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## **The presence of *Pneumocystis jirovecii* in critically ill patients with COVID-19**

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**Key words:** COVID-19; pneumocystosis; *Pneumocystis jirovecii*

1 Letters to the Editor

2 *Dear Editor,*

3 We read with interest the recent review on co-infections in coronavirus disease-2019 (COVID-19)  
4 patients<sup>1</sup> and believe that fungal co-infections as evaluated from selected studies are underestimated.  
5 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is still spreading pandemically.  
6 Approximately 5-10% of COVID-19 patients may require intensive care unit (ICU) management and  
7 30% may develop secondary pneumonia without identified etiology.<sup>2</sup> Hospital-acquired bacterial or  
8 fungal superinfections, as described in critically ill patients with *Influenza* virus, can be suspected.<sup>3</sup> Since  
9 pneumocystosis is usually reported in patients with T-cell immunodepression,<sup>4</sup> less attention has been  
10 paid to *Pneumocystis jirovecii* in non-immunocompromised ICU patients although it accounts for 7% of  
11 the co-infections reported in those admitted with Influenza.<sup>5</sup> Interestingly, COVID-19 patients may  
12 develop lymphocytopenia and acute respiratory distress syndrome (ARDS) requiring adjunctive steroids  
13 and/or immunomodulatory therapies, well-known susceptibility factors for developing pneumocystosis.<sup>5</sup>  
14 We designed this observational cohort study to investigate the prevalence of *P. jirovecii* acid nucleic  
15 detection in respiratory specimens sampled to identify co-infections in COVID-19 patients in the ICU.

16 All consecutive patients admitted to the ICU between 2020/03/15 and 2020/05/01 with a positive  
17 SARS-CoV-2 PCR (Cobas<sup>®</sup> SARS-CoV-2 Test, Roche, France) and  $\geq 1$  respiratory sample  
18 (bronchoalveolar lavage (BAL), tracheal aspirate, sputum) sent to the mycology department. This study  
19 was part of the COVID-ICU and French COVID-19 cohort registries. Our institutional ethics committee  
20 approved the study (IDRCB, 2020-A00256-33; CPP, 11-20-20.02.04.68737). When possible, signed  
21 informed consent was obtained from the patients or the next of kin.

22 Whenever possible, bronchoalveolar lavage (BAL) was performed in the middle lobe by a trained  
23 pneumologist in the ICU using at least 120 ml saline (yield, ~50%). Upon reception, specimens including  
24 BAL fluids and dTT-treated aspirations (dTT 1X at 37°C for 15min) were centrifuged, suspended in  
25 200 $\mu$ L of water and submitted to extraction (whole nucleic acids extraction) using the GeneLead-VIII  
26 extractor-thermocycler<sup>™</sup> (Precision System Science, Japan). *P. jirovecii* reverse transcriptase quantitative  
27 PCR (RTqPCR) was performed to amplify mtSSU and mtLSU RNA and DNA of *P. jirovecii* using the  
28 new R-DiaPnJ kit<sup>™</sup> (Diagenode, Belgium). Serum  $\beta$ -D-glucan was tested using the Fungitell kit<sup>™</sup> (Cape

29 Cod Inc, US) as recommended by the manufacturer. Data are presented as median [25<sup>th</sup>-75<sup>th</sup> percentiles]  
30 or percentages as appropriate. Comparisons were performed using Mann-Whitney or exact Fisher tests as  
31 required. *P*-values  $\leq 0.05$  were considered as significant.

32 One hundred-and-eight successive HIV-negative COVID-19 patients (Male/Female sex ratio, 4.4; age,  
33 62 years [56-68]) with the usual risk factors for severe COVID-19 presentation were included (Table 1).  
34 All except three patients were intubated on admission. Thirty-four patients (31.4%) who developed  
35 ARDS received at least one day of corticosteroids before BAL sampling. Respiratory samples included 80  
36 BALs (74.1%), 22 tracheal aspirates (20.4%), 4 sputa (3.7%) and two bronchial aspiration fluids (1.9%).  
37 In 10/108 patients (9.3%), *P. jirovecii* RTqPCR was positive. Median delay between sampling and ICU  
38 admission was 2 days [1-2]. The median quantitative cycle value was 32.6 [30.8-34.7]. Serum  $\beta$ -D-glucan  
39 were measured in nine patients and was negative ( $>80$ pg/mL) in seven patients.

