with a favorable benefit to risk 910 ratio, while avoiding the risk of cumulative 911 myelotoxicity of methotrexate and trimethoprim-912 sulfamethoxazole. Sarcoidosis seems to be another 913 emerging condition highly exposed to corticosteroids, 914 for which there are yet no Pneumocystis prophylaxis 915 recommendations. 916

917 Another important factor in improving the outcome of 918 patients with IMIDs with PcP would be to treat them 919 earlier. Identifying patients with IMIDs with features 920 compatible with a severe PcP diagnosis as early as 921 possible and ensuring prompt treatment is particularly 922 relevant. Our work suggests that delayed treatment in 923 patients with IMIDs has a potentially dramatic impact 924 on their prognosis. 925

926 Analysis of 90-day risk factors among patients who were 927 HIV-negative in the extended cohort confirms our 928 previous results that BAL examination can provide 929 several important markers of mortality, including direct 930 cyst examination, neutrophilic alveolitis profile, and 931 932 respiratory coinfection with CMV at the time of PcP 933 diagnosis. Furthermore, prior corticosteroid therapy has 934q16 been reported to impair the anti-pneumocystic immune 935 response leading to an inefficient neutrophilic alveolitis

936 and subsequent alveolointerstitial inflammatory lesions 937 in PcP.<sup>25-27</sup> Indeed, positive direct examination of cysts 938 in respiratory samples could indicate profound 939 immunosuppression. In patients who are HIV-positive, 940 highly active antiretroviral therapy may contribute to 941 more rapid control of the infectious process through 942 faster recovery of the immune system. In patients who 943 are HIV-negative, patterns of immunosuppression, 944 including long-term corticosteroid therapy, appear to be 945 associated with an inappropriate inflammatory response 946 in cases of high fungal load. 947

948 Because patients with IMIDs more frequently present, at 949 PcP diagnosis, a BAL pattern that associates 950 immunosuppression and inflammation markers, we can 951 hypothesize that their greater exposure to long-term 952 corticosteroid therapy may induce dysregulation of the 953 anti-Pneumocystis response, which in turn may be 954 responsible for a more severe disease. Such prior 955 956 exposure to immunosuppressive drugs in patients with 957 IMIDs has also been shown to be associated with poor 958 outcome of SARS-CoV-2 pneumonia.<sup>28</sup> Our study 959 indicates that patients with the most severe IMIDs did 960 not receive more adjuvant corticosteroids. Indeed, no 961 evidence is available to support adjuvant corticosteroid 962 therapy in patients who are HIV-negative presenting 963 with severe PcP. The low use of adjuvant corticosteroid 964 therapy to treat PcP in patients with IMIDs may be 965 related both to the lack of guidelines for adjuvant 966 corticosteroid therapy in patients who are HIV-negative 967 968 and the high rate of prior corticosteroid exposure in 969 these patients, which probably contributed to the 970 development of PcP. In a previous study, we reported 971 that adjuvant corticosteroid therapy was associated with 972 the highest mortality rates in patients with respiratory 973 CMV coinfection among patients who are HIV-negative, 974 and that such CMV coinfection was more common in 975 patients with IMIDs.<sup>10</sup> Patients already exposed to prior 976 long-term corticosteroid therapy may therefore not 977 benefit from higher doses of steroids adjunctive therapy 978 in cases of severe PcP. Therefore, to improve the 979 management of PcP in IMIDs, there is a need to assess 980 the benefit of immunomodulatory therapies, other than 981 982 corticosteroids, to reduce the damaging pulmonary 983 immune response. 984

This study presents several limitations because of the<br/>retrospective nature of the cohort. Indeed, this study was<br/>986986not designed to assess the incidence of PcP among<br/>underlying conditions, but rather to identify emerging<br/>diseases over this 10-year period. The higher rate of PcP<br/>989<br/>in patients with rheumatoid arthritis could reflect a987

