Pneumocystis jirovecii Pneumonia (PcP) in non HIV-Infected Hematology Patients: *Treatment Guidelines*

Final slide set; 23NOV15

Georg Maschmeyer (Germany, chair)

Jannik Helweg-Larsen (Denmark)

Livio Pagano (Italy)

Christine Robin (France)

Peter Schellongowski (Austria)

EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

ECIL 6 meeting
Juan-les-Pins, France
Sept. 11-12, 2015

ECIL-6 (2015)

Grading System

STRENGTH OF RECOMMENDATION (SoR)	
Grade	**Definition**
A	ECIL strongly supports a recommendation for use
B	ECIL moderately supports a recommendation for use
C	ECIL marginally supports a recommendation for use
D	ECIL supports a recommendation against use
QUALITY OF EVIDENCE (QoE)	
Level	**Definition**
I	Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)
II*	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from > 1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
ADDED INDEX FOR SOURCE OF LEVEL II EVIDENCE	
***Index**	**Source**
r	Meta-analysis or systematic review of RCT
t	Transferred evidence, that is, results from different patients'cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

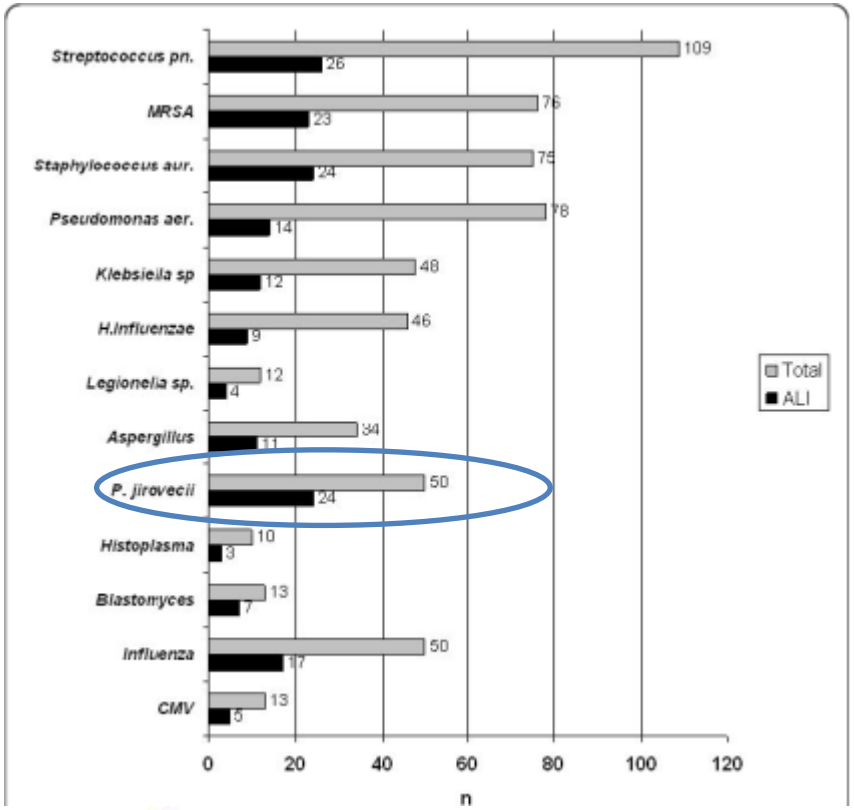
Questions to be addressed

- Background and clinical symptoms
- Criteria for initiation of PcP treatment
- Grading of PcP severity
- Prognostic factors
- First-line treatment (incl. route and duration)
- Assessment of treatment response
- Salvage treatment (2nd-line treatment)
- Management of side effects
- Intensive care management
- Adjunctive corticosteroids
- Secondary prophylaxis

PcP: Risk of ARDS/Acute & Chronic Lung Injury

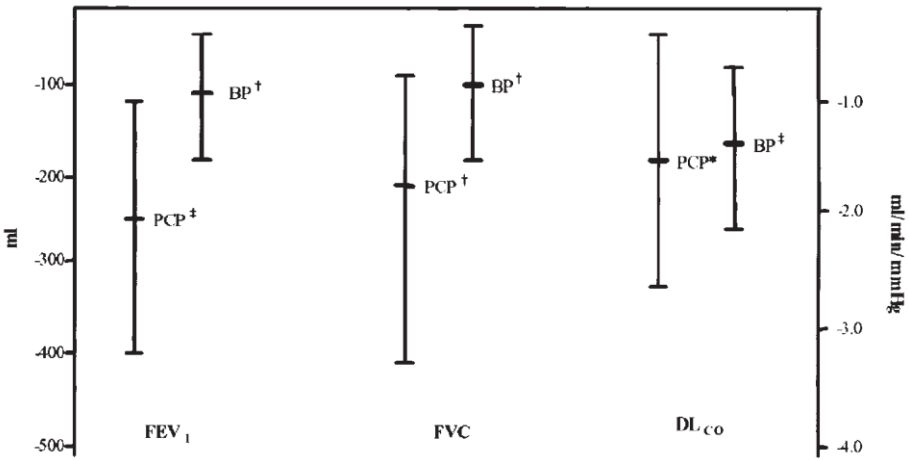
Increased risk of acute lung injury/ARDS

