EUROPEAN JOURNAL OF CANCER 45 (2009) 2462–2472

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: Guidelines of the infectious diseases working party of the German Society of Haematology and Oncology ☆

Georg Maschmeyer[a,*], *Thomas Beinert*[b], *Dieter Buchheidt*[c], *Oliver A. Cornely*[d], *Hermann Einsele*[e], *Werner Heinz*[e], *Claus Peter Heussel*[f], *Christoph Kahl*[g], *Michael Kiehl*[h], *Joachim Lorenz*[i], *Herbert Hof*[j], *Gloria Mattiuzzi*[k]

[a]*Klinikum Ernst von Bergmann, Dept. of Haematology and Oncology, Charlottenstrasse 72, D-14467 Potsdam, Germany*
[b]*Wartenberg Clinic, Dept. of Haematology and Medical Oncology, Badstrasse 43, D-85456 Wartenberg, Germany*
[c]*University Hospital of Mannheim, Dept. of Internal Medicine III, Theodor-Kutzer-Ufer 1-3, D-68305 Mannheim, Germany*
[d]*University Hospital of Cologne, Dept. I of Internal Medicine and Clinical Trials Center, Kerpener Strasse 62, D-50937 Cologne, Germany*
[e]*Julius Maximilian University Hospital, Dept. of Internal Medicine II, Klinikstrasse 6-8, 97070 Würzburg, Germany*
[f]*Thoraxklinik Heidelberg, Dept. of Radiology, Amalienstrasse 5, D-69126 Heidelberg, Germany*
[g]*University Hospital of Rostock, Dept. of Haematology and Oncology, Ernst-Heydemann-Strasse 6, D-18057 Rostock, Germany*
[h]*Klinikum Frankfurt/Oder, Dept. of Internal Medicine, Müllroser Chaussee 7, D-15236 Frankfurt/Oder, Germany*
[i]*Lüdenscheid District Hospital, Dept. of Internal Medicine II, Paulmannshöher Strasse 14, D-58515 Lüdenscheid, Germany*
[j]*Institute of Microbiology and Hygiene, University Hospital of Mannheim, Theodor-Kutzner-Ufer 1-3, D-68167 Mannheim, Germany*
[k]*Haematologic Malignancies Supportive Care Program, Department of Leukaemia, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA*

ARTICLE INFO

Article history:
Received 24 December 2008
Received in revised form 27 April 2009
Accepted 1 May 2009
Available online 23 May 2009

Keywords:
Lung infiltrates
Treatment
Aspergillosis
Febrile neutropenia
Infection

ABSTRACT

Patients with neutropenia lasting for more than 10 d, who develop fever and pulmonary infiltrates, are at risk of treatment failure under conventional broad-spectrum antibacterial therapy. Filamentous fungi are predominant causes of failure, however, multi-resistant gram-negative rods such as *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia* may be involved. Prompt addition of mould-active systemic antifungal therapy, facilitated by early thoracic computed tomography, improves clinical outcome. Non-culture-based diagnostic procedures to detect circulating antigens such as galactomannan or 1,3-beta-D-glucan, or PCR techniques to amplify circulating fungal DNA from blood, bronchoalveolar lavage or tissue specimens, may facilitate the diagnosis of invasive pulmonary aspergillosis. CT-guided bronchoalveolar lavage is useful in order to identify causative microorganisms such as multidrug-resistant bacteria, filamentous fungi or *Pneumocystis jiroveci*. For pre-emptive antifungal treatment, voriconazole or liposomal amphotericin B is preferred. In patients given broad-spectrum azoles for antifungal prophylaxis, non-azole antifungals

☆ This manuscript does not refer to patients undergoing allogeneic haematopoietic stem cell transplantation. These patients are subject to a separate guideline[1] (currently under revision).

* *Corresponding author:* Tel.: +49 331 241 6002; fax: +49 331 241 6000.
E-mail address: gmaschmeyer@klinikumevb.de (G. Maschmeyer).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.05.001

or antifungal combinations might become first choice in this setting. Antifungal treatment should be continued for at least 14 d before non-response and treatment modification are considered. Microbial isolates from blood cultures, bronchoalveolar lavage or respiratory secretions must be critically interpreted with respect to their aetiological relevance for pulmonary infiltrates.

1. Categories of evidence used in this guideline[2]

Category, Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of Evidence	
I	Evidence from $\geqslant$1 properly randomised, controlled trial
II	Evidence from $\geqslant$1 well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

2. Epidemiology

Lung infiltrates (LIs) emerge in 15–28% of patients with profound neutropenia following intensive chemotherapy.[3,4] Clinical outcome deteriorates with increasing patient age,[5] and is particularly dismal in patients with bacteraemia and shock[6] as well as in case of delayed appropriate antimicrobial treatment.[7] LIs become apparent in approximately two thirds of cases within 5 d after the onset of fever.[8] As compared with other types of infections, LIs in neutropenic patients are associated with a higher risk of mortality,[8–10] their treatment is more difficult and costly.[11] Histopathological findings show that these infiltrates may have numerous different causes, including multi-resistant bacteria[12,13] and pathogens not covered by beta-lactam antibiotics (e.g. filamentous fungi, *Pneumocystis jiroveci* and viruses), alveolar bleeding, infiltration by the underlying malignancy, cryptogenic organising pneumonia, immune reconstitution syndrome and lesions caused by chemotherapy or radiation.[14–25]

