

## ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients

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The initiation of systemic antimicrobial treatment of *Pneumocystis jirovecii* pneumonia (PCP) is triggered by clinical signs and symptoms, typical radiological and occasionally laboratory findings in patients at risk of this infection. Diagnostic proof by bronchoalveolar lavage should not delay the start of treatment. Most patients with haematological malignancies present with a severe PCP; therefore, antimicrobial therapy should be started intravenously. High-dose trimethoprim/sulfamethoxazole is the treatment of choice. In patients with documented intolerance to this regimen, the preferred alternative is the combination of primaquine plus clindamycin. Treatment success should be first evaluated after 1 week, and in case of clinical non-response, pulmonary CT scan and bronchoalveolar lavage should be repeated to look for secondary or co-infections. Treatment duration typically is 3 weeks and secondary anti-PCP prophylaxis is indicated in all patients thereafter. In patients with critical respiratory failure, non-invasive ventilation is not significantly superior to intubation and mechanical ventilation. The administration of glucocorticoids must be decided on a case-by-case basis.

### Introduction

The impact of *Pneumocystis jirovecii* pneumonia (PCP) on morbidity and mortality of immunocompromised patients is substantial. Up to 40% of patients with acute lymphoblastic leukaemia or lymphoproliferative diseases are affected, unless systemic prophylaxis is given.<sup>1</sup> Patients with PCP have an almost 50% incidence of acute lung injury,<sup>2</sup> while survivors have a higher risk of long-term deterioration of lung function (chronic lung injury) than survivors of bacterial pneumonia.<sup>3</sup> In HIV-positive patients, outcome has been improved over the past few decades by early diagnosis, refined intensive care management (low tidal volume, conservative fluid management), identification and effective treatment of co-infections, adjunctive glucocorticosteroids (GCS; in patients with an oxygen partial pressure PaO<sub>2</sub> <9.3 kPa), secondary PCP prophylaxis and early combination antiretroviral therapy.<sup>4</sup> We aimed to provide an updated, evidence-based guideline for the treatment and secondary prevention of PCP in patients with haematological diseases. Separate guidelines by

ECIL expert groups focus on epidemiology, risk factors, diagnosis and prevention of PCP.<sup>5–7</sup>

### Methodology

#### Search criteria

A systematic literature review was performed using the PubMed database for publications up to September 2015 for the following MeSH terms: 'pneumocystis OR *Pneumocystis carinii* OR *Pneumocystis jirovecii* AND pneumonia'; 'pneumonia AND neutropenia OR treatment OR haematological malignancies OR stem cell transplantation'. The group co-authoring this manuscript reviewed the 195 publications identified and prepared a slide set comprising evidence-based statements and recommendations presented to the plenary session at the ECIL-6 meeting, 11–12 September 2015, Nice, France. After revision according to the results of the plenary discussion, a summarizing slide set was made available at [www.kobe.fr/ecil](http://www.kobe.fr/ecil) in November 2015. The final manuscript has been written and revised by all co-authors. Recommendations were graded according to the ECIL-6 evidence-based medicine (EBM) grading system, compatible with the EBM grading system of ESCMID.<sup>6,8</sup>

## Symptoms of PCP in haematology patients

Among 55 patients with haematological malignancies who had PCP during the period 1990–99, the characteristic clinical presentation was acute onset with fever (86%), dyspnoea (78%), non-productive cough (71%) and severe hypoxaemia (71%), while thoracic pain (14%) and chills (5%) were less commonly observed.<sup>9</sup> In another retrospective analysis of 56 patients, of whom 44 (78.6%) had haematological malignancies, 18 had undergone HSCT and 12 patients had solid tumours, the main symptoms were fever (85.7%), dyspnoea (78.6%) and cough (57.1%). Their clinical course was rather acute with a median time from symptom onset of 7 (3–14) days. PCP presented as severe pneumonia [ $\text{PaO}_2$ , 58 mmHg/Torr (range 50–70)] with bilateral interstitial infiltrates (80.4%) and bilateral ground-glass attenuation (89.3%) on CT scans. Twenty-four patients (42.9%) required referral to an ICU, 11 (19.6%) underwent mechanical ventilation, and 11 patients died.<sup>10</sup>

Importantly, a wide range of co-infections, particularly pulmonary, are present in 28%–71% of patients, with multiple potentially involved pathogens such as *Staphylococcus aureus*, Gram-negative bacteria, *Aspergillus* species or cytomegalovirus (CMV).

