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

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Introduction

Pneumocystis jirovecii pneumonia (formerly named Pneumocystis carinii pneumonia or PCP) was initially described in the middle of the last century in premature neonates and malnourished infants. Most recently, PCP has been reported in severely immunocompromised patients with cancer therapy or HIV infection.1,2 Initially classified as a protozoan on the basis of morphological characteristics of trophic and cyst forms, P. jirovecii was reclassified as an ascomycetous fungus following analysis of the ribosomal RNA (rRNA) subunit.3 Transmission of P. jirovecii occurs during the first years of life via person-to-person contact, mostly asymptotically or as a mild, self-limiting infection of the upper respiratory tract. Two-thirds of immunocompetent individuals have specific antibodies by the age of 4 years. PCP still carries a high mortality rate in haematology patients and transplant recipients. Early recognition of at-risk patients, and the disease, is critical for optimal management.

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Pneumocystis jirovecii can cause life-threatening pneumonia following treatment for haematological malignancies or after HSCT. The mortality rate of P. jirovecii pneumonia (PCP) in these patients is 30%–60%, especially after HSCT. The clinical presentation of PCP in haematology differs from that associated with HIV infection, with the disease being acute and more often severe, having a lower fungal burden and being more frequently linked to treatment with corticosteroids. Most cases occur in patients not receiving adequate prophylaxis. The development of new therapies, including targeted treatments and monoclonal antibodies in various haematological diseases, justifies constant vigilance in order to identify new at-risk populations and give prophylaxis accordingly. The fifth and sixth European Conferences on Infections in Leukaemia (ECIL-5 and ECIL-6) aimed to review risk factors for PCP in haematology patients and to establish evidence-based recommendations for PCP diagnosis, prophylaxis and treatment. This article focuses on the magnitude of the problem, the main differences in clinical presentation between haematology patients and other immunocompromised populations, especially HIV-infected patients, and the main risk factors.
Since 2005, the European Conference on Infections in Leukemia (ECIL) has aimed to produce recommendations for the management of infections in patients with haematological disorders, including HSCT recipients. During the fifth and sixth meetings (19–21 September 2013 and 11–12 September 2015, Nice, France) we developed guidelines for diagnosis, prophylaxis and treatment of PCP in HIV-negative haematology patients. Owing to a group decision aimed at adapting the presentation of the guidelines to the more recent international rules, the grading systems used for ECIL-5 (diagnosis of PCP; prophylaxis of PCP) and ECIL-6 (treatment of PCP) changed slightly. ECIL-6 experts used an evidence-based medicine grading system that adds accurate information about the source for grading the quality of evidence. These grading systems are both presented in Table 1 to facilitate their comparison. Following these two meetings, presentations summarizing the results were posted at www.kobe.fri/ecil on 28 March 2014 (laboratory diagnosis and prophylaxis) and 1 December 2015 (treatment of PCP). This introductory paper focuses on epidemiology, risk factors, presentation and outcome of PCP in haematology patients. Recommendations for laboratory diagnosis, prophylaxis and treatment are presented in three companion papers.5–6

**Epidemiology of and risk factors for PCP in haematology patients**

Before the 1980s, PCP was recognized as a severe, potentially life-threatening infection, mainly in patients with ALL7,8 and in HSCT recipients.7 Thereafter, the HIV pandemic led to an unusually high prevalence of PCP and provided useful insights on the management of this disease. Following the introduction of HAART, the incidence of PCP in developed countries dropped dramatically in HIV-infected patients. In ALL patients, adequate prophylaxis also markedly reduced the incidence from its high historical level; recent data now show incidences as low as 0.09% in patients treated prophylactically.10 Prophylaxis has also reduced the incidence in HSCT recipients. Nowadays, ALL patients or HSCT recipients who develop PCP are usually not receiving adequate prophylaxis11–16 or do not comply with their prescribed prophylaxis.10 Nevertheless, the number of PCP cases in HIV-negative patients continues to increase worldwide. In the UK, the incidence rose from 3.15 cases per million inhabitants per year between 2000 and 2005 to 5.13 cases between 2006 and 2010.15

