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Pneumocystis pneumonia in intensive care: clinical spectrum, prophylaxis patterns, antibiotic treatment delay impact, and role of corticosteroids. A French multicentre prospective cohort study

Toufik Kamel[1], Ralf Janssen-Langenstein[2], Quentin Quelven[3], Jonathan Chelly[4], Xavier Valette[5], Minh-Pierre Le[6], Jeremy Bourenne[7], Denis Garot[8], Pierre Fillatre[9], Marie Labruyere[10], Nicholas Heming[11], Fabien Lambiotte[12], Jean-Baptiste Lascarrou[13], Olivier Lesieur[14], Konstantinos Bachoumas[15], Alexis Ferre[16], Eric Maury[17], Ludivine Chalumeau-Lemoine[18], David Bougon[19], Damien Roux[20], Olivier Guisset[21], Remi Coudroy[22,23] and Thierry Boulain[1*] on behalf of the PCP-MULTI Study group

Abstract

Purpose: Severe *Pneumocystis jirovecii* pneumonia (PJP) requiring intensive care has been the subject of few prospective studies. It is unclear whether delayed curative antibiotic therapy may impact survival in these severe forms of PJP. The impact of corticosteroid therapy combined with antibiotics is also unclear.

Methods: This multicentre, prospective observational study involving 49 adult intensive care units (ICUs) in France was designed to evaluate the severity, the clinical spectrum, and outcomes of patients with severe PJP, and to assess the association between delayed curative antibiotic treatment and adjunctive corticosteroid therapy with mortality.

Results: We included 158 patients with PJP from September 2020 to August 2022. Their main reason for admission was acute respiratory failure ($n=150$, 94.9%). 12% of them received antibiotic prophylaxis for PJP before ICU admission. The ICU, hospital, and 6-month mortality were 31.6%, 35.4%, and 40.5%, respectively. Using time-to-event analysis with a propensity score-based inverse probability of treatment weighting, the initiation of curative antibiotic treatment after 96 h of ICU admission was associated with faster occurrence of death [time ratio: 6.75; 95% confidence interval (95% CI): 1.48–30.82; $P=0.014$]. The use of corticosteroids for PJP was associated with faster occurrence of death (time ratio: 2.48; 95% CI 1.01–6.08; $P=0.048$).

Conclusion: This study showed that few patients with PJP admitted to intensive care received prophylactic antibiotic therapy, that delay in curative antibiotic treatment was common and that both delay in curative antibiotic treatment and adjunctive corticosteroids for PJP were associated with accelerated mortality.

Keywords: *Pneumocystis jirovecii*, Prophylaxis, Delayed treatment, Adjunctive corticosteroid therapy, Mortality, Intensive care

*Correspondence: thierry.boulain@chu-orleans.fr
[1] Service de Médecine Intensive-Réanimation, Centre Hospitalier Universitaire d'Orléans, 14 Avenue de l'Hôpital CS 86709, 45067 Orleans Cedex 2, France
Full author information is available at the end of the article

Members of the PCP-MULTI Study group are listed in the Acknowledgements Section.

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Introduction

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection affecting immunocompromised patients, and its incidence has risen in recent decades [1–4]. It now affects more patients not infected by human immunodeficiency virus (HIV) than HIV patients [5, 6]. PJP is potentially severe and is linked to a hospital mortality of about 5–15% in patients with HIV infection [7, 8]. Mortality escalates significantly beyond 50% when affecting patients with cancer, haematologic malignancy, pre-existing heart or respiratory failure, or is associated with the acute respiratory distress syndrome (ARDS) or septic shock requiring admission to intensive care [7, 9–14].

Evidence from the past 15 years indicates that patients with autoimmune rheumatic or vascular inflammatory diseases, among others, are increasingly susceptible due to immunosuppressive treatments [11, 15]. Within this specific population, antibiotic prophylaxis demonstrates divergent practices without a unified consensus [3, 16–23]. In immunocompromised individuals, PJP should be suspected in cases of diffuse pneumonia, with or without respiratory distress [24–26]. However, studies have underscored delays in initiating treatment among a subset of these patients during the initial hospitalization, potentially impacting in-hospital survival rates [11, 13, 27–29].

While corticosteroid therapy for PJP with hypoxemia in HIV patients has shown efficacy [30], uncertainties persist regarding its benefits in non-HIV patients [31–35].

There is a paucity of studies specifically dedicated to patients admitted to the intensive care unit (ICU) with PJP, leading to imprecise estimates of hospital mortality, long-term outcomes, and required supportive care for patients with the most severe forms of PJP.

In this context, we initiated a multicentre prospective observational study to describe ICU admission conditions for PJP patients, their clinical presentation, estimate the prevalence of prophylaxis, and finally, determine prevalence of delayed antibiotic treatment and corticosteroids use, and assess their association with 6-month mortality following ICU admission.

Methods

In January 2020, 100 French intensive care units (ICUs), all members of the French Intensive Care Society (SRLF) and/or the CRICS-TRIGGERSEP clinical research network (https://www.crics-triggersep.org/en), were invited to participate, of which 49 agreed. The study was conducted from September 1, 2020, to August 31, 2022. During this period, consecutive adult patients (≥ 18 years old) admitted to these ICUs with proven or probable PJP or diagnosed with PJP during ICU stay were prospectively included. Collected data included patient baseline clinical characteristics, type of immunocompromising disease, pre-ICU trajectory, reason for ICU admission, prophylaxis against PJP, diagnostic procedures for PJP, respiratory support, timing of curative antibiotic PJP treatment initiation, corticosteroids therapy for PJP, presence of lung co-infection, decisions of withholding or withdrawing therapy, and ICU, hospital, and 6-month mortality. The vital status at 6 months was obtained from hospital records or via direct contact with patients, their family, or their general practitioner, or by checking the national online database of deceased individuals at https://deces.matchid.io/about.