40 Clinical characteristics of the patients carrying *P. jirovecii* did not significantly differ from the other  
41 patients except for lower plasma D-dimer (1,270ng/mL [750-2,390] vs 2,610ng/mL [1,405-4,700],  
42 *P*=0.03) and more frequent lopinavir/ritonavir administration (40.0% vs 12.2%, *P*=0.04), while long-term  
43 corticosteroid prescription tended to be more frequent (30.0% vs 8.2%, *P*=0.06). Of note, among our 10  
44 *P. jirovecii* carriers, five concomitantly met the criteria for COVID-19-associated pulmonary  
45 aspergillosis.<sup>6</sup> Out of these patients, four (40%) received co-trimoxazole as prophylaxis (80/400mg once  
46 daily) whereas six including four who rapidly improved did not. One co-trimoxazole-treated and two non-  
47 treated patients died while the seven remaining patients were discharged. Mortality was similar in both  
48 groups.

49 We found an unexpectedly high proportion of critically ill COVID-19 patients detected with *P.*  
50 *jirovecii* (10/108 patients; 9.3%), similarly to previous findings in influenza patients (3/45; ~7%).<sup>5</sup>

51 The presence of *P. jirovecii* in the healthy adult population has been measured using oropharyngeal  
52 wash samples obtained by gargling and examined by conventional or nested PCR methods.<sup>7</sup> However,  
53 experts agree that the reported prevalence (~20%) has been overestimated due to technical issues such as  
54 contamination with amplicons responsible for false positives.<sup>4</sup> In our center managing almost exclusively  
55 immunocompromised patients, prevalence of qPCR-positive respiratory specimens with fungal load as  
56 low as in our COVID-19 patients, is ~13% (unpublished data), as reported elsewhere.<sup>3</sup> COVID-19

57 patients mostly exhibited marked lymphopenia and alterations in lymphocyte functions,<sup>8</sup> likely explaining  
58 the high-rate of *P. jirovecii* detection.

59 Since serum  $\beta$ -D-glucan is advocated in pneumocystosis diagnosis,<sup>4</sup> we measured its concentrations in  
60 four of our five *P. jirovecii* RTqPCR-positive patients and obtained low values (<120pg/mL) in  
61 accordance with the low nucleic acids fungal loads in the lung alveoli.<sup>9</sup> Of note, in two out of our nine  
62 tested *P. jirovecii* RTqPCR-negative patients, higher B-D-glucan concentrations (450 and 500pg/ml) lead  
63 to the diagnosis of pulmonary aspergillosis, another fungal infection of risk in COVID-19 patients.<sup>6</sup>  
64 Although a recent meta-analysis questioned its sensitivity in non-HIV patients,<sup>10</sup>  $\beta$ -D-glucan has been  
65 widely used to rule out pneumocystosis because of its high negative predictive value. This finding may  
66 support the hypothesis that our patients were carrying *P. jirovecii*, yet not being infected *per se*. Thus,  
67 although interesting in the context of invasive fungal infections diagnosis, serum  $\beta$ -D-glucan should be  
68 interpreted with caution when excluding the diagnosis of pneumocystosis.

69 Here, four out of ten *P. jirovecii* RTqPCR-positive patients received co-trimoxazole as prophylactic  
70 regimen, based on the treating physician's decision. Whether a positive result should be an indication to  
71 consider administering co-trimoxazole, at least at prophylactic dosage in COVID-19 patients remains  
72 questionable.

73 Our study limitations include the relatively small number of patients, the bi-center setting, and the  
74 short study period. However, to the best of our knowledge, this is the first study evaluating the prevalence  
75 of *P. jirovecii* in COVID-19 patients. Because we focused on critically ill COVID-19 patients, *P. jirovecii*  
76 prevalence in less severe patients remains to be determined.