In allogeneic HSCT recipients, PCP is associated with CMV pneumonia in ~50% of cases.<sup>11–14</sup>

## Criteria for initiation of PCP treatment

As delay of treatment increases the need for mechanical ventilation and mortality, prompt initiation of PCP-specific treatment is of critical importance.<sup>15–18</sup> Initiation of treatment should not be deferred by diagnostic procedures, such as bronchoalveolar lavage (BAL), since *P. jirovecii* remains detectable in bronchial secretions for many days after the start of systemic treatment.<sup>19</sup> PCP is highly likely in patients at risk who present with clinical symptoms mentioned above.<sup>20</sup> Prompt diagnostic procedures and antimicrobial treatment against *P. jirovecii* should be triggered by composite criteria (**A-III**) (Figure 1), as single clinical diagnostic criteria are insufficient to prove the diagnosis.

## Grading of PCP severity and prognostic factors

For the decision on the planned duration and the route of administration of systemic antimicrobial treatment, PCP in HIV-positive

patients has been categorized as mild, moderate or severe (Table 1).<sup>21</sup> For moderate and severe PCP, treatment recommendations do not differ substantially. In non-HIV patients, differentiation of PCP severity has not been specifically addressed in prospective clinical studies. However, recommendations regarding first-line antimicrobial treatment refer to a grading of PCP severity also in non-HIV patients, while in clinical practice most non-HIV patients do have severe disease at the time of diagnosis. It appears therefore appropriate to grade the severity of PCP in non-HIV patients into mild versus moderate-to-severe (**B-III**). For assessment of PCP severity, the use of conventional grading systems used for community-acquired pneumonia (such as A-DROP, CURB-65 or Pneumonia Severity Index) has been shown to underestimate the severity of PCP in non-HIV patients;<sup>22</sup> therefore, their use in this setting is not recommended (**D-IIu; formerly B-II against use**). The grading system of Miller<sup>21</sup> appears to provide the most useful criteria for PCP severity assessment in non-HIV patients (**B-III**). Importantly, not only oxygen saturation should be used, but also clinical criteria such as respiratory rate, age, co-morbidities or additional organ dysfunction must be taken into account (**A-IIu, formerly A-II**).

For prediction of poor clinical outcome in non-HIV patients with PCP, both factors present at treatment onset and factors presenting later during antimicrobial therapy have been identified (Table 2).

## First-line treatment

### Selection of drugs

In haematological patients, prospective randomized clinical trials on the optimal selection of antimicrobial agents for the treatment of PCP have not been conducted. Therefore, therapeutic recommendations are based on those in HIV-associated PCP and observational studies on treatment including haematological patients (Table 3). In a comprehensive literature review, we have assessed the outcome of different treatment regimens among non-HIV patients with PCP. Published reports on treatment results in this patient cohort included ~800 patients treated first-line with trimethoprim/sulfamethoxazole<sup>23–27</sup> and <40 patients who received this regimen in combination with other antimicrobials or other drugs including pentamidine, atovaquone or primaquine/clindamycin.<sup>9,13,28–31</sup> For first-line treatment (Table 4),

- Patient at risk
  - with
- Clinical signs and symptoms
  - Dyspnoea and/or cough
  - Fever (may rarely be absent)
  - Hypoxaemia (may not yet be present)
  - Chest pain (rare; from pneumothorax)
- with
- Suggestive radiology finding compatible with PCP (preferably thoracic CT scan)
  - with or without
- Unexplained serum lactate dehydrogenase (LDH) elevation

**Figure 1.** Indication for starting systemic antimicrobial treatment against *P. jirovecii* in patients with haematological diseases.