**Risk factors for adult patients**

**Non-haematopoietic stem cell transplant recipients**

**Underlying diseases.** The risk of developing PCP is strongly influenced by the underlying disease and its specific treatment. Historically, ALL patients have always been at high risk of PCP.18 Other populations at risk include those with lymphoproliferative disorders (LPDs), including chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma (NHL) and multiple myeloma. Patients with ALL and LPD constitute the vast majority (up to 83%) of patients with PCP in the haematology ward.13,16,17

There are only anecdotal reports of PCP in chronic myeloproliferative disorders; a single case was reported in a patient treated with dasatinib plus rapamycin for CML.18 Patients with aplastic anaemia receiving anti-thymocyte globulin and cyclosporin A are usually not considered at risk, since no cases of PCP have been reported in three large studies.19–21 PCP is also rare in AML and myelodysplastic syndromes.22 The difference in attack rates between ALL and AML can partly be explained by the use of corticosteroids; whether other factors contribute to this difference is unknown.

**Table 1.** Grading systems used at ECIL-5 and at ECIL-6 for levels of evidence and strength of recommendations

<table>
<thead>
<tr>
<th>Level/grade</th>
<th>ECIL-5</th>
<th>ECIL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence (QoE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>evidence from ≥1 properly randomized, controlled trial</td>
<td>evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)</td>
</tr>
<tr>
<td>IIα</td>
<td>evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from &gt;1 centre); from multiple time-series studies; or from dramatic results from uncontrolled experiments</td>
<td>evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytical studies (preferably from &gt;1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees</td>
<td>evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees</td>
</tr>
</tbody>
</table>

| Strength of recommendation (SoR) | | |
| A | good evidence to support a recommendation for or against use | ECIL strongly supports a recommendation for use |
| B | moderate evidence to support a recommendation for or against use | ECIL moderately supports a recommendation for use |
| C | poor evidence to support a recommendation | ECIL marginally supports a recommendation for use |
| D | | ECIL supports a recommendation against use |

αLevel II evidence abbreviations: r, meta-analysis or systematic review of randomized controlled trial; t, transferred evidence, i.e. results from different patient cohorts or similar immune status situation; h, comparator group was historical control; u, uncontrolled trials; a, published abstract presented at an international symposium or meeting.
Pre-existing respiratory diseases. Pre-existing diseases such as chronic obstructive pulmonary disease and asthma have been associated with PCP.15

Lymphocytopenia and low CD4+ cell counts. Most haematology patients with PCP are lymphocytopenic.13,23–26 Patients usually have lower than normal CD4+ lymphocyte counts,16,17,26–28 with as many as 9 out of 10 having CD4+ numbers below 0.3 × 10^9/L.27 However, while a low CD4+ cell count is likely to be a risk factor, PCP has also been observed in patients with normal CD4+ cell counts.

Genetic predisposition. In mice, dectin-1 polymorphisms have been linked to the risk of hypoxaemia in experimental PCP.29 In addition, AIDS patients in sub-Saharan Africa are at lower risk compared with AIDS patients elsewhere.30 Nevertheless, a genetic marker that can identify patients at high risk of PCP has not yet been described.

Specific therapies

(a) Corticosteroids. Corticosteroid administration is the main pre-disposing factor for PCP in non-HIV-infected haematology patients: 90% have received corticosteroids in the month preceding diagnosis.12,27,28,31,32 However, a ‘threshold’ dose and duration that better defines the risk cannot be clearly discerned from the literature and, most probably, varies with the underlying disease and its treatment. Moreover, the daily dose seems to be inversely related to the duration of exposure.31 In a retrospective series of 142 patients without HIV infection, the mean duration of corticosteroid treatment was 2 months, with a maximum dose of 40 mg prednisone equivalent/day. However, seven patients had received treatment but at a maximum dose of 120 mg/day for only ≤1 month. In another series of 116 patients who were HIV negative, PCP had already developed after ≤8 weeks at daily doses of prednisone equivalent as low as 16 mg/day, although most cases of PCP occurred after 12 weeks of treatment.34 Based on these observations, others have recommended starting prophylaxis for patients receiving ≥20 mg prednisone equivalent/day for >1 month.32,35