Efforts to identify the aetiology of LIs in febrile neutropenic patients by the use of invasive techniques have not clearly improved clinical outcome so far,[8,23,26,27] however, they may give reason for pathogen-directed antimicrobial treatment in up to 50% of patients.[28] Success rates under broad-spectrum antibacterial treatment are below 30%,[8,29] whereas prompt addition of mould-active systemic antifungals in all febrile, severely neutropenic patients with LIs increases the response rate to up to 78%.[30] The incidence of LIs in acute leukaemia patients could be reduced to 0% by voriconazole prophylaxis as compared with 33% under placebo.[31] These along with autopsy studies,[15,32,33] indicate that the majority of LIs in febrile neutropenic patients is caused by filamentous fungi.[8,19,34,35] Clinical outcome of proven invasive aspergillosis (IA) in neutropenic patients is poor,[36–38] so that early pre-emptive antifungal treatment should be used in febrile patients with prolonged severe neutropenia and LIs not typical for non-fungal origin [B-II].[39,40] This is strengthened by the facts that IA will have an unfavourable impact on long-term prognosis[41] and that early institution of systemic antifungal treatment against *Aspergillus* spp. improves survival of febrile neutropenic patients with LI.[36,42,43] This paradigm has been challenged by data on the use of *Aspergillus* galactomannan (GM) testing for decision on antifungal treatment.[44] In patients on broad-spectrum azole prophylaxis after intensive chemotherapy,[31,45] diagnostic efforts directed at less common fungal pathogens and non-fungal causes of LIs must be reinforced.[46,47]

With the use of nucleoside analogues for combination chemotherapy of relapsed or refractory acute leukaemias, microorganisms typically observed under prolonged cellular immunosuppression, such as cytomegalovirus, mycobacteria or yeasts, must be considered[48] as well as *Staphylococcus aureus, Pseudomonas aeruginosa*, *Aspergillus* spp. and pneumococci.[49] Respiratory viruses such as Influenza A or Respiratory Syncytial Virus have only rarely been identified as causes of LIs in hospitalised, febrile neutropenic patients,[22,50] predominantly during wintertime, and do not seem to occur more frequently in immunocompromised than in non-immunocompromised patients.[51] Patients older than 65 years of age and those with severe lymphocytopenia are at higher risk, and mortality rate may be 5–15%.[50]

3. Role of diagnostic procedures

3.1. *Imaging*

Conventional chest radiographs (CXRs) show LIs in <2% of febrile neutropenic patients without clinical signs of lower respiratory tract infections.[52,53] In patients refractory to broad-spectrum antibacterial therapy, CXRs show LIs in about 10%,[54] whereas computed tomography (CT) detects pulmonary lesions in approximately 50% of patients.[55–57] Early detection of lesions indicating invasive fungal infection helps for prompt institution of pre-emptive mould-active antifungal treatment[42,58,59] and may significantly reduce mortality due to invasive pulmonary aspergillosis (IPA).[42] CT findings such as consolidation, air-crescent and halo sign are classified as important signs of filamentous fungal disease.[60] CT findings indicating IPA are similar in neutropenic and non-neutropenic patients.[37] Apart from focus detection, characterisation of LIs by CT scan helps to distinguish fungal pneumonia from non-fungal LIs.[24,61–64] Nodular and/or cavitary lesions are suggestive for mould infection, but may be also caused by other microorganisms including mycobacteria as well as by progression of the underlying malignancy.[65] In most cases, however they have a typical CT appearance. Magnetic-resonance imaging (MRI) has become as clinically useful alternative to CT,[66] however, consensus definitions of invasive fungal diseases have not yet included thoracic MRI findings.[60] In case of IPA, the volume of LIs may markedly increase during the first week on follow-up CT scans despite effective antifungal therapy.[52] Reduction of halo or appearance of air-crescent sign may indicate favourable response.[67,68]

3.2. *Microbiological and histopathological samples*

Microbiological diagnosis is based on blood cultures, sputum and endoscopically obtained bronchial secretions or bronchoalveolar lavage (BAL) fluid. The diagnostic yield of these procedures is controversially debated.[26,69–77] Unselected samples obtained from neutropenic cancer patients with 'pneumonia' showed a predominance of microorganisms without aetiological relevance,[78] while autopsy results demonstrate that in the majority of patients who died from invasive fungal infection, diagnosis has not been established ante mortem.[79] The number of false-positive and false-negative findings, and their correlation to the results of allegedly targeted antimicrobial therapy are undetermined. *Aspergillus* spp. are rarely detected from throat swabs, oral washings or saliva, however, such a finding has a high positive predictive value in severely immunocompromised patients.[80]

The diagnostic yield of BAL ranges between 25%[71] and >50%[37,82–84] and depends on the risk profile of patients analysed.[37] A large retrospective survey on microbiological yield from BAL in cancer patients with LI post-chemotherapy showed 34% bacteria, 22% cytomegalovirus, 15% *Pneumocystis jiroveci* and 2% aspergilli.[83] An evaluation of 246 fibreoptic bronchoscopies in 199 febrile patients with haematological malignancies showed relevant pathogens in 118 cases. In 70 samples, only bacteria were detected, 13 samples showed both fungi and bacterial pathogens, 15 samples *Aspergillus* species, 16 samples *Candida* species and 2 samples both *Aspergillus* and *Candida*.[72] The relevance of polymicrobial aetiology of LIs has also been confirmed in a retrospective analysis,[73] reporting a mould (predominantly *Aspergillus* species) plus a bacterium in 12% and multiple potentially pathogenic fungi in 22% of samples. BAL findings may result in a change of antimicrobial treatment in 38–50% of patients.[28,72]

Cultural isolation of fungi and histological proof from lung tissue are the diagnostic 'gold standard' for the diagnosis of IA.[60] However, their predictive power is difficult to be assessed, as no quality standards exist with regard to the numbers of specimen, the technique and time schedule for work-up of samples or the interpretation of results. Patients undergoing biopsy are highly selected, invalidating conclusions regarding sensitivity and specificity of diverse biopsy techniques.