**Table 1.** Grading of severity of *Pneumocystis pneumonia*<sup>21</sup>

Variable	Severity grading		
	mild	moderate	severe
Symptoms and signs	increasing exertional dyspnoea with or without cough and sweats	dyspnoea on minimal exertion, occasional dyspnoea at rest, fever with or without sweats	dyspnoea at rest, tachypnoea at rest, persistent fever, cough
Arterial oxygen tension (PaO <sub>2</sub> ) at rest, room air	>11.0 kPa (>82.5 mmHg)	8.1–11.0 kPa (60.75–82.5 mmHg)	<8.0 kPa (<60 mmHg)
Arterial oxygen saturation (SaO <sub>2</sub> ) at rest, room air	>96%	91%–96%	<91%
Chest radiograph	normal or minor perihilar shadowing	diffuse interstitial shadowing	extensive interstitial shadowing with or without diffuse alveolar shadowing ('white out') sparing costophrenic angles and apices

**Table 2.** Poor prognostic factors for outcome in non-HIV patients with PCP<sup>13,20,23,25,28,31,40,56,75</sup>**Poor prognostic factors at onset**

Poor control of underlying disease  
 ECOG PS >2  
 Long-term glucocorticosteroids  
 Delayed onset of PCP treatment  
 Hypoalbuminaemia  
 Co-infection with HSV or CMV  
 High neutrophil count in BAL  
 High APACHE-II or SAPS-II score

**Poor prognostic factors during PCP treatment**

Vasopressor use/shock  
 Need for high-dose glucocorticosteroid treatment  
 Respiratory failure/high oxygen support  
 Need for mechanical ventilation  
 ARDS  
 Clinical worsening at day 8

ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; ECOG, Eastern Cooperative Oncology Group; HSV, herpes simplex virus; PS, performance score; SAPS, simplified acute physiology score.

trimethoprim/sulfamethoxazole at a dosage of 15–20 mg/kg (trimethoprim) and 75–100 mg/kg (sulfamethoxazole) for  $\geq 14$  days is recommended as primary choice (**A-IIr, formerly A-II**). Co-medication with methotrexate should be avoided because of potentially serious adverse drug effects. For very obese patients, no specific dose limits have been defined. While not routinely available, therapeutic drug monitoring may be recommended in individual patients<sup>32,33</sup> with target peak concentration for sulfamethoxazole of 100–200 mg/L.<sup>34</sup> Alternative treatment regimens for patients with contraindications to trimethoprim/sulfamethoxazole include intravenous pentamidine (4 mg/kg/day),<sup>29</sup> primaquine/clindamycin (30 mg/day + 600 mg every 8 h daily)<sup>30</sup> and atovaquone (750 mg every 8–12 h daily)<sup>30,31</sup> (**C-IIi, formerly C-II**, for each regimen). Prior to the use of primaquine, patients

should be checked for glucose-6-phosphate dehydrogenase deficiency.

**Route of administration**

In patients with mild PCP (which are rarely seen in haematology), an oral strategy is possible from the beginning for compliant patients in whom enteral absorption is not compromised (**B-IIi, formerly B-II**).<sup>35</sup> The dosage of drugs should be identical for oral and intravenous administration (**A-IIi, formerly A-II**). In patients with moderate-to-severe PCP, treatment should be started intravenously (**A-IIu, formerly A-II**). A switch to oral therapy can be considered, once clinical improvement is achieved in compliant patients in whom enteral absorption is not compromised (**A-IIu, formerly A-II**).<sup>36,37</sup>

**Assessment of treatment response**

The efficacy of systemic antimicrobial treatment should be assessed on a daily basis. While early clinical deterioration (within the first 3–5 days after treatment initiation) is common, re-evaluation should not be done before 8 days of full-dose treatment (**A-III**). In a study on non-HIV patients with PCP, radiologic improvement by repeated thoracic CT scan during treatment was seen in 57% of patients at a median of 13 days after initiation of therapy.<sup>38</sup>