Mayo Clinic 2005-2007; *Kojicic M et al. Crit Care 2012;16:R46*



Permanent decline in lung function after HIV-PcP: significantly higher than bacterial pneumonia (BP); n=141.

Morris A et al. AJRCC 2000;162:612-6



ARDS: Acute respiratory distress syndrome

PcP: Factors for Improved Outcome in HIV-Positive Patients

- Early diagnosis
- Secondary PcP prophylaxis
- Adjunctive steroids (PaO_2 < 9.3 kPa)
- Improved intensive care (ICU) management
  - Low tidal volume
  - Conservative fluid
- Management/detection of co-infections
- Early combination antiretroviral therapy (cART)*

**Zolopa AR et al. PloS One 2009;4:e5575*

PcP: Symptoms in Hematological Patients

- N = 55 (1990-99)
- Acute onset
- **Fever (86%), dyspnea (78%), non-productive cough (71%), severe hypoxemia (71%)**, thoracic pain (14%) and chills (5%).

Pagano L et al. Br J Haematol 2002;117:379-86

- N = 56, 44 patients (78.6%) with hematologic malignancies (HM) (18 stem cell transplant recipients) and 12 patients with solid tumors
- Main symptoms: **fever (85.7%), dyspnea (78.6%), cough (57.1%)**.
- Time from symptom onset: 7 days (3-14).
- PcP presented as severe pneumonia (PaO_2, 58 mm Hg [50-70]) with bilateral interstitial infiltrates (80.4%) and bilateral ground-glass attenuation (89.3%) on CT scans.
- 24 ICU (42.9%), 11 (19.6%) mechanical ventilation, 11 (19.6%) died.

Bollée G et al. Chest 2007;132:1305-10

PcP in non-HIV Patients:

Co-Infections

- Co-infections in 28 to 71% of patients, especially pulmonary
- Multiple pathogens: *S. aureus*, Gram-negative bacteria, *Aspergillus sp*., CMV…
- In allogeneic HSCT recipients, PcP is associated with CMV pneumonia in around 50% of cases

HSCT: hematopoietic stem cell transplant

Ewig S et al. Eur Respir J 1995;8:1548-53
Toper C et al. Rev Pneumol Clin 2011;67:191-8
Torres HA et al. Eur J Clin Microbiol Infect Dis 2006;25:382-8
Yale SH & Limper AH. Mayo Clin Proc 1996;71:5-13

Slide adapted from ECIL-5 (2013)

PcP in Non-HIV Patients: Assessment of Severity

- In non-HIV patients, differentiation of PcP severity has not been specifically addressed in prospective clinical studies.
- Recommendations regarding first-line antimicrobial treatment refer to a grading of PcP severity.
- Those recommendations are based on studies in HIV-positive patients with PcP, where the severity of PcP has been graded into mild, moderate and severe *or* mild and moderate-to-severe.
- **Most non-HIV patients do have severe disease at the time of diagnosis.**

PcP in Non-HIV Patients: Grading of Severity

- Severity of PcP in non-HIV patients should be graded into **mild** and **moderate-to-severe (B-III).**
- The grading system of Miller & Mitchell (*Miller RF & Mitchell DM. Thorax 1992;47:305-14*) may provide the most useful criteria for PcP severity assessment in non-HIV patients **(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) is discouraged **(D-II*u*).**
- Importantly, not only oxygen saturation should be used, but clinical criteria such as respiratory rate, age, co-morbidities or additional organ dysfunction must be taken into account **(A-II*u*).**

Indication for Antimicrobial Treatment

As no single diagnostic criterion to proof PcP is available, timely diagnostic efforts and prompt antimicrobial treatment against *P.jirovecii* **should be triggered by composite criteria (A-III):**