Due to safety concerns, transbronchial biopsy is rarely used in severely neutropenic and thrombocytopenic patients with lung infiltrates.[28,81,85]

Open-lung biopsy (OLB) is performed primarily in patients with treatment-refractory LIs not clarified by other techniques, in order to rule out non-infectious origin.[21,46,84] The diagnostic yield of OLB was reported to be particularly high in a paediatric population,[86] and may show up to 40% non-specific inflammatory processes.[23,26,87] Notably, significant discrepancies between findings from OLB and BAL have been reported.[26] Adverse events may emerge in up to 43% of OLB[86] with up to 15% risk of bleeding,[87] in spite of sufficient platelet counts.[88,89] False-negative results may occur, particularly if the infectious focus has been missed, necrotic tissue been obtained, or biopsy has been taken very late after onset of infiltrates.

CT-guided transcutaneous needle biopsy may provide useful results, particularly by using molecular methods for tissue work-up [B-II].[90–95] However, this procedure requires platelet counts >50,000/μl and should not be performed in patients with a significant risk of respiratory failure in case of pneumothorax. Prospective studies on the clinical use of needle biopsies are not available.

3.3. *Non-culture-based diagnostics*

Since the early 1990s, techniques for detection of fungal cells by *Aspergillus* galactomannan (GM), 1,3-beta-D-glucan or molecular methods have been introduced for early non-invasive detection of IPA.[96–106] Updated consensus definitions of invasive fungal infections include a positive GM test from serum, plasma or BAL samples as an important finding.[60] In patients with IPA it is controversial whether serum GM test will become positive prior to major signs on CT scans.[107] The test is not suitable for identifying infections from non-*Aspergillus* fungi and may be false-positive in the presence of other infections or semisynthetic beta-lactam antibiotics.[108] Details regarding antigen testing that indicate or exclude fungal infection other than aspergillosis[109] are discussed in a separate guideline.[110]

Studies on polymerase chain reaction (PCR) assays, either panfungal or *Aspergillus*-specific, indicated a higher clinical usefulness of these techniques applied to BAL as compared to blood samples, particularly under antifungal treatment.[100,102,105,111–113] When applied to lung biopsy specimens,

superior diagnostic yield for detection of invasive filamentous fungi by PCR compared to histopathology and culture was shown.[95] There is no standardisation of these methodically different assays as yet. The use of a commercial test using multiplex PCR for numerous microbial pathogens (Septifast®, Roche Diagnostics) has not been tested in patients with LIs. Generally, PCR is used not as a single tool, but as part of a complex diagnostic programme including chest CT scans and serology.[114,115]

3.4. *Serum markers and cytokines*

An assessment of laboratory parameters such as C-reactive protein, interleukin-6,[116] interleukin-8, Tumour Necrosis Factor-alpha[117] or procalcitonin plasma levels[118] has not been established in febrile neutropenic patients with LIs so far. The predictive value of cytokines and chemokines in BAL fluid[119,120] is subject to further clinical studies.

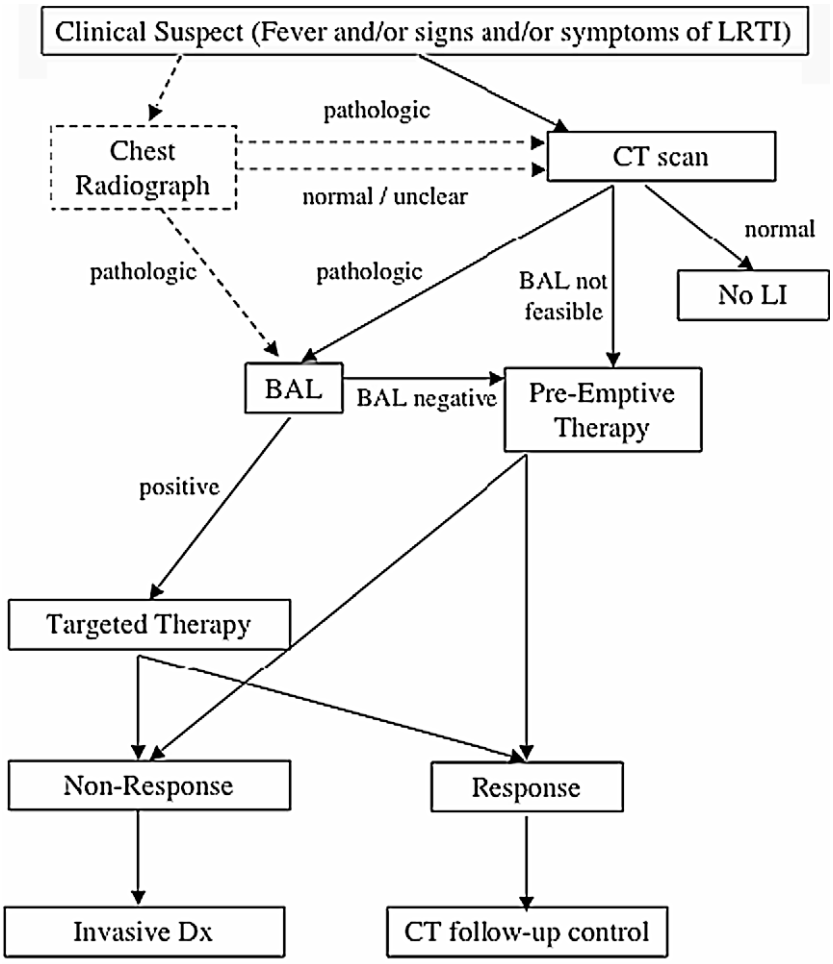
Diagnostic techniques for aetiological work-up of LIs should be standardised with respect to methodology. Their role should be investigated in prospective studies providing that diagnostic procedures do not critically delay early initiation of an adequate antimicrobial therapy.

4. Practice of diagnostic procedures

An algorithm for the clinical management of febrile neutropenic patients with LIs [B-III] is shown in Fig. 1.