In patients without clinical improvement and/or with worsening of respiratory function documented by arterial blood gases after 8 days of adequate anti-PCP treatment, clinical failure should be suspected.  $\beta$ -D-Glucan monitoring is not recommended for response assessment (**D-IIu**), as there are conflicting data for serum  $\beta$ -D-glucan during the course of PCP; elevated levels may indicate treatment failure or another fungal co-infection, whereas decreasing levels are not clearly predictive of treatment success.<sup>29,39</sup>

In patients with clinically documented treatment failure at day 8, a repeat bronchoscopy and BAL to look for co-infections should be ordered (**A-III**). Co-infections are present in 20% of patients at time of admission to an ICU, while another 22% of patients with PCP acquire relevant second infections during ICU treatment.<sup>40</sup>

**Table 3.** Studies on first-line and salvage antimicrobial treatment of PCP

Population	Intention	Intervention	References	Comment
First-line treatment HM, SOT, cancer, autoimmune/inflammatory diseases	cure	TMP/SMX 15–20 mg/kg (TMP) 75–100 mg/kg (SMX) per day for ≥14 days	9,24,26–29,31,45	no randomized trials; high number of cases; low toxicity
		pentamidine iv 4 mg/kg/day	29	retrospective; 5 non-HIV patients
		primaquine + clindamycin 30 mg/day + 600 mg×3/day	30	retrospective; 5 non-HIV patients
		atovaquone 750 mg×2 (or 3)/day	30,31	retrospective; 3 non-HIV patients
Second-line (salvage) treatment HM, SOT, cancer, autoimmune diseases	cure	primaquine (30 mg) + clindamycin (600 mg×3) per day	23,44,45	few cases
		pentamidine iv 4 mg/kg/day	9,28,44,45	few cases
		TMP/SMX (15–20 mg/kg) + caspofungin (70–50 mg/day)	47–49	few cases, no haematological patients
		echinocandin alone	76,77	only case reports

HM, haematological malignancies; iv, intravenously; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

**Table 4.** Recommended first-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune/ inflammatory diseases	to cure	TMP/SMX 15–20 mg/kg (TMP) 75–100 mg/kg (SMX) per day for ≥14 days	<b>A</b>	<b>IIr</b>
		pentamidine iv 4 mg/kg/day	<b>C</b>	<b>IIt</b>
		primaquine + clindamycin 30 mg/day oral + 600 mg×3/day iv or oral	<b>C</b>	<b>IIt</b>
		atovaquone 750 mg×2(or 3)/day oral	<b>C</b>	<b>IIt</b>

HM, haematological malignancies; iv, intravenously; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

For evaluation of BAL findings, the persistence of a positive *P. jirovecii* PCR should not be interpreted as treatment failure (**D-IIIt, formerly A-II against use**), as *P. jirovecii* will remain detectable for days or even weeks under systemic anti-PCP treatment.<sup>19</sup> With respect to BAL *P. jirovecii* load using quantitative PCR, there are currently no data on the kinetics under treatment. For β-D-glucan in follow-up BAL, no data from clinical studies have been reported so far.

In addition, a new thoracic CT scan should be ordered to monitor the course of PCP-related lung infiltrates and to check for PCP complications such as spontaneous pneumothorax or pleural effusion (**A-III**).<sup>13</sup>

An unnecessary switch to second-line PCP treatment in patients receiving high-dose trimethoprim/sulfamethoxazole should be avoided (**A-IIIt, formerly A-II**), as the efficacy of second-line treatment is less well documented than that of front-line trimethoprim/sulfamethoxazole. A switch to second-line treatment should therefore only be considered after exclusion of a co-infection or another cause of (clinical and/or radiologic) deterioration.