(b) Chemotherapeutic agents. Chemotherapeutic agents associated with an increased risk of PCP include vincristine,16 cyclophosphamide,36 methotrexate37,38 and cytarabine (only in LPD).36 However, most of these reports are of cases or small case-controlled series. Fludarabine induces profound and prolonged lymphocytopenia38 and has been associated with an increased risk of PCP, even when administered without rituximab.39–41

(c) Monoclonal antibodies. Rituximab induces a profound and prolonged B cell defect; treatment with the drug is a risk factor for PCP, even when it is administered alone.33,42 When given in combination with CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone, one course every 14 days) to treat LPD, the addition of rituximab given every 2 weeks increased the risk of PCP from 4% to 13% in the absence of PCP prophylaxis.43–46 Dose intensity also increases the risk of PCP since cycles given every 14 days have a higher risk than cycles given every 21 days.46,47 Of note, the at-risk period may be delayed. One study that combined rituximab, fludarabine and cyclophosphamide in 66 patients (who received prophylaxis for up to 1 month after the end of therapy) showed a 12% incidence.46 However, seven out of eight cases occurred at a median of 6 months after the end of treatment.46

The humanized anti-CD52 monoclonal IgG1 antibody alemtuzumab induces long-lasting T cell suppression and the risk of PCP was recognized early on.47 In seven recent trials of alemtuzumab for the treatment of LPD, PCP prophylaxis was recommended until 2 months after completion of therapy. The incidence of PCP was 0.9% (4/417), with the only cases being seen in patients who had not received prophylaxis.48–50 Consequently, PCP remains a concern, whatever the indication for alemtuzumab.51

HSCT recipients

In the early 1980s, the risk of PCP in HSCT recipients without adequate prophylaxis was almost 16% within the first 6 months.5,56 Following this observation, most centres routinely initiated prophylaxis for 4 months after autologous HSCT and for at least 6 months following allogeneic HSCT. Larger series in the 1990s57–60 reported an incidence rate between 0%57,60 and 2.5% in allogeneic HSCT recipients58 and 1.4% in autologous HSCT recipients.57 There was only one report of an incidence of 7.2% after allogeneic HSCT among patients who could not tolerate trimethoprim/sulfamethoxazole and had received low doses of dapsone instead.61 Nowadays, PCP is rare in HSCT recipients unless patients do not comply with their prophylaxis. Given this rarity, it is difficult to determine risk factors as well as incidences in different types of HSCT.56 However, HSCT recipients who develop PCP have some particular characteristics.57–60,63,64 Most cases occur late, typically >6 months, and even up to several years after transplant.58 Most patients have acute or chronic graft-versus-host disease at diagnosis, with many receiving corticosteroids or other immunosuppressive drugs. It is not clear whether HSCT recipients with low circulating CD4+ cell counts are at higher risk than recipients with normal counts.

Risk factors for children. Children at risk of PCP include those with lymphoid malignancies, especially ALL and NHL, HSCT recipients, those being treated with corticosteroids, and patients with severe lymphocytopenia due to treatment with fludarabine, temozolomide or alemtuzumab, or who have severely impaired immunity following the administration of anti-TNF monoclonal antibodies. In the absence of prophylaxis, the incidence of PCP was 5%–15% in children undergoing HSCT, 22%–45% in patients with ALL or NHL, and around 25% in patients with severe combined immunodeficiency.65 In children, a corticosteroid dose of 16–20 mg/day or 0.4 mg/kg/day for ≥1 month is considered a significant risk of PCP.63,68 Other groups with an increased risk include patients with Wiskott–Aldrich syndrome, X-linked hyper-IgM, X-linked agammaglobulinemia, other inborn errors and solid tumours.43,67 Moreover, in several studies, children with AML who were at risk of PCP also received PCP prophylaxis.60,63,68