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991 higher prevalence of this disease among patients with 992 IMIDs. In addition, the lack of standardization of 993 adjuvant corticosteroid therapy does not allow any 994 conclusions regarding its efficacy in patients who are 995 HIV-negative. Finally, determining the exact cause of 996 mortality after hospital discharge represents a significant 997 challenge, especially in a retrospective cohort of patients 998 with severe chronic diseases that involve potential 999 limitations in intensive care, which may have 1000 overestimated PcP mortality in each of the subgroups. 1001 1002

#### 1003 Interpretation

1004 This large multicenter PcP cohort is the first to identify 1005 IMIDs, solid tumors, and long-term corticosteroid 1006 therapy as independent mortality factors in patients who 1007 are HIV-negative. Patients with IMIDs are the most 1008 exposed to long-term corticosteroid therapy and have 1009 the worst prognosis because of PcP when compared with 1010 other immunocompromised conditions. The onset of 1011 PcP in patients with solid tumors is associated with the 1012 1013 highest 90-day mortality and is probably related to very advanced tumor disease. Broadening indications for 1014 1015 primary prophylaxis against P jirovecii in patients with 1016

underlying immunocompromised conditions, earlier1046awareness, diagnosis and probabilistic treatment, and1047new therapeutic approaches for severe forms are the1048three key factors which could contribute to reducing P1049jirovecii mortality in patients who are HIV-negative.1051

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1026 R. contributed to interpretation of results and revision of the manuscript. R. L., N. I., and B.
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#### <sup>1033</sup> \*PRONOCYSTIS Study Group

1034 Collaborators: Francois Raffi, David

- 1035 Boutoille, Charlotte Biron, Maeva Lefebvre,
- Benjamin Jean Gaborit, Paul Le Turnier, 1036 Colin Deschanyres Raphael Lecomte Marie
- 1036 Colin Deschanvres, Raphael Lecomte, Marie 1037 Chauveau, Romain Lécuyer, and Antoine
- 1038 Asquier-Khati (Department of Infectious
- 1038 Asquier-Knati (Department of Infectiou Diseases, Nantes University Hospital);
- 1039 Patrice Le Pape, Florent Morio, Rose-Anne
- 1040 Lavergne, and Fakhri Jeddi (Department of
- 1041 Parasitology-Mycology, Nantes University Hospital); Stéphane Corvec, Pascale Bemer,
- 1042 Jocelyne Caillon, Aurélie Guillouzouic, and
- 1043 Anne-Gaëlle Leroy (Department of
- 1044 Bacteriology, Nantes University Hospital); Karim Lakhal, Raphaël Cinotti, and
- 1045 Antoine Roquilly (Department of

Anesthesiology and Intensive Care Medicine, Nantes University Hospital); Jean Reignier and Emmanuel Canet (Medical Intensive Care, Nantes University Hospital); François Xavier Blanc, Cédric Bretonniere, and Paul Morin (Service de Pneumologie, Nantes University Hospital); Fabrice Camou, Nahéma Issa, Olivier Guisset, and Gaelle Mourissoux (Intensive Care and Infectious Disease, Groupe Saint André, Bordeaux University Hospital); Isabelle Accoceberry, Frederic Gabriel, Isabelle Accoceberry, Noémie Coron, Laurence Delhaes, Sébastien Imbert, Maxime Lefranc, Florian Lussac-Sorton, and Amandine Rougeron (Laboratoire de Mycologie, Groupe Pellegrin, Bordeaux University Hospital); Marie Gousseff, Yoann Crabol, Grégory Corvaisier, Florent Lautredoux, and Romain Lécuyer (Department of Internal Medicine and Infectious Diseases, Centre Hospitalier Bretagne-Atlantique, Vannes); and Anne Cady, Myriam Auger, and Pascal Pouedras (Department of Microbiology, Centre Hospitalier Bretagne-Atlantique, Vannes).

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10 Original Research

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