Dihydropteroate synthase gene mutations, while associated with failure of sulfa-based PCP prophylaxis,<sup>41</sup> are not associated

with failure of high-dose trimethoprim/sulfamethoxazole treatment in HIV-positive or -negative patients.<sup>42,43</sup>

### Salvage treatment (second-line treatment)

In patients with intolerance to or treatment failure under high-dose trimethoprim/sulfamethoxazole treatment, second-line (or 'salvage') therapy is required (Table 5). While clinical trials on this indication in non-HIV patients have not been reported, reports from the literature<sup>23,44,45</sup> suggest that first choice of drugs in this setting is the combination of primaquine and clindamycin (**B-IIIt, formerly B-II**). In the setting of HIV-positive patients with PCP, Helweg-Larsen *et al.*<sup>46</sup> reported the results of a large observational study, in which second-line treatment with primaquine/clindamycin was superior to pentamidine, translating into reduced mortality. Prior to the use of primaquine, patients should be checked for glucose-6-phosphate dehydrogenase deficiency. Alternatives are intravenous pentamidine (4 mg/kg/day) (**B-III**)<sup>9,28,44,45</sup> or the combination of high-dose trimethoprim/sulfamethoxazole with caspofungin (70–50 mg per day) (**C-IIu, formerly C-II**); however, the possible efficacy of this combination

**Table 5.** Options for second-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune diseases	cure	primaquine (30 mg) + clindamycin (600 mg×3) per day	<b>B</b>	<b>II<sub>t</sub></b>
		pentamidine iv 4 mg/kg/day	<b>B</b>	<b>III</b>
		TMP/SMX (15–20 mg/kg/day) + caspofungin (70–50 mg/day)	<b>C</b>	<b>II<sub>u</sub></b>
		echinocandin alone	<b>D</b>	<b>II<sub>u</sub></b>

HM, haematological malignancies; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

**Table 6.** PCP treatment: main drug-related adverse events

TMP/SMX	Clindamycin/primaquine	Pentamidine iv
<ul style="list-style-type: none"> <li>rash and fever</li> <li>nephrotoxicity</li> <li>electrolyte disorders</li> <li>bone marrow depression</li> <li>hepatotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>nausea and vomiting</li> <li>neutropenia</li> <li><i>Clostridium difficile</i>-associated diarrhoea</li> <li>haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency</li> </ul>	<ul style="list-style-type: none"> <li>bone marrow suppression</li> <li>nephrotoxicity</li> <li>electrolyte disorders</li> <li>dysglycaemia, insulin-dependent diabetes mellitus</li> <li>pancreatitis</li> <li>Q-T prolongation</li> </ul>

TMP/SMX, trimethoprim/sulfamethoxazole.

has only been reported in individual patients.<sup>47–49</sup> An echinocandin alone should not be considered (**D-II<sub>u</sub>, formerly A-II against use**), because a sufficient anti-PCP efficacy has not been demonstrated,<sup>45,50</sup> and reports of breakthrough PCP in patients being treated with an echinocandin for other purposes have been published.<sup>51</sup>

## Drug-related side effects and drug–drug interactions

Most of the drugs recommended for PCP treatment are associated with a substantial rate of drug-related adverse events (AEs). While a detailed discussion of these potential AE exceeds the scope of this guideline, an overview of the main side effects is given in Table 6.

Clinically important drug–drug interactions may be relevant in patients being treated for PCP. Atovaquone interacts with rifampicin and rifabutin, clindamycin with macrolide antibiotics, dapsone with rifampicin, trimethoprim and probenecid, pentamidine with foscarnet, and trimethoprim/sulfamethoxazole with dapsone and rifampicin. It is of utmost importance to check all co-medications for drug–drug interactions in patients treated for PCP.