Presentation and outcome

Clinical presentation

PCP classically manifests with fever, non-productive cough, dyspnoea and diffuse interstitial pneumonitis both in children and adults. Extra-pulmonary infections have been reported, though...
almost exclusively in HIV-infected patients who were receiving aerosolized pentamidine as prophylaxis. 69

In the haematology population, fever is present in almost 90% of cases, though it may be absent or of low grade, especially when patients receive concomitant corticosteroids or antipyretic drugs. When PCP progresses slowly, respiratory symptoms may be minimal for several days. 26,28,31,58,70-72 Therefore, bronchoscopy with lavage should be performed promptly in high-risk patients when indirect and non-invasive methods have failed to demonstrate the aetiology of respiratory symptoms or isolated fever. 4

Despite obvious similarities, there are important differences in the presentation of PCP between patients with and without HIV infection (Table 2). Firstly, patients without HIV infection are more likely to receive corticosteroids at the time of diagnosis. 12,27,28,31,32 In some cases, PCP is only diagnosed after withdrawal or during tapering of the corticosteroid. So patients may be receiving low doses of the drugs at diagnosis. 73-75 In children and adolescents, PCP may also develop during phases of immune recovery (e.g. after reduction of immunosuppression, such as tapering of corticosteroids) or reduction in the dose intensity of chemotherapy (e.g. maintenance phase for ALL). 66,76 Therefore, the severity of disease might be more related to the inflammatory process rather than to the fungal burden. 25,77

A list of other features of PCP in haematology is shown below and these are summarized in Table 2:

- The disease is more often rapidly evolving, with a mean interval between first symptoms to diagnosis of only a few days. 71,77,78
- Hypoxaemia is more frequently present. 25,27,35
- Elevation of lactate dehydrogenase at diagnosis is less frequent 12 and has a poor predictive value. 79
- Patients have a lower number of P. jirovecii cysts in bronchoalveolar lavage (BAL) fluid and a higher number of inflammatory cells (especially neutrophils in BAL fluid), making diagnosis by staining and immunofluorescence more difficult. 25,35,71 The lower fungal burden and the decreasing gradient of colonization between alveoli and the upper respiratory tract further explain the low diagnostic yield of sputum examination for PCP in this population. 4
- Pulmonary co-infections seem to be particularly frequent in haematology. These are reported in 29%–75% of patients, mostly due to Staphylococcus aureus, Gram-negative bacilli, cytomegalovirus or Aspergillus spp. 12,26,28,34,80 PCP occurring after allogeneic HSCT is associated with cytomegalovirus pneumonia in about half of the cases. 26 Hence, a diagnostic strategy exclusively focused on the detection of PCP runs the risk of missing clinically important co-pathogens. It is unclear whether these co-infections, particularly with herpes viruses, 81 are a risk factor for developing PCP or just a marker of profound immunosuppression.

### Imaging

Initially the conventional chest X-ray may be normal 26,28,31,70-72,82 but it can rapidly evolve to diffuse, interstitial pneumonia in 60%–80% of cases. 13,83 Alveolar or alveolo-interstitial patterns are less frequent than in HIV infection. Multi-slice or high-resolution CT scanning is more sensitive, 84 though none of the radiological features is very specific or pathognomonic for PCP. Usually the CT scan shows bilateral, patchy ground-glass opacities, predominantly in the perihilar regions without affecting the periphery. Consolidations can be present. Cysts are detected in 10% of cases, especially in the upper lobes, and may lead to pneumothorax. 25,26,78,85 Pleural effusions are rare, except for HSCT recipients. 26 Single or multiple nodules have also been reported. 72,78,86 Of note, patients in haematology tend to have more cystic lesions and fewer ground-glass opacities. 72,86 Unusual imaging features, including the reversed halo sign or cavities, have also been described. 87,88 Additionally, co-infections may influence imaging features.