Patients and families received both verbal and written information about the study upon PJP identification, with the option to consent or decline participation. The study protocol received approval from the ethics committee of the French Intensive Care Society on May 20, 2020 (#CE SRLF 20–48).

Take-home message

Hospital and 6-month mortality of patients with *Pneumocystis jirovecii* pneumonia admitted to the intensive care unit is high, especially among patients not infected by human immunodeficiency virus, with delays in treatment linked to poorer survival.

Lack of antibiotic prophylaxis in immunocompromised patients is notable, and adjunctive corticosteroid therapy may adversely affect outcomes.

Definitions

In this prospective study, investigators were asked to include only patients with proven or probable PJP based on specific biological tests and concordant clinical and radiologic presentations, as per the European definition [36, 37]. In every case, PJP diagnosis was retained after diagnostic workup had ruled out alternative plausible diagnoses. Cases where *P. jirovecii* was detected through non-quantitative polymerase chain reaction (PCR) in oral or lower respiratory tract samples, or via quantitative PCR with high cycle threshold values [38] (determined by the clinician's judgment) and lacked corresponding clinical and radiological features, should not be included.

Investigators gathered data on prior or ongoing prophylaxis of PJP upon ICU admission or upon PJP diagnosis, through interviews with patients, family members, or their primary care providers. The prophylaxis included oral trimethoprim/sulfamethoxazole (TMP-SMX), atovaquone, dapsone, or aerosolized pentamidine, without specific differentiation in the data collection regarding the type of prophylaxis.

Data were gathered on the current or recent (within 4 weeks before ICU admission) use of immunosuppressive or immunomodulatory medications (including corticosteroid therapy) and the specific type of medication utilized. The criterion for defining corticosteroid-induced immunosuppression was established as a daily dosage of ≥ 15 mg of prednisone-equivalent for a period of ≥ 4 weeks, or the receipt of a bolus of ≥ 500 mg within the preceding 3 months.

Statistical analysis

The sample size was determined to assess the association of late treatment of PJP on patient mortality 6 months post-admission to the ICU. Given the available literature [11, 24, 28, 29], we opted to compare patients receiving the first dose of curative antibiotic treatment for PJP before or on the fourth day of ICU stay with those treated after the fourth day. Based on an anticipated 55% overall mortality rate at 6 months and a death hazard ratio of 2.4 for the late treatment cohort, a total of 103 patients were required with a type I alpha risk set at 5%, and a 90% statistical power.

To assess the association of late treatment of PJP with patient mortality, we excluded patients who had received curative treatment for PJP before ICU admission due to uncertainty regarding the exact time of PJP onset. We set time zero at the exact time of ICU admission. Since the variable "early/late curative treatment" violated the proportional hazards assumption, we used an accelerated failure time (AFT) model with a Weibull distribution [39] to estimate the time ratio, representing the relative change in the mean time to death associated with a given independent variable. We used stabilized propensity score-based inverse probability of treatment weighting (PS-IPW) [40] to estimate the average treatment effect (ATE). We adjusted our analysis (1) for established predictors of mortality in ICU patients, i.e., age, sex, Simplified Acute Physiology Score (SAPS II) [41], and Sequential Organ Failure Assessment (SOFA) score [42] on Day 1, and (2) for covariables that still were unbalanced between groups after weighing (imbalance was defined as a standardized difference > 0.1). The propensity score (PS), reflecting the likelihood of receiving curative PJP treatment after the fourth day in the ICU, was computed via multivariable logistic regression using all available baseline covariates upon ICU admission as independent variables (see electronic supplementary material [ESM] for details). We trimmed extreme PS values at the 2.5 and 97.5% percentiles [43].

The association of the use of corticosteroids with 6-month mortality was analyzed using the same approach but used the entire study population from which we excluded 2 patients who were enrolled in a multicentre, double-blind randomized trial comparing corticosteroids to placebo (ClinicalTrials.gov identifier: NCT02944045). Time zero was set at the time of first administration of curative antibiotic treatment for PJP. Whether patients were on corticosteroids before PJP onset was added to the list of covariables used for adjustment. A specific PS was calculated for estimating the probability of receiving corticosteroids during treatment of PJP. We classified patients in the corticosteroids group when they either received adjunctive corticosteroid therapy specifically for PJP as declared by investigators, or when they received corticosteroid therapy (≥ 40 mg/prednisone-equivalent) during at least the first week of treatment of PJP for other reasons.

We performed several exploratory subgroup analyses.

Continuous variables are summarized using median and interquartile range (IQR) (i.e., 25th and 75th percentiles). Groups were compared by Pearson χ^2, Fisher, Kruskal–Wallis, or Mann–Whitney U tests as appropriate.

The analyses were conducted using R software version 4.1.3 (R Foundation for Statistical Computing). A two-tailed P value < 0.05 was considered significant. However, analyses were not adjusted for multiple testing.

Results

During the 2-year study period, 36 out of 49 participating ICUs (see their location on the French territory in Figure S1 of ESM) admitted a total of 158 patients with PJP. These patients had a mean age of 62 years (IQR 48–71), with 62% being male. Figure 1 provides an overview of the patient trajectory before ICU admission. The primary reason for ICU admission was acute respiratory failure, accounting for 150 (94.9%) patients. Table S1 of ESM summarizes other causes of ICU admission. Patients' characteristics and outcomes are summarized in Table 1. One hundred and forty-five (91.8%) patients underwent lung high-resolution computed tomography (CT) scan within the first week of ICU stay. The various biological/clinical scenarios that led to PJP diagnosis are outlined in Fig. 1 and further details are provided in Table S2. Notably, upon data review, it was observed that 70 cases (44.3%) could not be definitively classified as proven or probable PJP. However, these cases had been classified as such by bedside clinicians, and thus, for the sake of thorough analysis, were retained in the dataset.