## Treatment duration

Standard duration of drug treatment in PCP is 3 weeks (**B-II<sub>t</sub>**). In mild cases, it should be at least 2 weeks (**A-II<sub>t</sub>, formerly A-II**). In case of slow clinical improvement, the unmodified treatment

should be continued for at least 3 weeks (**A-II<sub>u</sub>, formerly A-II**).<sup>13,30</sup>

## ICU management

Short- and long-term survival rates of ICU patients with haematological malignancies have improved markedly in recent years,<sup>52,53</sup> and haematological outcomes may not be affected by temporary organ dysfunction(s).<sup>52,54,55</sup> Therefore, evidence-based expert consensus recommends full ICU support for a growing number of patients.<sup>53</sup>

Almost every second patient with haematological malignancy and PCP develops acute respiratory failure (ARF) requiring ICU admission.<sup>9,10,56</sup> While mortality rates of non-HIV patients with PCP-associated ARF are generally higher than in HIV-positive patients,<sup>57–59</sup> the prognosis of haematological patients with PCP-associated ARF may not be different from ARF due to other aetiologies.<sup>60</sup> In patients with haematological malignancies, any signs or symptoms of respiratory deterioration (dyspnoea, cough, sputum, chest pain, rales, haemoptysis, increasing pulmonary infiltrates, demand for O<sub>2</sub> >1 L/min) are associated with the development of ARF, ICU admission and adverse outcome.<sup>61,62</sup> Timely recognition of such situations in patients with PCP is crucial, since late ICU transfers are associated with increased mortality rates (**A-II<sub>h</sub>, formerly A-II**).<sup>63,64</sup>

Historical data suggested that non-invasive ventilation (NIV) was associated with reduced intubation rates and improved mortality in immunosuppressed patients with hypoxic ARF, when compared with standard oxygen.<sup>65</sup> In accordance, a current meta-analysis of earlier, mainly observational data showed a survival benefit with NIV used as an initial ventilatory strategy when compared with invasive mechanical ventilation in patients with haematological malignancies.<sup>66</sup> However, a recently published large propensity score matched analysis in haematological patients<sup>67</sup> and a large interventional trial in immunosuppressed (mainly haematological) patients with hypoxic ARF did not show any harm or benefit of early NIV when compared with standard oxygen.<sup>68</sup> The discussion of these study results prompted a revision of the provisional preference (**B-I**) of the group for NIV, as stated in the original ECIL-6 slide set. While survival rates of primarily intubated haematological patients with ARF have improved steadily over the last two decades,<sup>60</sup> NIV failure with secondary intubation may be associated with excess mortality in (at least subgroups of) haematological patients.<sup>66,69–71</sup> In general, NIV failure rates in haematological patients with severe hypoxic ARF (acute respiratory distress syndrome)<sup>60</sup> and specifically in those with PCP are particularly high (~70%).<sup>58</sup> If clinicians decide to

**Table 7.** Adjunctive GCS in non-HIV patients with PCP

First author (year)	Number (haematological malignancy)	Years	n (%); mortality (%)		Mortality, total (%)
			with GCS	without GCS	
Bollée <sup>a</sup> (2007) <sup>10</sup>	56 (44)	2001–06	21 (38); 10	35 (62); 26	20
Burke (1973) <sup>78</sup>	46 (20)	1959–71	—	—	80
Delclaux (1999) <sup>79</sup>	31 (24)	1988–96	23 (74); 39	8 (26); 50	42
Overgaard <sup>b</sup> (2007) <sup>80</sup>	44 (33)	2002–04	33 (77); 12	11 (23); 20	14 (PCP)
Kofteridis (2014) <sup>26</sup>	62 (31)	2004–13	50 (81); 30	12 (19); 25	29 (PCP)
Lemiale <sup>a</sup> (2013) <sup>40</sup>	139 (55)	1988–2011	107 (77); 26	32 (23); 25	26 (ICU)
Moon (2011) <sup>27</sup>	88 (26)	2007–10	59 (67); 31	29 (33); 34	32 (3 months)
Pagano (2002) <sup>9</sup>	55 (55)	1990–99	22 (37); 36	33 (63); 36	29 (PCP)
Pareja <sup>a</sup> (1998) <sup>81</sup>	30 (8)	1989–95	16 (53); 44	14 (47); 36	40
Roblot (2002) <sup>31</sup>	103 (60)	1995–99	58 (56); ND	42 (51); ND	38 (1 month)
Zahar <sup>a</sup> (2002) <sup>82</sup>	39 (28)	1989–99	33 (79); 68	6 (15); 20	33 (3 months)

GCS, glucocorticosteroids; ND, no difference.