- Patient at risk

  with
- Clinical signs and symptoms
  - Dyspnea and/or cough
  - Fever (may be absent)
  - Hypoxemia (may not yet be present)
  - Chest pain (rare; from pneumothorax)

  with
- Suggestive radiology compatible with PcP (preferably thoracic CT scan)

  with or without
- Unexplained LDH elevation

PcP in Non-HIV Patients:
Start of Antimicrobial Treatment

- Appropriate systemic antimicrobial treatment should be started as early as possible **(A-II*u*)**
  - Bronchoscopy and BAL may also provide reliable results several days after start of antimicrobial therapy

Roger PM et al. Clin Infect Dis 1998;26:509–10

  - Any delay in starting the specific treatment has negative impact on prognosis

Roux A et al (France). Emerg Infect Dis 2014;20:1491-7
Li MC et al (Taiwan). J Microbiol Immunol Infect 2014;47:42-7
Guo F et al (Beijing). PloS One 2014;9:e101943
Asai N et al. J Infect Chemother 2012; 18: 898–905

PcP: Poor Prognostic Factors for Outcome in Non-HIV Patients

- **Poor prognosis factors at onset:**
  - Poor control of underlying disease
  - ECOG PS > 2
  - Long-term corticosteroids
  - Delayed onset of PcP treatment
  - Hypoalbuminemia
  - Coinfection with HSV or CMV
  - High neutrophil count in BAL
  - High APACHE-II or SAPS-II score
- **During PcP treatment:**
  - Clinical worsening at day 8
  - Vasopressor use/shock
  - High-dose steroid treatment
  - Respiratory failure/high oxygen support
  - Mechanical ventilation
  - ARDS

ECOG: Eastern Cooperative Oncology Group; PS: performance score; HSV: Herpes simplex virus; CMV: cytomegalovirus; APACHE: Acute physiology and chronic health evaluation; SAPS: Simplified acute physiology score

PcP – Recommendations for Front-line Treatment

Population	Intention	Intervention	SoR	QoE	Reference	Comment
HM, SOT, cancer, autoimmune / inflammat diseases	To cure	TMP-SMX* 15-20 mg/kg (TMP) 75-100 mg/kg (SMX) for ≥14 days	A	IIr	Ko 2014 Ceron 2014 Pagano 2002 Roblot 2002 Matsumura 2011 Moon 2011 Kofteridis 2014 Kim 2014	No randomized trials; high number of cases; low toxicity
		Pentamidine iv 4 mg/kg/d	C	IIt	Matsumura 2011	No randomized trials; low number of non-HIV pts
		Primaquine** + clindamycin 30 mg/d + 600 mg x 3/d	C	IIt	McKinnell 2012	Low number of non-HIV pts
		Atovaquone 750 mg x 2(-3)/d	C	IIt	McKinnell 2012 Roblot 2002	Low number of non-HIV pts

*For appropriate dosing in very obese patients, see separate slide; Avoid methotrexate co-medication (toxicity)

**Check for G-6-PD deficiency prior to the use of primaquine

SOT: solid organ transplantation; TMP: trimethoprim; SMX: sulfamethoxazole; G-6-PD: glucose-6-phosphate dehydrogenase

For patients who do not tolerate TMP-SMX => see 2nd-line treatment recommendations

PcP – Dosing of TMP-SMX in Very Obese Patients

- No upper dose limit in obese patients defined
- No results from appropriate clinical studies available
- Pharmacokinetics in HIV and non-HIV patients are similar *(Chin TWF et al. Antimicrob Agents Chemother 1995;39:28-33)*
- Therapeutic drug monitoring may be recommended in individual patients *(Brown GR, Ann Intensive Care 2014;4:13; Dao BD et al. Curr Ther Res 2014;76:104-9)*
  - Target peak concentration of sulfamethoxazole is 100-200 µg per ml; higher levels may be associated with unnecessary toxicity *(Chin et al, see above)*

PcP Treatment: Recommendations for Route of Administration

- Mild PcP:
  - Oral strategy is **possible** from the beginning for compliant patients in whom enteral absorption is not compromised **(B-II*t*)**
  - Dose for oral = IV **(A-II*t*)**

- Moderate-to-Severe PcP:
  - IV treatment should be started **(A-II*u*)**
  - Switch to oral therapy, once clinical improvement is achieved in compliant patients in whom enteral absorption is not compromised **(A-II*u*)**

Cooley L et al. Intern Med J 2014;44:1350-63
Carmona EM & Limper AH. Ther Adv Respir Dis. 2011;5:41-59

PcP in non-HIV Patients: Assessment of Treatment Response

- **Efficacy has to be assessed daily, evaluation after 8 days is recommended (A-III)**
  - Early deterioration (3-5 days) is common
  - Rapid radiological improvement (CT scan) under treatment expected in 57% of patients *(Vogel MN et al. Eur J Radiol 2012;81:1315-20)*
- **Clinical failure: lack of improvement or worsening of respiratory function documented by arterial blood gases after 8 days of adequate anti-PcP treatment.**
  - Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease in HIV-positive patients