77 In conclusion, an unexpectedly high proportion of *P. jirovecii*-positive pulmonary samples is observed  
78 in critically ill COVID-19 patients. Based on our findings, we advocate systematically searching for *P.*  
79 *jirovecii* in deep respiratory specimens in these patients. We believe that this strategy may be useful in  
80 limiting enhanced inflammation due to the presence of *P. jirovecii* in the lung and avoiding inter-patient  
81 *P. jirovecii* transmission.

82

### 83 **Declaration of Competing Interest**

84 The authors declare that they have no competing interests.

85

86 **Ethics approval and consent to participate**

87 This study was part of the French COVID-19 cohort registry conducted by the REACTing consortium  
88 (REsearch and ACTion targeting emerging infectious diseases) and directed by INSERM (Institut national de la  
89 santé et de la recherche médicale) and ISARIC (International Severe Acute Respiratory and Emerging Infection  
90 Consortium). Our institutional ethics committee approved the study (N°, IDRCB, 2020-A00256-33; CPP, 11-20-  
91 20.02.04.68737).

92

93 **Availability of data and materials**

94 Drs. Alanio, Mégarbane and Bretagne conceived of and designed the study. Drs. Voicu, Azoulay and  
95 Mégarbane managed the patients. Drs. Alanio, Dellière and Bretagne performed the microbiological analysis. All  
96 authors acquired, analyzed the data and interpreted the results. Drs. Alanio, Mégarbane and Bretagne drafted the  
97 manuscript. All authors participated to the critical revision of the manuscript for important intellectual content.  
98 Dr. Alanio has full access to all data and takes responsibility for the data integrity and its analysis accuracy.

99

100 **Consent for publication**

101 All the authors agree to publish.

102

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105 at the university hospital.

106

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137 *Microbiol Infect* 2020;S1198-743X(20)30301-3. doi:10.1016/j.cmi.2020.05.024



138 **Table 1**

139 Characteristics of hundred-and-eight critically ill COVID-19 patients according to *Pneumocystis jirovecii*  
 140 detection in the respiratory samples. Data are presented as percentages or medians [25<sup>th</sup>-75<sup>th</sup> percentiles].  
 141 Comparisons were performed using Mann-Whitney (◦) or Fisher exact tests (\*), as appropriate.

142

	<b>Total (N=108)</b>	<b>No detection of <i>P. jirovecii</i> (N=98)</b>	<b>Detection of <i>P. jirovecii</i> (N=10)</b>	<b><i>P</i></b>
<b>Male gender, N (%)</b>	88 (81.5%)	80 (81.6%)	8 (80.0%)	1*
<b>Age (years)</b>	62 [56-68]	62 [56-68]	59 [46-68]	0.40◦
<b>COVID-19 risk factors</b>				
<b>Past hypertension, N (%)</b>	64 (59.3%)	58 (59.2%)	6 (60.0%)	1*
<b>Diabetes, N (%)</b>	40 (37.0%)	37 (37.8%)	3 (30.0%)	0.74*
<b>Obesity, N (%)</b>	35 (32.4%)	32 (32.7%)	3 (30.0%)	1*
<b>Coronary disease, N (%)</b>	15 (13.9%)	14 (14.3%)	1 (10.0%)	1*
<b>Body-mass index (kg/m<sup>2</sup>)</b>	28 [25-31]	28 [25-31]	28 [27-32]	0.61◦
<b>Other remarkable comorbidities</b>				
<b>Asthma, N (%)</b>	5 (4.6%)	4 (4.1%)	1 (10.0%)	0.39*
<b>Chronic obstructive pulmonary disease, N (%)</b>	2 (1.9%)	2 (2.0%)	0 (0.0%)	1*
<b>Immunocompromised patient, N (%)</b>	10 (9.3%)	10 (10.2%)	0 (0.0%)	0.59*
<b>Long-term corticosteroids, N (%)</b>	11 (10.2%)	8 (8.2%)	3 (30.0%)	0.06*
<b>Biological data of interest on admission</b>				
<b>PaO<sub>2</sub>/FiO<sub>2</sub> (mmHg)</b>	137 [83-247]	134 [83-239]	177 [108-253]	0.60◦