<sup>a</sup>Substantial overlap of patients.

<sup>b</sup>Data reanalysed in 2015 by J. H.-L.

use NIV as primary ventilation strategy, the development of incipient NIV failure must be monitored closely: poor tolerance of NIV, no clinical improvement within 6 h, no improvement of arterial blood gases within 6 h, respiratory rate remaining >30/min, NIV dependency >3 days, clinical or respiratory deterioration, unknown aetiology of ARF (**A-IIh, formerly A-II**).<sup>72</sup> If NIV failure becomes imminent, patients must be evaluated for prompt intubation and invasive mechanical ventilation (**A-III**).

## Glucocorticosteroids as adjunctive therapy in non-HIV patients with PCP

In HIV-positive patients with moderate-to-severe PCP, evidence derived from a meta-analysis on six randomized controlled trials suggests a survival benefit of adjunctive GCS therapy.<sup>73</sup> Accordingly, in these patients, adjunctive GCS are strongly recommended by current guidelines.<sup>74</sup> However, there are no interventional trials in non-HIV patients with PCP and the results of several retrospective observations are conflicting. All reports have typical limitations of retrospective observational analyses with a substantial risk of confounding by indication: most report on small patient numbers, different doses and (often non-reported) timing of GCS treatment, different definitions regarding PCP severity, as well as considerably heterogeneous cohorts with respect to underlying diseases and proportions of haematological malignancies. No detailed data on patients with leukaemia (or subgroup analyses) are available. Furthermore, there may be considerable patient overlap between some studies (Table 7). The most recent investigation with the largest number of patients performed a pooled analysis of 139 non-HIV ICU patients with severe PCP by first employing multi-variable statistics. High-dose GCS treatment (>1 mg/kg body-weight per day) was an independent predictor of ICU mortality but not associated with the rate of ICU-acquired infections.<sup>40</sup>

The routine adjunctive use of GCS in non-HIV patients with PCP and respiratory failure is not recommended. The decision to add GCS in a non-HIV patient with PCP and respiratory failure has to be made on an individual basis (**B-IIh, formerly B-II**). A significant

proportion of non-HIV patients with PCP have been treated with GCS prior to PCP onset. It remains unclear how to treat these patients (maintaining the dose versus escalation versus tapering). Investigational trials on the use of GCS accounting for previous GCS treatment and PCP severity are needed in haematology patients with PCP.

## Secondary anti-PCP prophylaxis

All non-HIV patients who have been successfully treated for PCP, should be given secondary anti-PCP prophylaxis (**A-IIh, formerly A-II**). Preferred and alternative regimens for secondary PCP prophylaxis should be chosen as for primary prophylaxis.<sup>7</sup> Co-medication with methotrexate may cause substantial toxicity.

A stopping rule for secondary PCP prophylaxis in patients whose immune system is recovering has not yet been defined; therefore, the decision to discontinue secondary PCP prophylaxis has to be made on an individual basis.

## Conclusions

Early treatment of PCP through intravenous antimicrobial therapy is of high importance in patients with haematological malignancies, and high-dose trimethoprim/sulfamethoxazole is currently the treatment of choice. Recent recommendations from ECIL-6 provide updated, evidence-based guidelines for the treatment of PCP in this patient population, including guidance on first-line and salvage treatment, therapy duration, assessment of the treatment response and ICU management in non-HIV patients with PCP.

High-dose trimethoprim/sulfamethoxazole for over 2 weeks remains the recommended treatment in non-HIV patients with PCP (**A-II**), with primaquine plus clindamycin the preferred second-line therapy (**B-II**). The routine adjunctive use of GCS in non-HIV patients with PCP and respiratory failure is not recommended but may be used on an individual patient basis (**B-IIh**).

These recommendations should assist healthcare professionals in making timely and effective decisions in regards to treatment of PCP in this patient population.

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### ECIL-6 meeting participants

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## Author contributions

All authors developed the content of the manuscript. G. M. drafted the manuscript, and all authors approved the final version.

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