In patients at high risk of invasive fungal infection, i.e. those with acute myeloid leukaemia or myelodysplastic syndrome undergoing aggressive myelosuppressive chemotherapy resulting in profound neutropenia for more than 10 d, serial monitoring of *Aspergillus* galactomannan 1,3-beta-D-glucan and/or (preferably within a clinical study) fungal PCR from blood samples is encouraged [B-II]. Samples should be taken at least twice weekly [B-II]. Non-culture-based procedures do not replace clinical, imaging, endoscopic or microbiological diagnostics [B-III].

Diagnostic efforts aim at early detection of LIs and obtaining reliable microbiological results that confirm, or help to



LRTI, lower respiratory tract infection; CT, computed tomography; LI, Lung infiltrate; BAL, bronchoalveolar lavage; Invasive Dx, invasive diagnostic procedures such as open lung biopsy or fine-needle biopsy

Dotted lines indicate exceptions from recommended procedure

Fig. 1 – Algorithm for the clinical management of patients with febrile neutropenia and suspected or proven lung infiltrates.

modify, the antimicrobial therapy initiated pre-emptively. Clinical, imaging and laboratory procedures required for neutropenic patients with fever of unknown origin (FUO) are described in detail by Link et al.[121]

Patients with FUO or documented infections other than lung infiltrates not responding to antimicrobial therapy during the first 72–96 h should be subjected to repeated clinical, imaging and microbiological examination [B-II]. Thoracic CT scan should be done within 24 h [B-II]. A higher rate of pathological findings is obtained by the use of high-resolution or thin-section multi-slice techniques [B-II].[55–57,122]

In patients who cannot undergo thoracic CT scan, MRI is a suitable alternative [B-II].[66] In patients with pathological findings on CXR, a thoracic CT scan in order to specify the cause of LIs has become a clinical standard [B-II].

In patients with LIs, a fibreoptic bronchoscopy (FBO) with bronchoalveolar lavage (BAL) of the affected region is recommended [B-III]. FBO and BAL are safe procedures,[28] however, in critically ill patients with a significant risk of respiratory failure or pulmonary bleeding, their indication must be carefully re-considered [B-III].[28] Protected brush and protected BAL are not superior to BAL for diagnosing LIs in neutropenia [D-II].[82] When sending BAL samples to the laboratory for microbiological work-up, current systemic antimicrobial therapy as well as relevant clinical data must be provided, and the maximum period between sampling and start of laboratory work-up should be less than 4 h [A-III]. Samples should be transported under cooling conditions (+4 °C) [A-III]. The recommended programme for microbiological work-up is shown in Table 1.

Patients with LIs remaining aetiologically undetermined despite diagnostic procedures and urgently requiring histological identification (e.g. suspected invasive fungal infection or non-infectious LIs) should undergo invasive procedures such as open lung or fine-needle biopsy [B-II].

5. Pre-emptive antimicrobial therapy (Table 2)

Pre-emptive therapy is defined as the administration of antimicrobial agents on the basis of clinical, imaging and/or laboratory findings indicative of a particular infection in patients at risk for, but without proof of this infection.

5.1. *Patients with acute leukaemia and other aggressive haematological malignancies*

In order to early and effectively cover filamentous fungi, predominantly *Aspergillus* spp. in febrile neutropenic patients with severe neutropenia lasting for more than 10 d and LIs,[8,10,30] initial antimicrobial therapy should consist of an anti-pseudomonal beta-lactam antibacterial agent plus voriconazole (6 mg/kg every 12 h on day 1, 4 mg/kg every 12 h thereafter) or liposomal amphotericin B (3 mg/kg daily)[40] [B-II]. Liposomal amphotericin B is preferred in patients in whom a pulmonary zygomycosis is considered and in those who have recently been treated with voriconazole or posaconazole [B-III]. This recommendation is based on the results of prospective clinical trials in febrile neutropenic patients with LIs,[8,30] benefitting significantly from prompt[30] as compared to

Table 1 – Processing of bronchoalveolar lavage (BAL) material and microbiological analyses [B-III].

Recommended diagnostic programme [B-III]

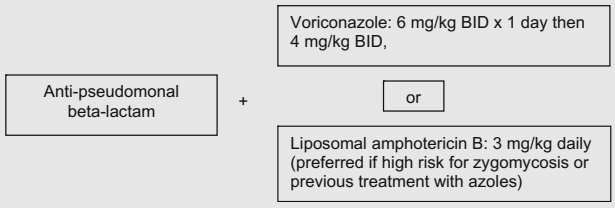
- Cytospin preparations for distinguishing intracellular from extracellular pathogens and identifying infiltration by underlying malignancy
- Gram stain
- Giemsa/May-Grünwald-Giemsa stain (assessment of macrophages, ciliated epithelium, leukocytes)
- Calcofluor white or equivalent (assessment of fungi and *Pneumocystis jiroveci*)
- Direct immunofluorescence test for *Pneumocystis jiroveci* (confirmatory)
- Direct immunofluorescence test for *Legionella* spp.
- Ziehl-Neelsen/Auramin staining
- *Aspergillus* antigen (Galactomannan Sandwich ELISA)
- Quantitative cultures: dilutions of 10^{-2} and 10^{-4}; culture media: blood, McConkey/Endo, Levinthal/blood (bacterial culture), Legionella-BCYE α or equivalent (*Legionella* spp.), Löwenstein-Jensen or equivalent (mycobacteria), Sabouraud/Kimmig or equivalent (fungal culture)

Optional programme [B-III]

- Enrichment culture (Brain-Heart Infusion, dextrose broth)
- Direct immunofluorescence test for *Chlamydia pneumoniae*
- Culture for *Chlamydia pneumoniae*
- *Legionella* PCR
- Shell vial technique and PCR for influenza, parainfluenza and adenovirus
- Culturing or antigen detection of Herpes simplex and Varicella zoster virus
- Cytomegalovirus early antigen; rapid culture
- CMV antibody (ELISA, IgG/IgM)
- HSV antibody (ELISA, IgG/IgM)
- VZV antibody (ELISA, IgG/IgM/IgA)
- Respiratory syncytial virus (PCR, ELISA)
- Panfungal/*Aspergillus* PCR
- Peripheral blood cultures 1 h after bronchoscopy to detect transient bacteraemia
- Throat swab to assess oral flora in comparison with BAL
- *Pneumocystis jiroveci* PCR

Table 2 – Pre-emptive antimicrobial therapy.