<b>Serum creatinine</b> ( $\mu\text{mol/L}$ )	80 [64-111]	80 [63-111]	80 [67-104]	0.99 $\circ$
<b>Plasma D-dimer</b> (ng/mL)	2,2395 [1,193-4,635]	2,610 [1,405-4,700]	1,270 [750-2,390]	0.03 $\circ$
<b>Serum lactate dehydrogenase</b> (IU/L)	687 [540-901]	687 [568-903]	708 [436-893]	0.65 $\circ$
<b>Bronchoalveolar lavage characteristics</b>				
<b>% BAL macrophages</b>	28 [15-46]	27 [14-42]	51 [49-55]	0.13 $\circ$
<b>% BAL polymorphonuclear cells</b>	37 [26-81]	46 [26-81]	29 [18-32]	0.54 $\circ$
<b>% BAL Lymphocytes</b>	13 [6-32]	14 [5-34]	13 [10-23]	0.81 $\circ$
<b>Specific anti-COVID-19 therapy, N (%)</b>				
<b>Azithromycin, N (%)</b>	34 (31.5%)	30 (30.6%)	4 (40.0%)	0.72*
<b>Hydroxychloroquine, N (%)</b>	34 (31.5%)	30 (30.6%)	4 (40.0%)	0.72*
<b>Hydroxychloroquine + Azithromycin, N (%)</b>	29 (26.9%)	26 (26.5%)	3 (30.0%)	1*
<b>Lopinavir-ritonavir, N (%)</b>	16 (14.8%)	12 (12.2%)	4 (40.0%)	0.04*
<b>Polyvalent immunoglobulins, N (%)</b>	3 (2.8%)	3 (3.1%)	0 (0.0%)	1*
<b>Sarilumab, N (%)</b>	1 (0.9%)	1 (1.0%)	0 (0.0%)	1*
<b>Eculizumab, N (%)</b>	6 (5.6%)	4 (4.1%)	2 (20.0%)	0.10*
<b>Tocilizumab, N (%)</b>	4 (3.7%)	4 (4.1%)	0 (0.0%)	1*
<b>Dexamethasone, N (%)</b>	53 (49.1%)	46 (46.9%)	7 (70.0%)	0.19*
<b>Dexamethasone cumulative dose &gt;100mg, N (%)</b>	16 (14.8%)	15 (15.3%)	1 (10.0%)	1*
<b>Severity during hospitalization and outcome</b>				
<b>SAPS II on admission</b>	37 [31-49]	38 [31-51]	34 [28-37]	0.16 $\circ$
<b>SOFA on admission</b>	6 [3-8]	6 [3-8]	5 [2-7]	0.43 $\circ$

<b>Lowest PaO<sub>2</sub>/FiO<sub>2</sub> (mmHg)</b>	71 [58-89]	71 [59-89]	65 [53-102]	0.79 <sup>o</sup>
<b>Vasopressors, N (%)</b>	89 (82.4%)	81 (82.7%)	8 (80.0%)	1*
<b>Renal replacement therapy, N (%)</b>	38 (35.2%)	35 (35.7%)	3 (30.0%)	1*
<b>ECMO, N (%)</b>	10 (9.3%)	9 (9.2%)	1 (10.0%)	1*
<b>SAPS II on admission</b>	37 [31-49]	38 [31-51]	34 [28-37]	0.16 <sup>o</sup>
<b>ICU length of stay (days)</b>	20 [12-32]	20 [12-33]	10 [6-19]	0.03 <sup>o</sup>
<b>Mortality, N (%)</b>	47 (43.5%)	44 (44.9%)	3 (30.0%)	0.51 *

143 BAL, bronchoalveolar lavage; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SOFA, Sepsis-  
144 related Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II.

1 **Table 1**

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<b>ICU length of stay (days)</b>	20 [12-32]	20 [12-33]	10 [6-19]	0.03 <sup>o</sup>
<b>Mortality, N (%)</b>	47 (43.5%)	44 (44.9%)	3 (30.0%)	0.51 *

6 BAL, bronchoalveolar lavage; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SOFA, Sepsis-  
7 related Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II.