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Comment on: *Pneumocystis jirovecii* pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients

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Sir,

We have read with interest the paper by Cordonnier *et al.*[1] introducing the European Conference on Infections in Leukemia (ECIL) guidelines for *Pneumocystis jirovecii* pneumonia (PJP), and would like to comment on some assertions that we believe are somewhat outdated or not fully correct.

First of all, the authors repeat the old mantra that the 'transmission of *P. jirovecii* occurs during the first years of life via person-to-person contact', and that 'two-thirds of immunocompetent individuals have specific antibodies by the age of 4 years'.[1] At the beginning of the AIDS pandemic, this assumption, which is based on many now-dated studies of healthy children, led to the formulation of the long-lived 'reactivation theory': i.e. PJP is the consequence of a reactivation of long-term colonization, and the disease develops when the immune system is profoundly affected by HIV infection or another condition causing immunodeficiency.[2] However, this theory has been challenged by Yiannakis and Boswell[3] in a recent review of 30 outbreaks occurring among kidney transplant patients and patients with haematological malignancies: extensive molecular genotyping of a number of these outbreaks indicates *de novo* acquisition from an environmental source or patient-to-patient transmission. Furthermore, Choukri *et al.*[4] have demonstrated that the aerosol dispersion of *P. jirovecii* DNA into the environment occurs up to 8 m from a patient with PJP, and an elegant study by Gits-Muselli *et al.*[5] found a single genotype among PJP patients sharing the same hospital environment. These findings raise the question of controlling hospital infections among immunocompromised patients, and the CDC has recommended that a patient with confirmed PJP should not share a room with another immunocompromised patient.[6]

The second point we would like to discuss is the reported clinical differences between HIV-positive and HIV-negative patients. The authors state that hypoxaemia is 'mild' among HIV-positive patients but 'often severe' among HIV-negative patients. However, the studies supporting this view are based on small sample sizes or unbalanced groups: Mansharamani *et al.*[7] compared 442 HIV-positive patients with 33 HIV-negative patients; Kovacs *et al.*[8] considered 49 episodes in AIDS patients and 39 episodes in other immunosuppressed patients; and Limper *et al.*[9] compared 19 AIDS patients with 56 patients without AIDS. Moreover, the HIV-negative populations in these studies included patients with heterogeneous immunosuppressive conditions (i.e. haematological or solid malignancies, steroid therapy, solid organ transplantation and primary immunodeficiency), and extrapolating the findings to haematological patients alone may not be appropriate. It is also clear that the time to medical attention and to treatment initiation is critically important in determining the evolution of hypoxaemia and the related PaO_2 values of PJP patients, regardless of underlying clinical condition. As shown in Table 1, we found admission PaO_2 values were <60 mmHg in 37.4% of our 468 patients experiencing a first episode of HIV-associated PJP confirmed by bronchoalveolar lavage and/or autopsy, and 60–70 mmHg in a further 27.1% (Table 1). Furthermore, during hospitalization, 51.1% of the patients required adjunctive steroids, 31.0% required continuous positive airway pressure therapy and 4.9% were intubated and mechanically ventilated in our ICU.

We also do not agree with the statement based on the findings of McKinnell *et al.*[10] and Vogel *et al.*[11] that high lactate dehydrogenase (LDH) levels are more specific and sensitive in HIV-positive than in HIV-negative patients. McKinnell *et al.*[10] found no difference in LDH levels between the two groups (496 $\pm$ 50.5 IU/L versus 354.9 $\pm$ 29.2 IU/L; $P = 0.10$), and no difference in hypoxaemia, dyspnoea or the rate of mechanical ventilation. Moreover, the sensitivity and specificity values of high LDH levels in HIV-positive patients reported by Vogel *et al.*[11] were obtained in a very small sample of only eight patients. Twenty-one percent of our 468 patients had normal LDH values, whereas the highest median levels were observed among those patients who had concurrent AIDS-related or AIDS-unrelated malignancies (particularly lymphomas). Given the high LDH levels often observed among patients with several

Table 1. Characteristics of first episodes of HIV-related PJP observed at the Clinic of Infectious Diseases, Luigi Sacco Hospital, Milan, between January 1985 and June 2016; $N = 468$