(1) For patients with acute leukaemia and other aggressive haematological malignancies



(2) For patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation (AHSCT)
– No prompt systemic antifungal required
– After CD34-selected AHSCT: Ganciclovir 5 mg/kg BID if positive rapid culture for CMV

delayed[8] mould-active antifungal therapy, as well as on trials including patients with proven or probable aspergillosis[123] or proven, probable and possible aspergillosis[124] treated with voriconazole and in patients with proven or probable mould infections treated with liposomal amphotericin B.[125] The place for echinocandin antifungals in this situation remains to be defined. Data on the use of caspofungin in febrile neutropenic patients refractory to broad-spectrum antibacterial therapy included a small number of patients with LIs at baseline, but also showed breakthrough LIs on caspofungin therapy.[126] The addition of an aminoglycoside or flucytosine does not improve treatment results[30,127] [E-I]. Antifungal treatment should be continued until haematopoietic recovery and regression of clinical and radiological signs of infection [B-III]. Efforts to identify the origin of LIs should be reinforced, particularly in patients after broad-spectrum azole prophylaxis, to identify non-fungal causes of infiltrates as well as potentially azole-resistant fungal pathogens.

Empirical administration of antiviral drugs, glycopeptide or macrolide antibiotics without a target pathogen isolated from clinically significant samples is not recommended [D-II].

5.2. *Patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation (AHSCT)*

Patients after AHSCT have a very low risk of fungal pneumonia.[128–130] Therefore, pre-emptive antifungal therapy should be restricted to individual patients [B-II]. In patients with LIs of unknown aetiology after CD34-selected HSCT,[131] FBO with BAL should be considered to eventually diagnose CMV infection [B-III]. In case of a positive rapid culture or 'immediate early antigen', ganciclovir treatment (5 mg/kg every 12 h) is indicated [B-III]. Foscarnet has not been investigated in this setting. Data on serial blood PCR or pp65 antigen monitoring for CMV in these patients are not available.

6. Therapy in patients with documented pathogens

Microbiological findings from neutropenic patients must be interpreted critically with respect to their aetiological significance, also when obtained from blood cultures or BAL samples. Detection of aetiologically significant pathogens, particularly multi-resistant bacteria, should prompt immediate modification of antimicrobial treatment to avoid fatal outcome due to delayed effective therapy.[132]

Aetiologically significant findings are:

- *Pneumocystis jiroveci*, Gram-negative aerobic pathogens, pneumococci, *Mycobacterium tuberculosis* or *Aspergillus* spp. or *Aspergillus* galactomannan (sandwich ELISA; *note: a threshold of positivity remains to be defined*) or zygomycetes obtained from bronchoalveolar lavage or sputum samples; positive rapid culture for CMV, detection of CMV 'immediate early antigen'.
- Isolation of pneumococci, alpha-haemolytic streptococci or Gram-negative aerobic pathogens from blood culture.
- Any detection of pathogens in biopsy material.
- Positive *Legionella* or pneumococcal antigen in urine.
- Positive *Aspergillus* galactomannan in blood samples.

Findings insignificant for lung infiltrates are:

- Isolation of enterococci from blood culture, smears, sputum or BAL.
- Coagulase-negative staphylococci or *Corynebacterium* spp. obtained from any sample.
- Isolation of *Candida* spp. from swabs, saliva, sputum or tracheal aspirates.
- Findings from surveillance cultures, faeces and urine cultures.

Note: Detection of these pathogens may indicate other infections.

Other findings such as community respiratory viruses, isolation of *Staphylococcus aureus*, *Legionella* spp. or atypical mycobacteria from respiratory secretions or a positive CMV-PCR from BAL must be interpreted critically with respect to their aetiologic significance, before specific antimicrobial treatment is given.

7. Treatment of documented fungal pneumonia

Detailed recommendations for treatment of patients with documented fungal pneumonia are the subject of a separate guideline.[133] Voriconazole or liposomal amphotericin B is the agent of choice for primary treatment of IPA,[40,133] whereas

for zygomycosis, liposomal amphotericin B is recommended. Antifungal therapy should be continued after patient discharge [B-III]. In patients with progressive LIs and worsening gas exchange, failure of antifungal treatment should only be considered after other causes such as second infection, immune reconstitution or too short duration of treatment have been ruled out [B-II].[14,58,134]

8. Treatment of *Pneumocystis jiroveci* pneumonia (PcP)

Patients with proven PcP should be treated with trimethoprim-sulphamethoxazole (TMP/SMX, co-trimoxazole) at a daily dosage of TMP 15–20 mg/kg plus SMX 75–100 mg/kg, divided into 3–4 doses [A-II]. In non-responders to at least 14 d of treatment, a second infection should be discussed. If a repeated bronchoscopy has confirmed persistent PcP without any evidence for another infection, dihydropteroate synthase gene mutation may be present.[135] In case of confirmed sulpha resistance or TMP/SMX intolerance, atovaquone oral suspension (750 mg three times daily), aerosolised pentamidine (600 mg daily), intravenous pentamidine (4 mg/kg daily) or clindamycin (600 mg three times daily) *plus* primaquine (30 mg daily) are treatment alternatives,[136] of which clindamycin/primaquine appears to be the most effective [C-III].[137] Treatment duration is 2–3 weeks [B-II]. Secondary prophylaxis with oral TMP/SMX at a daily dosage of 160/800 mg at 3 d per week or with pentamidine inhalation of 300 mg once a month is required [A-II].