Lung co-infections (bacterial, viral or fungal, either documented or only suspected, see Table 1) were common (69/158, 43.7%) during treatment of PJP.

Cause of immunosuppression

Upon ICU admission, 105 patients (66.5%) were on ongoing or recent immunosuppressive drug therapy, including corticosteroids. Of these, 66 patients (41.8%) were using more than one type of immunosuppressive drug, and 29 patients (18.4%) were on more than two. Immunosuppression was associated with various conditions: solid-organ cancer or haematologic malignancies in 66 (41.8%) patients (details are provided in Table S3 and S4), HIV infection in 29 (18.4%) patients, and solid-organ transplant in 14 (8.9%) patients. Among the remaining 49 (31%) patients, 36 (73.5%) presented diverse inflammatory/autoimmune diseases (details in Table S5), 7 (14.3%) were solely on corticosteroid therapy causing immunosuppression, and 6 (12.2%) had no identified cause of immunosuppression.

Prophylaxis

Nineteen patients out of 158 (12%) were prescribed and consistently adhered to prophylaxis for PJP before ICU admission. The proportion of patients under such prophylaxis varied notably among different causes of immunosuppression (Table 1).

Respiratory support

Ninety-three (58.9%) patients required invasive mechanical ventilation during ICU stay. Patients with HIV infection were less frequently mechanically ventilated than organ transplant receivers ($P=0.027$) or patients with other immunocompromising conditions than solid-organ or haematologic neoplasms ($P=0.008$) (Table 1). Acute respiratory distress syndrome occurred in 82 (88.2%) of patients who required invasive mechanical ventilation.