Cooley L et al. Intern Med J 2014;44:1350-63
Kaplan JE et al. MMWR Recomm Rep 2009;58(RR-4):1-207
Limper AH et al (ATS). Am J Respir Crit Care Med 2011;183:96-128
Maschmeyer G et al (DGHO). Ann Oncol 2015;26:21-33

PcP: Beta-D-Glucan (BDG) for Assessment of Treatment Response

- **BDG monitoring is not recommended for response assessment (D-II*u*)**

- Conflicting data for BDG in the **serum** during the course of PcP:
  - Elevated levels: failure or fungal co-infection?
  - Decreasing levels not predictive of treatment success *(Matsumara Y et al. BMC Infect Dis. 2011;11:76)*
  - Decreasing levels correlate with clinical course *(Held D et al. Clin Microbiol Infect. 2011;17:1118-22.)*

- No data on BDG in follow-up BAL

PcP: Recommendations for Management of Clinical Failure (1)

Clinical **failure at day 8** => we recommend to do:

- **A new bronchoscopy and BAL to look for co-infections (A-III)**
  - Co-infections are common: 20% at time of ICU admission
  - ICU-acquired infections: 22%

Lemiale V et al. Respir Res 2013;14:87

  - The **persistence of positive PCR is no criterion for treatment failure - should not be used for treatment assessment (D-II*t*)**

Roger PM et al. Clin Infect Dis 1998;26:509–10

- **A new thoracic CT scan to check for complications (A-III)**
  - Spontaneous pneumothorax
  - Pleural effusion

Torres HA et al. Eur J Clin Microbiol Infect Dis 2006;25:382-8

PcP: Recommendations for Management of Clinical Failure (2)

- **Unnecessary switch to 2nd-line PcP treatment in patients receiving high-dose TMP-SMX should be avoided (A-II*t*)**
  - Efficacy of second-line treatment is less well documented than that of front-line TMP-SMX => switch to second-line treatment should be considered after exclusion of a co-infection or another cause of deterioration.
  - DHPS mutations are not associated with failure of high-dose TMP-SMX treatment.

PcP: Relevance of DHPS Gene Mutations

- **Clinical significance of DHPS mutations**
  - Evidence to suggest a contributory role for DHPS mutations in breakthrough PcP in patients using alternative sulfa prophylaxis (dapsone, pyrimethamine).
  - DHPS mutations contribute to low-level sulfa resistance, and may be most important in failure of second-line sulfa prophylaxis.
  - However, the major reason for PcP breakthrough continues to be poor adherence to chemoprophylaxis.
  - **DHPS mutations and PcP treatment with high-dose TMP-SMX: No evidence for increased failure or mortality.**

DHPS: dihydropteroate synthetase

PcP – Recommendations for Second-line Treatment

Population	Intention	Intervention	SoR	QoE	Reference	Comment
HM, SOT, cancer , autoimmune diseases	To cure	Primaquine* (30 mg) + clindamycin (600 mg x 3)	B	II*t*	Soo Jung Kim 2014 Boornsarngsuk 2009 Kim 2009	Few cases
		Pentamidine IV 4 mg/kg/day	B	III	Ko 2014 Pagano 2002 Soo Jung Kim 2014 Kim 2009	Few cases
		TMP-SMX (15-20 mg/kg) + caspofungin (70-50 mg/day)	C	II*u*	Utili *Transpl 2007* Guo-Wei Tu *Nephrology 2013* Armstrong-James *Thorax 2011*	Few cases
		Echinocandin alone	D	II*u*	Annaloro 2007 Hof 2008 Kim et al. *Scand J Infect Dis 2013*	Only case reports

*Check for G-6-PD deficiency prior to the use of primaquine

N.B. In a large series of HIV+ pts, Helweg-Larsen et al showed that 2nd-line with prima+clinda was superior to penta with a lower mortality (non-randomized study)

Helweg-Larsen J et al. J Antimicrob Chemother 2009;64:1282-90.

PcP: Echinocandins for Second-line Treatment?

- **Insufficient evidence, but may be considered as adjunctive salvage treatment (C-III). Not suitable for monotherapy (D-II*u*).**

– Echinocandins are active *in vitro* against *P.jirovecii* cysts with β(1,3)D-glucan, but only minor effect against trophic forms, which have only little BDG.