In patients with emerging respiratory failure, non-invasive continuous positive airway pressure mask ventilation to avoid intubation and mechanical ventilation might be useful [B-II].[138] The adjunctive use of corticosteroids is unclear in the setting addressed here.[139,140]

9. Referral to intensive care unit

Neutropenic cancer patients with respiratory failure caused by LIs may have a favourable outcome under intensive care, including mechanical ventilation.[9,141–143] Therefore, it is not justified to withhold intensive care from cancer patients with respiratory failure caused by lung infiltrates only with respect to their underlying malignancy [A-II].[144]

Conflict of interest statement

Georg Maschmeyer has served as a consultant for Gilead Sciences, MSD, Pfizer, Essex (Schering-Plough), Novartis and Sanofi-Aventis and has been on the Speakers' Bureau for Gilead Sciences, MSD, Pfizer and Cephalon.

Dieter Buchheidt has received grants and research support from Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough) and has been on the Speakers' Bureau for Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough).

Oliver Cornely has received grants and research support from Astellas, Basilea, Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough), served as a consultant for Astellas, Basilea, F2G, Gilead Sciences, MSD, Pfizer, Essex (Schering-Plough) and Cephalon and has been on the Speakers' Bureau for Gilead Sciences, MSD, Pfizer and Cephalon.

Hermann Einsele has served as a consultant for MSD.

Werner Heinz has received grants and research support from Astellas, Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough), has served as a consultant for Pfizer and Essex (Schering-Plough) and has been on the Speakers' Bureau for Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough).

Claus Peter Heussel has received grants and research support from AstraZeneca, Bayer, Bracco, General Electric, Intermun, Merck, Novartis, Pfizer, PneumRx, PulmonRx, ROX, Essex (Schering-Plough), Siemens, Roche, Wyeth and ZLB Behring. He has served as a consultant for AstraZeneca, Basilea, Baxter, Bracco, Essex (Schering-Plough), Systema, Gilead Sciences, Pfizer, Perceptive, Phillips and Siemens.

Herbert Hof has served as a consultant for Gilead Sciences and MSD, and has been on the Speakers' Bureau for Gilead Sciences, MSD, Pfizer and Essex (Schering-Plough).

Michael Kiehl has served as a consultant for Gilead Sciences and Essex (Schering-Plough) and has been on the Speakers' Bureau for Gilead Sciences, MSD and Essex (Schering-Plough).

Gloria Mattiuzzi has received grants and research support from Astellas, MGI Pharma Inc. and Novartis.

Thomas Beinert, Christoph Kahl and Joachim Lorenz have declared no potential conflicts of interest.

REFERENCES

1. Einsele H, Bertz H, Beyer J, et al. Infectious complications after allogeneic stem cell transplantation: epidemiology and interventional therapy strategies. *Ann Hematol* 2003;**82**(Suppl. 2):S175–85.
2. Kish MA. Infectious diseases society of America. Guide to development of practice guidelines. *Clin Infect Dis* 2001;**32**:851–4.
3. Link H, Maschmeyer G, Meyer P, et al. Interventional antimicrobial therapy in febrile neutropenic patients. *Ann Hematol* 1994;**69**:231–43.
4. Rossini F, Verga M, Pioltelli P, et al. Incidence and outcome of pneumonia in patients with acute leukemia receiving first induction therapy with anthracycline-containing regimens. *Haematologica* 2000;**85**:1255–60.
5. Specchia G, Pastore D, Carluccio P, et al. Pneumonia in acute leukemia patients during induction therapy: experience in a single institution. *Leuk Lymphoma* 2003;**44**:97–101.
6. Carratalà J, Rosón B, Fernández-Sevilla A, Alcaide F, Gudiol F. Bacteremic pneumonia in neutropenic patients with cancer: causes, empirical antibiotic therapy, and outcome. *Arch Intern Med* 1998;**158**:868–72.
7. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. *Antimicrob Agents Chemother* 2008;**52**:3188–94.
8. Maschmeyer G, Link H, Hiddemann W, et al. Pulmonary infiltrations in febrile neutropenic patients. *Risk factors and outcome under empirical antimicrobial therapy in a randomized multicenter trial*. *Cancer* 1994;**73**:2296–304.
9. Azoulay E, Thiery G, Chevret S, et al. The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine* 2004;**83**:360–70.
10. Ewig S, Glasmacher A, Ulrich B, et al. Pulmonary infiltrates in neutropenic patients with acute leukemia during chemotherapy. *Chest* 1998;**114**:444–51.

11. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;**106**:2258–66.
12. Hachem RY, Chemaly RF, Ahmar CA, et al. Colistin is effective in treatment of infections caused by multidrug-resistant Pseudomonas aeruginosa in cancer patients. *Antimicrob Agents Chemother* 2007;**51**:1905–11.
13. Safdar A, Rolston KV. Stenotrophomonas maltophilia: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis* 2007;**45**:1602–9.
14. Azoulay E, Darmon M, Delclaux C, et al. Deterioration of previous acute lung injury during neutropenia recovery. *Crit Care Med* 2002;**30**:781–6.
15. Bodey G, Bueltmann B, Duguid W, et al. Fungal infections in cancer patients: an international autopsy survey. *Eur J Clin Microbiol Infect Dis* 1992;**11**:99–109.
16. Canham EM, Kennedy TC, Merrick TA. Unexplained pulmonary infiltrates in the compromised patient. *Cancer* 1983;**52**:325–9.
17. Cazzadori A, di Perri G, Todeschini G, et al. Transbronchial biopsy in the diagnosis of pulmonary infiltrates in immunocompromised patients. *Chest* 1995;**107**:101–6.
18. Cheson BD, Samlowski WE, Tang TT, Spruance SL. Value of open-lung biopsy in 87 immunocompromised patients with pulmonary infiltrates. *Cancer* 1985;**55**:453–9.
19. Commers JR, Robichaud KJ, Pizzo PA. New pulmonary infiltrates in granulocytopenic cancer patients being treated with antibiotics. *Pediatr Infect Dis J* 1984;**3**:423–8.
20. Danés C, Gonzalez-Martin J, Pumarola T, et al. Pulmonary infiltrates in immunosuppressed patients: analysis of a diagnostic protocol. *J Clin Microbiol* 2002;**40**:2134–40.
21. Daniels CE, Myers JL, Utz JP, Markovic SN, Ryu JH. Organizing pneumonia in patients with hematologic malignancies: a steroid-responsive lesion. *Respir Med* 2007;**101**:162–8.
22. Martino R, Ramila E, Rabella N, et al. Respiratory virus infections in adults with hematologic malignancies: a prospective study. *Clin Infect Dis* 2003;**36**:1–8.
23. Singer C, Armstrong D, Rosen PP, Walzer PD, Yu B. Diffuse pulmonary infiltrates in immunosuppressed patients. Prospective study of 80 cases. *Am J Med* 1979;**66**:110–20.
24. Suzuki HI, Asai T, Tamaki Z, Hangaishi A, Chiba S, Kurokawa M. Drug-induced hypersensitivity syndrome with rapid hematopoietic reconstitution during treatment for acute myeloid leukemia. *Haematologica* 2008;**93**:469–70.
25. Torres HA, Aguilera EA, Mattiuzzi GN, et al. Characteristics and outcome of Respiratory Syncytial Virus infection in patients with leukemia. *Haematologica* 2007;**92**:1216–23.
26. Ellis ME, Spence D, Bouchama A, et al. Open lung biopsy provides a higher and more specific diagnostic yield compared to bronchoalveolar lavage in immunocompromised patients. *Scand J Infect Dis* 1995;**27**:157–62.
27. Rossiter SJ, Miller DC, Churg AM, Carrington CB, Mark JBD. Open lung biopsy in the immunocompromised patient. Is it really beneficial? *J Thorac Cardiovasc Surg* 1979;**77**:338–45.
28. Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. *Mayo Clin Proc* 2005;**80**:1414–20.
29. Raad II, Whimbey EE, Rolston KVI, et al. A comparison of aztreonam plus vancomycin and imipenem plus vancomycin as initial therapy for febrile neutropenic cancer patients. *Cancer* 1996;**77**:1386–94.
30. Schiel X, Link H, Maschmeyer G, et al. A prospective, randomized multicenter trial of the empirical addition of antifungal therapy for febrile neutropenic cancer patients. *Infection* 2006;**34**:118–26.
31. Vehreschild JJ, Böhme A, Buchheidt D, et al. A double-blind trial on prophylactic voriconazole or placebo during induction chemotherapy for acute myelogenous leukaemia. *J Infect* 2007;**55**:445–9.
32. Donhuijsen K, Pfaffenbach B, Samandari S, Leder LD. Autopsy results of deep mycoses in hematologic neoplasms. *Mycoses* 1991;**34**(Suppl.):25–7.
33. Groll AH, Shah PM, Mentzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996;**33**:23–32.
34. Akova M, Paesmans M, Calandra T, Viscoli C. A European Organization for Research and Treatment of Cancer-International Antimicrobial Therapy Group study of secondary infections in febrile, neutropenic patients with cancer. *Clin Infect Dis* 2005;**40**:239–45.
35. Mattiuzzi GN, Alvarado G, Alvarez R, Giles F, Lopez-Roman I, Estey E. Incidence of pulmonary infiltrates in patients with acute myelogenous leukemia and myelodysplastic syndrome undergoing induction chemotherapy: retrospective analysis of 5 years. In: *43rd Interscience conference on antimicrobial agents and chemotherapy*, Chicago, IL, September 14–17; 2003 [abstr # K-1368].
36. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006;**91**:1068–75.
37. Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. *Clin Infect Dis* 2006;**43**:577–84.
38. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001;**32**:358–66.
39. Maschmeyer G, Beinert T, Buchheidt D. Et al. Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients. *Ann Hematol* 2003;**82**(Suppl):S118–26.
40. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;**46**:327–60.
41. Offner F, Cordonnier C, Ljungman P, et al. Impact of previous aspergillosis on the outcome of bone marrow transplantation. *Clin Infect Dis* 1998;**26**:1098–103.
42. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997;**15**:139–47.
43. Von Eiff M, Roos N, Schulten R, et al. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration* 1995;**62**:341–7.
44. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection. *Clin Infect Dis* 2005;**41**:1242–50.
45. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. *Fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med* 2007;**356**:348–59.
46. Camus P, Costabel U. Drug-induced respiratory disease in patients with hematological diseases. *Semin Respir Crit Care Med* 2005;**26**:458–81.
47. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis* 2007;**44**:402–9.
48. Samonis G, Kontoyiannis DP. Infectious complications of purine analog therapy. *Curr Opin Infect Dis* 2001;**14**:409–13.