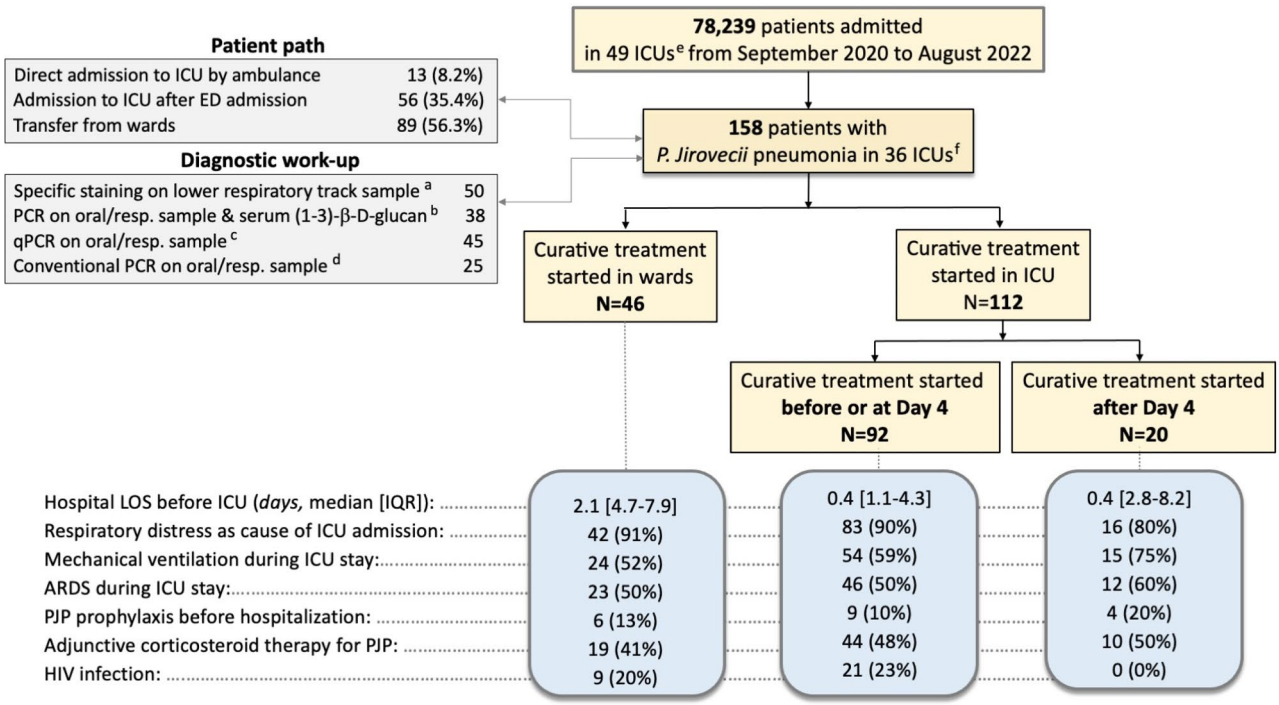

Fig. 1 Flow chart. *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *PCR* polymerase chain reaction (either conventional i.e., not quantitative or quantitative), *PJP Pneumocystis jirovecii* pneumonia, *qPCR* quantitative PCR. ARDS was defined according to the Berlin definition [47]. [a]Diagnostic of PJP made by the pathologist using microscopy and specific staining (modified Toluidine Blue O, Grocott-Gomori methenamine silver, or Immunofluorescent-antibody staining). [b]In every case, the diagnosis of PJP was based on a positive quantitative or non-quantitative PCR test performed on oral wash (%) or on lower respiratory tract sample, and serum (1–3)-b-D-glucan positivity (threshold for positivity left to the appreciation of the attending intensivist) [48], but also on the presence of bilateral interstitial pneumonia and a diagnostic workup that ruled out other diagnoses. [c]In every case, the diagnosis of PJP was based on a positive quantitative PCR test with sufficiently low cycle threshold (Ct) (left to the appreciation of the attending intensivist), but also on the presence of bilateral interstitial pneumonia and a diagnostic workup that ruled out other diagnoses. [d]In every case, the diagnosis of PJP was based on a positive non-quantitative PCR test performed on oral wash (%) or on lower respiratory tract sample, but also on the presence of either bilateral interstitial infiltrates on chest X-ray or bilateral ground glass opacities on high-resolution lung computed tomography and a diagnostic workup that ruled out other diagnoses. [e]Among the 36 participating ICUs, 18 were in university affiliated hospitals. [f]13 ICUs, including 6 ICUs in university affiliated hospitals, did not admit any patient with PJP during the study period

Table 1 Patients characteristics and outcomes

	Entire study population *N* = 158	Immunocompromising condition				
		Solid tumor or haematologic malignancy *N* = 66	HIV infection *N* = 29	Solid-organ transplant *N* = 14	Others [i] *N* = 49	*P* value
Male sex	98 (62)	37 (56.1)	21 (72.4)	9 (64.3)	31 (63.3)	0.50
Age, year	62 [48–71]	65 [52–72]	48 [42–56]	62[56–72]	66 [56–73]	< 0.001
SAPSII score on ICU day 1	41 [30–48]	42 [29–48]	41 [35–50]	40 [34–44]	37 [29–48]	0.83
SOFA score on ICU day 1	5 [3–8]	4.5 [3–10]	3 [2–7]	4.5 [3–9]	6 [3–8]	0.20
Mean arterial blood pressure at ICU admission, mmHg	85 [75–98]	84 [73–95]	89 [76–98]	87 [76–102]	87 [76–103]	0.76
Vasopressor use on ICU admission	18 (11.4)	7 (10.6)	3 (10.3)	2 (14.3)	6 (12.2)	0.95
Vasopressor use during ICU stay	85 (53.8)	31 (47)	9 (31)	11 (78.6)	34 (69.4)	0.002
Days on vasopressor (*n* = 84; 1 missing value)	5 [3–10]	5 [3–8]	2 [2–4]	8 [5–16]	6 [4–12]	0.024
FirstSpO_2 on ICU admission, %	95 [92–98]	95 [91–97]	96 [94–99]	95 [92–99]	95 [92–97]	0.33
PaO_2/FiO_2 ratio[a] on ICU admission	130 [95–185]	115 [85–165]	142 [126–219]	132 [95–160]	146 [95–190]	0.040
Mechanical ventilation and complications						
Invasive mechanical ventilation during ICU stay[b]	93 (58.9)	34 (51.5)	12 (41.4)	11 (78.6)	36 (73.5)	0.008
Invasive mechanical ventilation duration, days (*n* = 92; 1 missing value)	12 [6–19]	12 [7–18]	7 [5–17]	14 [6–38]	13 [8–23]	0.63
Prone positioning during ICU stay	38 (24.1)	15 (22.7)	5 (17.2)	9 (64.3)	9 (18.4)	0.003
Veno-venous extracorporeal membrane oxygenation therapy during ICU stay	4 (2.5)	0 (0)	2 (6.9)	2 (14.3)	0 (0)	0.004
ARDS[c] during ICU stay (1 missing)	81 (52.2)	34 (51.5)	10 (35.7)	9 (64.3)	28 (57.1)	0.23
Ventilator-associated pneumonia[d] during ICU stay (1 missing)	37 (23.6)	15 (22.7)	2 (7.1)	5 (35.7)	15 (30.6)	0.06
Occurrence of pneumothorax (1 missing)	14 (8.9)	3 (4.5)	2 (7.1)	3 (21.4)	6 (12.2)	0.14
Occurrence of mediastinal emphysema (1 missing)	5 (3.2)	2 (3)	0 (0)	0 (0)	3 (6.1)	0.64
Difficult weaning[e] (1 missing)	26 (16.6)	10 (15.2)	3 (10.7)	4 (28.6)	9 (18.4)	0.50
Tracheostomy (1 missing)	8 (5.1)	1 (1.5)	1 (3.6)	4 (28.6)	2 (4.1)	0.003
Antibiotic prophylaxis for PJP[f]	19 (12)	12 (18.2)	1 (3.4)	5 (35.7)	1 (2)	< 0.001
Treatment of PJP						
Delay between ICU admission and initiation of curative antibiotic treatment, *hours*, (*n* = 112)	4 [16–69]	7 [3–48]	6 [3–30]	110 [5–197]	23 [6–85]	0.039

Table 1 (continued)