Characteristic	
Period of PJP diagnosis, *n* (%)	
before 1997	276 (59)
after 1997	192 (41)
Gender, *n* (%)	
males	356 (76)
females	112 (24)
Age (years), median (range)	35 (21–75)
Characteristics of HIV infection, *n* (%)	
known HIV infection prior to PJP diagnosis	123 (26.3)
blood CD4 cells/μL	
<200	455 (97.2)
<50	298 (63.7)
PJP prophylaxis administered	65 (13.9)
AIDS-related comorbidities at time of PJP diagnosis	269 (57.5)
Clinical characteristics of PJP	
PaO_2 breathing room air upon admission, *n* (%)	
<60 mmHg	175 (37.4)
60–70 mmHg	127 (27.1)
>71 mmHg	166 (35.5)
serum LDH level (IU/L), median (range)	728 (98-5710)
normal serum LDH level, *n* (%)	98 (20.9)
serum LDH level in patients with concurrent neoplasia (IU/L) ($n = 49$), median (range)	854 (160–5710)
serum LDH level in patients with concurrent lymphoma (IU/L) ($n = 18$), median (range)	1279 (431–5710)
radiographic pattern, *n* (%)	
interstitial	316 (67.5)
alveolar	88 (18.8)
mixed	37 (7.9)
normal	27 (5.8)
presence of cysts or pneumothorax	15 (3.2)
presence of pleural effusion	8 (1.7)
initial treatment with trimethoprim/sulfamethoxazole, *n* (%)	402 (85.9)
adjunctive corticosteroids, *n* (%)	239 (51.1)
continuous positive airway pressure therapy required, *n* (%)	145 (31.0)
mechanical ventilation required, *n* (%)	23 (4.9)
30 day mortality, *n* (%)	
before 1997	38 (13.8)
after 1997	9 (4.7)

types of cancers, it may not be appropriate to use them as the basis for a suspicion of PJP, even in the context of HIV infection.

Finally, the 17%–30% mortality rate of HIV-positive patients shown in Table 2 of the paper by Cordonnier *et al.*[1] refers to studies conducted during the 1980s and early 1990s. Our early mortality rate of <5% confirms other reports[12] that the mortality of HIV-positive patients with PJP has significantly decreased since then due to the effects of HAART or to general improvements in ICU care.

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Transparency declarations

None to declare

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Pneumocystis jirovecii pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients—authors' response

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Sir,

We would like to thank Antinori *et al*.[1] for their comments on the European Conference on Infections in Leukemia (ECIL) guidelines for the management of *Pneumocystis jirovecii* pneumonia (PCP).[2]

Antinori *et al*.[1] listed four points, which we would like to address one by one.

Mode of acquisition of PCP in haematology patients

The mode of acquisition of PCP in haematology patients is uncertain, but there is no reason to think that it is different from that in other immunocompromised patients. Exposure to *P. jirovecii* through inhalation begins early in life, as shown by autopsy series, and PCR and serological screenings.[3–6] The high rate of mixtures of genotypes during PCP (up to 90%) also supports continuous exposure to *P. jirovecii* from the environment via other humans.[7] When investigating outbreaks in solid organ transplant units using genotyping, only some of the cases were shown to be due to inter-human or environmental transmission.[8,9] To our knowledge, only two outbreaks have been reported in haematology wards. The first one included five cases in 6 months in the same haematology unit, but without any molecular investigation.[10] The second study established a genetic link using internal transcribed spacer (ITS) sequencing between the strains for two out of eight haematology patients (and two out of six HIV-positive patients), suggesting that person-to-person transmission was relatively infrequent.[11] Recently, transmission between patients from different wards was reported with the help of six new short tandem repeat markers located in the nuclear genome.[12] However, even with this highly discriminant genotyping method, we could not differentiate between reactivation and a new infection.[12] Despite the lack of solid data reflected by a grading of only C-III, ECIL proposed that patients in haematology should, nonetheless, avoid contact with those infected with PCP.[13]

Differences in clinical presentation and hypoxaemia between patients with and without HIV infection

Antorini *et al*.[1] show that two-thirds of their patients with HIV infection had a $PaO_2 < 70$ mmHg. However, the PaO_2 of patients with PCP, but without HIV infection, was not presented. This makes any conclusion about PaO_2 at diagnosis difficult. We agree with Antorini *et al*.[1] that PaO_2 at presentation can be