– Rodent studies suggest effect in combination with TMP-SMX, but insufficient activity as monotherapy (*Lobo ML et al. PLoSOne 2013;8:e70619).*

– Clinical failure in 2/4 HIV-neg pts with PcP treated with 2nd-line caspofungin and 2/4 3th line *(Kim T et al. Scand J Infect Dis 2013;45:484-8).*

– Progress of PcP described in patients treated with caspofungin *(Kamboj M et al. Clin Infect Dis 2006;43:e92-4).*

– Conflicting evidence of echinocandin efficacy, some reports suggest possible effect as adjunctive salvage treatment *(Armstrong-James D et al. Thorax 2011;66:537-8; Utili R et al. Transplantation 2007;84:685-8).*

PcP: Main Drug-Related Adverse Events

TMP-SMX	Clindamycin-primaquine	Pentamidine
• Rash and fever • Nephrotoxicity • Electrolyte disorders • Bone marrow suppression • Hepatotoxicity	• Nausea and vomiting • Neutropenia • *Clostridium difficile*-associated diarrhea • Primaquine may cause hemolysis in patients with G-6-PD deficiency	• Bone marrow suppression • Nephrotoxicity • Electrolyte disorders • Dysglycemia, insulin-dependent diabetes mellitus • Pancreatitis • Q-T prolongation

PcP: Recommendations for Treatment Duration

- Standard treatment duration is 3 weeks **(B-II*t*)**
- In mild cases, it should be at least 2 weeks **(A-II*t*)**
- In case of slow clinical improvement, the unmodified treatment should be continued for at least 3 weeks **(A-II*u*)**

PcP: Intensive Care in Patients with Respiratory Failure (ARF)

Early recognition of impeding ARF

- Signs and symptoms of respiratory deterioration (dyspnea, cough, sputum, chest pain, rales, hemoptysis, increasing pulmonary infiltrates, or already mild oxygenation impairments) are associated with the development of ARF, ICU admission and adverse outcome.
- Timely recognition of such situations is crucial, since *late* ICU transfers are associated with increased mortality rates. **(A-II*h*)**

PcP: Intensive Care in Patients with Respiratory Failure

Ventilation strategies (1)

- **In hematologic patients with hypoxic ARF, non-invasive ventilation (NIV) is preferred, as it appears to be associated with decreased intubation and mortality rates. (B-I)**
- NIV-failure rates in non-HIV PcP patients are particularly high.
  - Irrespective of PcP, NIV-failure with secondary intubation may be associated with excess mortality in hematologic patients.
- Survival rates of primarily intubated hematology patients with ARF have improved over the last two decades.

PcP: Intensive Care in Patients with Respiratory Failure

Ventilation strategies (2)

- **If NIV is used as primary ventilation strategy, clinical response must be monitored closely (tolerability, arterial blood gases, respiratory rate </> 30/min, clinical deterioration) (A-II*h*)**
- **If NIV failure becomes imminent, patient must be evaluated for prompt intubation and invasive mechanical ventilation. (A-III)**

PcP in Non-HIV Patients:
Criteria to Switch from NIV to MV in Patients with Respiratory Failure

Risk factors associated with NIV failure:

- Patient does not tolerate NIV
- No clinical improvement within 6 h
- No improvement of arterial blood gases within 6 h
- Respiratory rate remains > 30/min
- NIV dependency > 3 days
- Unknown etiology of the acute respiratory failure.

Soares M et al. J Crit Care. 2010;25:37-8

PcP: Recommendations on Adjunctive Glucocorticosteroids in Non-HIV Patients

- **The *routine* adjunctive use of glucocorticosteroids (CS) in non-HIV patients with PcP and respiratory failure is not recommended. The decision to add glucocorticosteroids in a non-HIV patient with PcP and respiratory failure has to be made on an individual basis (B-II*h*).**
  - There are **conflicting data on the benefit** from adjunctive CS in non-HIV patients with PcP in general (and specifically in hematology patients).
  - A significant proportion of non-HIV patients with PcP are treated with CS prior to PcP onset. It remains unclear how to treat these patients (maintaining the dose *vs.* escalation *vs.* tapering).
  - Investigational trials on the use of CS are needed in hematology patients with PcP. These trials should account for previous CS treatments as well as PcP severity.

PcP: Secondary Prophylaxis

- Non-HIV patients who have been successfully treated for PcP should be given secondary prophylaxis **(A-II*h*)**.
  - Preferred and alternative regimens for secondary PcP prophylaxis should be chosen as for primary prophylaxis *(see ECIL-5 guideline by Maertens et al.).*
  - 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.
  - Co-medication of methotrexate may cause substantial toxicity.