	Entire study population *N* = 158	Immunocompromising condition				*P* value
		Solid tumor or haematologic malignancy *N* = 66	HIV infection *N* = 29	Solid-organ transplant *N* = 14	Others [i] *N* = 49	
Initiation of curative antibiotic treatment after 96 h (*n* = 112)	20 (12.7)	6 (9.1)	0 (0)	5 (35.7)	9 (18.4)	0.003
Corticosteroid therapy *during* PJP[g] treatment	102 (64.6)	44 (66.7)	24 (82.8)	10 (71.4)	24 (49)	0.015
Lung co-infection during treatment of PJP[h]						
All	69 (43.7)	21 (31.8)	13 (44.8)	8 (57.1)	27 (55.1)	0.06
Bacterial	39 (24.7)	9 (13.6)	7 (24.1)	6 (42.9)	17 (34.7)	0.024
Viral	36 (22.8)	11 (16.7)	8 (27.6)	3 (21.4)	14 (28.6)	0.44
Fungal	7	2	0	1	4	_
Length of stay and mortality						
Hospital length of stay before ICU admission, days	1.9 [0.4–6]	2.3 [0.5–6.5]	0.9 [0.2–3]	3.9 [1.1–7]	1.2 [0.1–6.3]	0.12
ICU length of stay, days	11.2 [5.3–19]	10.7 [5.4–17.4]	6.3 [3.9–16.4]	12.9 [4.9–47.5]	14.2 [8.9–26.5]	0.024
Total hospital length of stay, days	23.7 [15.3–42.1]	23.2 [13.5–37.1]	23.4 [17.2–33.6]	28.9 [18.5–65.9]	25.5 [17.5–44.5]	0.51
ICU mortality	50 (31.6)	22 (33.3)	3 (10.3)	6 (42.9)	19 (38.8)	0.029
Hospital mortality	56 (35.4)	25 (37.9)	3 (10.3)	8 (57.1)	20 (40.8)	0.005
PJP as cause of hospital death, as declared by investigators (*n* = 56)	20/56 (35.7)	10/25 (40)	2/3 (66.7)	6/8 (75)	11/20 (55)	0.09
6-month mortality	64 (40.5)	31 (47)	3 (10.3)	9 (64.3)	21 (42.9)	< 0.001
Decision of treatment withholding or withdrawal during ICU stay						
Decision of treatment limitation during ICU stay	46 (29.1)	24 (36.4)	3 (10.3)	5 (35.7)	14 (28.6)	0.016
ICU mortality (*n* = 46)	38 (82.6)	20 (83.3)	2 (66.7)	4 (80)	12 (85.7)	0.79
Hospital mortality (*n* = 46)	41 (89.1)	22 (91.7)	2 (66.7)	5 (100)	12 (85.7)	0.43

ARDS acute respiratory distress syndrome, HIV human immunodeficiency virus, *ICU* Intensive care unit, *PJP Pneumocystis jirovecii* pneumonia *SAPSII* Simplified acute physiology score II [43], *SOFA* Sequential Organ Failure assessment score [44]

[a] For patients on standard oxygen therapy, the $PaO_2/FiO2$ ratio was estimated according to [49]

[b] Only 9 patients were treated with non-invasive ventilation, including 5 patients who subsequently needed intubation

[c] According to the Berlin definition [47]

[d] As declared by investigators

[e] According to the European consensus definition [50]

[f] The prophylaxis may include oral trimethoprim/sulfamethoxazole (TMP-SMX), atovaquone, dapsone, or aerosolized pentamidine,which we did not distinguish

[g] We classified patients in the corticosteroids group when they either received adjunctive corticosteroids therapy specifically for PJP as declared by investigators or when they received corticosteroids therapy (≥ 40 mg/day prednisone-equivalent) during at least the first week of treatment of PJP for other reasons

[h] The presence of pulmonary co-infections was determined based on investigators' declarations. Bacterial lung co-infections were predominantly associated with gram-negative bacilli. Investigators confirmed that antibiotic therapy administered in all cases was considered appropriate. Viral infections included 4 cases of SARS-CoV-2 pneumonia

[i] Mainly (36/49) patients with autoimmune/inflammatory diseases (see Table S5 of ESM)

Mortality

Overall, the ICU, hospital, and 6-month mortality rates were 31.6%, 35.4%, and 40.5%, respectively (Table 1).

Mortality at 6 months was lower for patient with HIV infection (3/29, 10.3%) than for patients with malignancies (31/66, 47.0%) ($P=0.001$), organ transplant recipients (9/14, 64.3%) ($P=0.0005$) or other causes of immunosuppression (21/49, 2.9%) ($P=0.006$).

Forty-six (29.1%) patients underwent treatment withholding or withdrawal, with the lowest incidence observed among those with HIV infection (Table 1) (see details in Table S6).

Timing of antibiotic treatment of PJP

One patient had a documented allergy to TMP-SMX and received treatment with atovaquone. Among the remaining 157 patients initially treated with TMP-SMX, one patient was switched to pentamidine due to toxidermia, and another patient was switched to atovaquone due to bone marrow toxicity; both adverse events resolved subsequently without any lasting effects.

For the 112 patients whose curative treatment began in the ICU (while others started treatment on regular wards), initiation occurred at a median of 4 h (IQR 16–69) following ICU admission. Patients with immunosuppression classified as "other" (Table 1), mainly patients with autoimmune/inflammatory diseases (Table S5), had significantly delayed treatment initiation (23 h [IQR 6–85]) compared to those with solid-organ or hematologic malignancies (4 h [IQR 16–69]) ($P=0.040$). All patients with HIV infection whose curative treatment commenced in the ICU ($n=21$) were administered the first dose before the 96th hour. Decision of treatment withholding or withdrawing occurred in 8 (40%) patients treated late and in 22 (23.9%) patients treated earlier ($P=0.23$). Terminal extubation occurred in two (10%) patients treated late and in eight (8.7%) patients treated earlier ($P>0.99$). Lung co-infection was present during the first week of treatment of PJP for 10/20 (50%) patients treated late and for 42/92 (45.6%) patients treated earlier ($P=0.92$).