Fluorodeoxyglucose (FDG) integrated with computed tomography (FDG–PET) shows an increased uptake of FDG in the lungs; however, this is not specific. Hence, PET scans should not be used routinely to diagnose PCP. 82,89

### Diagnosis

Bronchoscopy with BAL remains the gold standard method for diagnosing PCP in non-HIV-infected haematology patients.

### Table 2. Main differences in clinical presentation of Pneumocystis pneumonia between HIV-positive and HIV-negative patients

<table>
<thead>
<tr>
<th>Difference</th>
<th>HIV-positive</th>
<th>HIV-negative</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP may reveal the underlying disease</td>
<td>yes</td>
<td>exceptional (three cases of adult T cell leukaemia due to HTLV infection revealed by PCP)</td>
<td>90,91</td>
</tr>
<tr>
<td>Corticosteroids received before the diagnosis of PCP</td>
<td>no</td>
<td>yes (90%), mostly during tapering or after withdrawal</td>
<td>12,27,28,31,32</td>
</tr>
<tr>
<td>Onset</td>
<td>progressive</td>
<td>acute</td>
<td>71,86,92</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis</td>
<td>long (3–5 weeks)</td>
<td>short (4–8 days)</td>
<td>72,78,86</td>
</tr>
<tr>
<td>Hypoxaemia</td>
<td>mild</td>
<td>often severe</td>
<td>25,27,35</td>
</tr>
<tr>
<td>LDH elevation</td>
<td>good</td>
<td>low</td>
<td>12,79</td>
</tr>
<tr>
<td>Specificity and sensitivity levels</td>
<td>high</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Characteristics of BAL fluid</td>
<td>high number of cysts; few neutrophils</td>
<td>low number of cysts; many neutrophils</td>
<td>25,35,71</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>17%–30%</td>
<td>28%–53%; especially high after HSCT</td>
<td>13,26,28,31,70,80</td>
</tr>
</tbody>
</table>

HTLV, human T cell leukaemia virus; LDH, lactate dehydrogenase.
because (i) the low number of cysts compared with the high number in HIV-positive patients impairs the diagnostic yield of using upper respiratory tract samples, and (ii) BAL is the preferred method to identify or exclude pulmonary co-infections. The ECIL guidelines on laboratory diagnosis of PCP in haematology patients are presented in a companion paper.4

Mortality rates remain very high in haematology patients, from 30% to 59%,14,26,31,70,71,80 especially in HSCT recipients (48%–70%),14,26,63 compared with 17%–30% in patients with HIV infection.

Conclusions

Although rare, PCP is a severe, but preventable disease. The main haematology populations at risk are patients with ALL and allogeneic HSCT recipients; in the absence of adequate prophylaxis the risk ranges between 15% and 45%. Absence of prophylaxis or poor compliance are the main risk factors in high-risk populations. PCP deserves constant attention in haematology patients in order to identify new at-risk populations, implement prophylactic procedures and check medication compliance. Three companion papers will present the ECIL guidelines for laboratory diagnosis,4 prevention5 and treatment6 of PCP.

Acknowledgements

We thank Patricia Munoz (Madrid) and J. Peter Donnelly (Nijmegen) for their helpful support of the plenary debate of this guideline at ECIL-5. We also thank Jean-Michel Gosset and the staff of KOBE, group Global-Events, Lyon, France, for the organization of the ECIL-5 meeting.

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Funding

The ECIL-5 meeting was supported by unrestricted educational grants from Astellas Pharma, Gilead Sciences, Merck, and Pfizer. The ECIL-6 meeting was supported by unrestricted educational grants from Basilea, Gilead Sciences, Merck, and Pfizer.

Transparency declarations

S. B. received a consultant honorarium from Myconostica. All the remaining authors have none to declare.

Author contributions

All authors developed the content of the manuscript. C. C. and J. M. drafted the manuscript and all authors approved the final version.

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