Six-month mortality was 55% (11/20) for patients who started curative treatment late, and 30.4% (28/92) for patients treated earlier ($P=0.06$ by χ^2 test). Time-to-event analysis with PS-IPW revealed that initiating curative treatment late was linked to a time ratio of 6.75 (95% confidence interval [95% CI]: 1.48–30.82) ($P=0.014$). This indicates that, on average, patients receiving late treatment had a 6.75 times faster occurrence of death (i.e., shorter survival) compared to those treated early. Results of the full AFT model are provided in Table S7. Weighted Kaplan–Meier survival curves are shown in Fig. 2. When restricted to the 91 patients without HIV infection, time-to-event analysis still showed an accelerated time to death in the late treatment group (time ratio = 6.24 [95% CI 1.39–28.00]; $P=0.017$) (see Figure S2 detailing subgroup exploratory analyses). Patients classified as proven or probable cases (Table S2) had a 6-month mortality of 55.6% (5/9) when treated late and 28% (14/50) when treated earlier ($P=0.13$). The other cases had a 6-month mortality of 55.5% (6/11) when treated late and 33.3% (14/42) when treated earlier.

Corticosteroid therapy

The proportion of patients who received corticosteroid therapy during their curative antibiotic treatment of PJP was 64.6% (102/158), with the highest proportion seen in patients with HIV infection (24/29 [82.8%]). In 71 (45.5%) cases, corticosteroids were given specifically for PJP (or for PJP but also other reason), as declared by investigators, at a median daily dose of 80 (IQR 60–95) mg prednisone-equivalent. When given exclusively for other reason (see details in Table S8), corticosteroids were administered at a median daily dose of 75 (IQR 50–131) mg prednisone-equivalent.

Decision of treatment withholding or withdrawing occurred in 32 (31.4%) patients treated with corticosteroids and in 14 (25.4%) not treated with corticosteroids ($P=0.60$). Terminal extubation occurred in 10 (9.7%) patients of the corticosteroids group and in seven (12.7%) patients not receiving corticosteroids ($P=0.75$). Lung co-infection was present during the first week of treatment of PJP for 46/102 (45.1%) and 23/54 (42.6%) patients of the corticosteroids and no corticosteroids groups, respectively ($P=0.90$).

The 6-month mortality was not different between patients receiving or not receiving corticosteroids (40.2% [41/102] and 40.7% [22/54], respectively; $P>0.99$]. Time-to-event analysis revealed that the use of corticosteroids during treatment of PJP was linked to a time ratio of 2.48 (95% CI 1.01–6.08) ($P=0.048$), meaning that, on average, patients receiving corticosteroids had a 2.48 times faster occurrence of death compared to those not receiving corticosteroids. Results of the full AFT model are provided in Table S6. Weighted Kaplan–Meier survival curves are shown in Fig. 3. The use of corticosteroids was not associated with faster occurrence of death in the 29 patients with HIV infection (time ratio: 0.26 [95% CI 0.02–3.7], $P=0.32$) but still showed a significant association in the 127 patients without HIV infection (time ratio: 2.56 [95% CI 1.03–6.39], $P=0.043$) (see Figure S3 detailing subgroup exploratory analyses). Additionally, within the subgroup of patients classified as proven or probable PJP cases (as detailed in Table S2), the use of corticosteroids

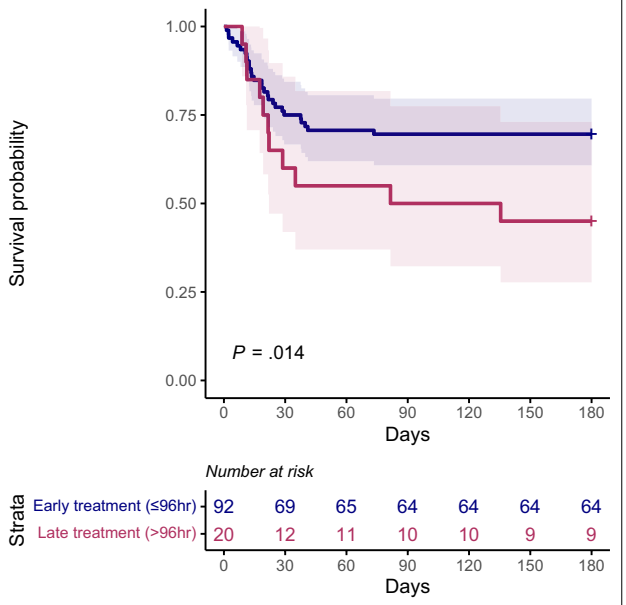

Fig. 2 Survival probability according to early or late (after the 96th hour of ICU) curative antibiotic treatment of PJP. The upper panel shows the weighted Kaplan–Meier curves for each group obtained by propensity score-based inverse probability of treatment weighting (PS-IPW, see "Methods" for details). In contrast, the risk table (lower panel) shows *raw* numbers at risk for each group (i.e., not in the weighted population constructed by PS-IPW for statistical analysis). The *P* value is the one obtained by accelerated failure time modeling (see "Methods") for the comparison of late versus early treatment. Time zero was the time of ICU admission

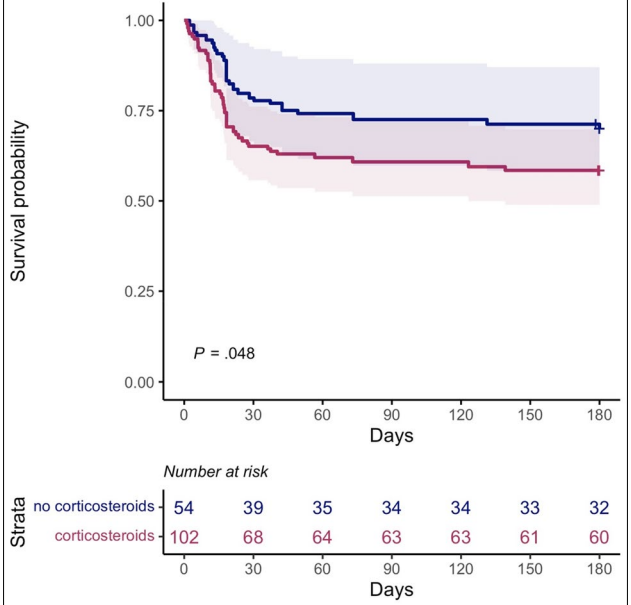

Fig. 3 Survival probability according to the use of adjunctive corticosteroid therapy for PJP in the whole study population ($N = 158$). The upper panel shows the weighted Kaplan–Meier curves for each group obtained by propensity score-based inverse probability of treatment weighting (PS-IPW, see "Methods" for details). In contrast, the risk table (lower panel) shows raw numbers at risk for each group (i.e., not in the weighted population constructed by PS-IPW for statistical analysis). The *P* value is the one obtained by accelerated failure time modeling (see "Methods") for the comparison of use of adjunctive corticosteroid therapy versus no use. Time zero was the time at which curative antibiotic treatment for PJP was started. Patients were right censored at Day 180 after the beginning of curative treatment. Note that one patient of the no corticosteroids group could be followed up only until the 178th day

was significantly associated with faster occurrence of death (time ratio: 5.71 [95% CI 1.85–17.61], $P = 0.003$) (Figure S3).

Discussion

The present study confirms that mortality associated with PJP is high, with severe PJP requiring ICU admission now primarily affecting non-HIV patients. Notably, a significant proportion (88%) of immunocompromised patients did not receive antibiotic prophylaxis. Delays in curative antibiotic therapy were common and associated with faster occurrence of death. Finally, corticosteroid treatment, once the diagnosis of PJP is confirmed, might be linked to faster occurrence of death.

The few studies exclusively focused on patients with PJP admitted to ICU [9, 10, 44–46] have been retrospective and are now dated. One focused exclusively on patients with HIV infection [44] and two exclusively on patients without [9, 45]. Therefore, comparing our results with these studies may pose challenges in interpretation, potentially influenced by changes in the epidemiology of PJP patients admitted to ICU and shifts in the overall approach to care, particularly in the management of ARDS. Our findings confirm that the proportion of patients with HIV infection requiring ICU admission for PJP is no longer predominant. The observed proportion of 18.4% in our study is lower than the roughly 29% observed in the early 2000s [10], but it remains non-negligible and appears stable when compared with data from 2016 to 2020 (19.5%) [45], highlighting the ongoing nature of the HIV infection epidemic.

Our findings also confirm that beyond the increasing proportions of patients with solid or hematologic cancer and organ transplant recipients, patients with inflammatory/ autoimmune diseases constitute more than 30% of PJP cases admitted to the ICU.

The observed ICU mortality in our study among non-HIV patients was high (32.3%), aligning with some observations [45] but considerably lower than reported by others, ranging from 48% to roughly 60% [9, 10]. Similarly, our overall 6-month mortality rate was 40.5%,

whereas the most recent retrospective study reported a 90-day mortality rate of 67% [46].

An unexpected result was that only 12% of patients were under prophylaxis, despite being almost immunocompromised and potentially eligible for prophylaxis according to current guidelines [23]. This situation may have improved since the 2000s–2010s, as the proportion of patients under prophylaxis was reported to be 1.1–3.6% [45, 46], results that should be considered with caution given the retrospective nature of these studies.

The second unexpected finding was that a non-negligible proportion of patients received the first dose of curative antibiotic treatment for PJP late: among patient not yet treated upon ICU admission, 12.7% received the first dose after the 96th hour. This is in line with what was reported years ago [11, 24, 27–29], suggesting that the practices of intensivists may not have evolved since then. Despite a rich literature emphasizing the high index of suspicion of PJP when caring for immunocompromised patients with diffuse pneumonia, there still remains a considerable gap between theory and practice. Our study further suggests that early treatment is of paramount importance, as it reveals that a delay of 4 days accelerated the time to death by a factor 6.75. This aligns with findings from earlier retrospective studies [24, 28, 29] and one prospective study, encompassing all PJP cases, whether requiring intensive care admission or not. That study demonstrated an increased risk of mortality of 1.11 for each day of delayed treatment [11]. For obvious ethical reasons, a randomized controlled trial comparing early versus delayed treatment is not feasible. Our study, utilizing propensity score weighting, represents the highest methodological standard achievable in this scenario. Hence, based on common sense (early treatment seems inherently preferable) and our study's findings, along with prior evidence, the question appears settled: PJP should be treated as soon as the suspicion stage, and should be systematically considered in immunocompromised individuals presenting to the ICU with pneumonia and/or acute respiratory failure.

Adjunctive corticosteroid therapy in non-HIV patients with PJP has been the subject of several studies, all retrospective, some of which suggesting that corticosteroids, akin to their effects in HIV-infected patients, might improve survival, while others found no significant impact [31–35, 45]. Two recent studies, one monocentric including 130 patients [34], and the other multicentric including 172 solid-organ transplant receivers [35], used PS-IPW as we did, and found no difference in mortality between patients treated with corticosteroids at the initiation of curative antibiotic treatment and those either untreated with corticosteroids or treated late. Our results, on the other hand, suggest that corticosteroid therapy may be associated with a twofold faster occurrence of death. Therefore, to date, there is still no unequivocal answer to the question of adjunctive corticosteroid therapy for PJP in non-HIV patients. A definitive answer may come from a recently completed randomized trial, the results of which are pending (NCT02944045).

Our study has several limitations. First, despite being prospective and encompassing 49 ICUs, our investigation cannot claim to accurately depict the epidemiology of severe PJP in France, as it only involves approximately one-fifth of French ICUs. Secondly, like previous studies in this area, our investigation faces limitations in assessing the effects of delayed antibiotic treatment on patient outcomes due to its observational design (i.e., non-randomized). This prohibits complete certainty in controlling for all potential confounding factors, particularly within the heterogeneous population of immunocompromised patients characterized by diverse clinical profiles and case mixes. In this context, distinguishing confirmed (proven or probable cases) from equivocal cases of PJP is complicated. Third, the assessment of the utility of adjunctive corticosteroid therapy faces similar methodological limitations.

Conclusions

This prospective observational study pinpoints that few patients with PJP admitted to the ICU had benefited from antibiotic prophylaxis despite being highly immunocompromised, that delayed antibiotic treatment is frequent and associated with faster occurrence of death, and suggests that adjunctive corticosteroid therapy for PJP in non-HIV patients may also be associated with faster occurrence of death.

Supplementary Information

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Author details

[1] Service de Médecine Intensive-Réanimation, Centre Hospitalier Universitaire d'Orléans, 14 Avenue de l'Hôpital CS 86709, 45067 Orleans Cedex 2, France. [2] Médecine Intensive-Réanimation, Hôpital de Hautepierre, Centre Hospitalier Universitaire de Strasbourg, Avenue Molière, 67200 Strasbourg, France. [3] Médecine Intensive-Réanimation, Centre Hospitalier Universitaire Rennes, Pontchaillou, 2, Rue Henri Le Guilloux, 35000 Rennes, France. [4] Réanimation Polyvalente, Centre Hospitalier Intercommunal Toulon La Seyne Sur Mer, 54 Rue Henri Sainte Claire Deville, 83100 Toulon, France. [5] Médecine Intensive-Réanimation, Centre Hospitalier Universitaire de Caen Normandie, 14000 Caen, France. [6] Médecine Intensive-Réanimation, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France. [7] Réanimation des Urgences et Dechocage Hôpital de La Timone, 264 Rue Saint-Pierre, 13005 Marseille, France. [8] Médecine Intensive-Réanimation, Centre Hospitalier Régional Universitaire Bretonneau, Tours, 37044 Tours, France. [9] Réanimation Polyvalente, Centre Hospitalier Yves-Le Foll, 10, Rue Marcel Proust, 22000 Saint Brieuc, France. [10] Médecine Intensive-Réanimation, Centre Hospitalier Universitaire de Dijon, 14 Rue Gaffarel, BP 77908, 21079 Dijon Cedex, France. [11] Médecine Intensive-Réanimation, Hôpital Raymond-Poincaré, 104, Boulevard Raymond-Poincaré, 92380 Garches, France. [12] Médecine Intensive-Réanimation,

Centre Hospitalier de Valenciennes-CHV, Avenue Désandrouin CS 50479, 59322 Valenciennes Cedex, France. [13] Médecine Intensive-Réanimation, Centre Hospitalier Universitaire de Nantes, Hôtel-Dieu-HME, 1 Place Alexis Ricordeau, 44093 Nantes, France. [14] Médecine Intensive-Réanimation, Hôpital Saint-Louis, Rue Du Dr Schweitzer, 17019 La Rochelle, France. [15] Médecine Intensive-Réanimation, Centre Hospitalier Départemental Vendée, Boulevard Stéphane Moreau, 85000 La Roche-Sur-Yon, France. [16] Intensive Care Unit, Versailles Hospital, 177 Rue De Versailles, 78157 Le Chesnay, France. [17] Médecine Intensive-Réanimation, Hôpital Saint-Antoine, 184 Rue du Faubourg Saint-Antoine, 75012 Paris, France. [18] Service de Réanimation Médico-Chirurgicale, Hôpital Privé Claude Galien, 20 Route de Boussy, 91480 Quincy-Sous-Sénart, France. [19] Médecine Intensive-Réanimation, CH Annecy-Genevois, Site Annecy, 1 Avenue De L'Hôpital, 74370 Annecy, France. [20] Université Paris Cité, AP-HP, Hôpital Louis Mourier, DMU ESPRIT, Service de Médecine Intensive Réanimation, Colombes, France. [21] Médecine Intensive-Réanimation, Centre Hospitalier Universitaire-SAINT-ANDRE, Bordeaux, 1 Rue Jean Burguet, 33075 Bordeaux, France. [22] Médecine Intensive Réanimation, CHU de Poitiers, Poitiers, France. [23] INSERM CIC 1402, IS-ALIVE Research Group, Université de Poitiers, Poitiers, France.

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Author contributions
TK and TB had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors give their agreement to be accountable for all aspects of the work and ensure the accuracy and integrity of any part of the work. Concept and design: TK and TB. Acquisition, analysis, or interpretation of data: all the authors. Drafting of the manuscript: TK and TB. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: TB. Administrative, technical, or material support: TK and TB. Supervision: TK and TB. The corresponding author (TB) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest
There are no competing interests for any author concerning the submitted work.

Ethics approval and consent to participate
This study adhered to French legal regulations for prospective non-interventional studies and was conducted in accordance with the Declaration of Helsinki and its later amendments. Patients and families received both verbal and written information about the study upon patient eligibility, with the option to consent or decline participation. The study protocol received approval from the ethics committee of the French Intensive Care Society on May 20, 2020 (#CE SRLF 20-48).

Consent for publication
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