49. Ahmed S, Siddiqui AK, Rossoff L, Sison CP, Rai KR. Pulmonary complications in chronic lymphocytic leukemia. *Cancer* 2003;**98**:1912–7.
50. Chemaly RF, Torres HA, Aguilera EA, et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. *Clin Infect Dis* 2007;**44**:964–7.
51. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005;**352**:1749–59.
52. Korones DN. Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer? *Pediatr Blood Cancer* 2004;**43**:715–7.
53. Navigante AH, Cerchietti LC, Costantini P, et al. Conventional chest radiography in the initial assessment of adult cancer patients with fever and neutropenia. *Cancer Control* 2002;**9**:346–51.
54. Oude Nijhuis CS, Gietema JA, Vellenga E, et al. Routine radiography does not have a role in the diagnostic evaluation of ambulatory adult febrile neutropenic cancer patients. *Eur J Cancer* 2003;**39**:2495–8.
55. Heussel CP, Kauczor HU, Heussel G, Fischer B, Mildenberger P, Thelen M. Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. *Am J Roentgenol* 1997;**169**:1347–53.
56. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: Use of high-resolution computed tomography. *J Clin Oncol* 1999;**17**:796–805.
57. Rámila E, Sureda A, Martino R, et al. Bronchoscopy guided by high-resolution computed tomography for the diagnosis of pulmonary infections in patients with hematologic malignancies and normal plain chest X-ray. *Haematologica* 2000;**85**:961–6.
58. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol* 2001;**19**:253–9.
59. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis* 2007;**44**:373–9.
60. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group. *Clin Infect Dis* 2008;**46**:1813–21.
61. Escuissato DL, Gasparetto EL, Marchiori E, et al. Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. *Am J Roentgenol* 2005;**185**:608–15.
62. Gasparetto EL, Escuissato DL, Marchiori E, et al. High-resolution CT findings of respiratory syncytial virus pneumonia after bone marrow transplantation. *Am J Roentgenol* 2004;**182**:1133–7.
63. Hachem R, Sumoza D, Hanna H, Girgawy E, Munsell M, Raad I. Clinical and radiologic predictors of invasive pulmonary aspergillosis in cancer patients: should the European Organization for Research and Treatment of Cancer/Mycosis Study Group criteria be revised? *Cancer* 2006;**106**:1581–6.
64. Heussel CP, Kauczor HU, Ullmann AJ. Pneumonia in neutropenic patients. *Eur Radiol* 2004;**14**:256–71.
65. Shorr AF, Susla GM, O'Grady NP. Pulmonary infiltrates in the non-HIV-infected immunocompromised patient: etiologies, diagnostic strategies, and outcomes. *Chest* 2004;**125**:260–71.
66. Eibel R, Herzog P, Dietrich O, et al. Pulmonary abnormalities in immunocompromised patients: comparative detection with parallel acquisition MR imaging and thin-section helical CT. *Radiology* 2006;**241**:880–91.
67. Brodoefel H, Vogel M, Hebart H, et al. Long-term CT follow-up in 40 non-HIV immunocompromised patients with invasive pulmonary aspergillosis. *Am J Roentgenol* 2006;**187**:404–13.
68. Horger M, Hebart H, Einsele H, et al. Initial CT manifestations of invasive pulmonary aspergillosis in 45 non-HIV immunocompromised patients: association with patient outcome? *Eur J Radiol* 2005;**55**:437–44.
69. Azoulay E, Mokart D, Rabbat A, et al. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure. *Crit Care Med* 2008;**36**:100–7.
70. Brown MJ, Worthy SA, Flint JDA, Muller NL. Invasive aspergillosis in the immunocompromised host: Utility of computed tomography and bronchoalveolar lavage. *Clin Radiol* 1998;**53**:255–7.
71. Cordonnier C, Escudier E, Verra F, et al. Bronchoalveolar lavage during neutropenic episodes. *Eur Respir J* 1994;**7**:114–20.
72. Hummel M, Rudert S, Hof H, Hehlmann R, Buchheidt D. Diagnostic yield of bronchoscopy with bronchoalveolar lavage in febrile patients with hematologic malignancies and pulmonary infiltrates. *Ann Hematol* 2008;**87**:291–7.
73. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. *Clin Infect Dis* 2007;**45**:228–33.
74. Levy H, Horak DA, Tegtmeier BR, Yokota SB, Forman SJ. The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. *Respir Med* 1992;**86**:243–8.
75. Pisani RJ, Wright AJ. Clinical utility of bronchoalveolar lavage in immunocompromised hosts. *Mayo Clin Proc* 1992;**67**:221–7.
76. Reichenberger F, Habicht J, Matt P, et al. Diagnostic yield of bronchoscopy in histologically proven invasive pulmonary aspergillosis. *Bone Marrow Transplant* 1999;**24**:1195–9.
77. Saito H, Anaissie EJ, Morice RC, Dekmezian R, Bodey GP. Bronchoalveolar lavage in the diagnosis of pulmonary infiltrates in patients with acute leukemia. *Chest* 1988;**94**:745–9.
78. Dettenkofer M, Wenzler-Rottele S, Babikir R, et al. Surveillance of nosocomial sepsis and pneumonia in patients with a bone marrow or peripheral blood stem cell transplant. *Clin Infect Dis* 2005;**40**:926–31.
79. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). *Haematologica* 2006;**91**:986–9.
80. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. *Am J Med* 1996;**100**:171–8.
81. Boersma WG, Erjavec Z, van der Werf TS, et al. Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. *Respir Med* 2007;**101**:317–25.
82. Jain P, Sandur S, Meli Y, et al. Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. *Chest* 2004;**125**:712–22.
83. Joos L, Tamm M. Breakdown of pulmonary host defense in the immunocompromised host: cancer chemotherapy. *Proc Am Thorac Soc* 2005;**2**:445–8.
84. Zihlif M, Khanchandani G, Ahmed HP, Soubani AO. Surgical lung biopsy in patients with hematological malignancy or hematopoietic stem cell transplantation and unexplained pulmonary infiltrates: improved outcome with specific diagnosis. *Am J Hematol* 2005;**78**:94–9.
85. Mulabecirovic A, Gaulhofer P, Auner HW, et al. Pulmonary infiltrates in patients with haematologic malignancies:

transbronchial lung biopsy increases the diagnostic yield with respect to neoplastic infiltrates and toxic pneumonitis. *Ann Hematol* 2004;**83**:420–2.
86. Armenian SH, La Via WV, Siegel SE, Mascarenhas L. Evaluation of persistent pulmonary infiltrates in pediatric oncology patients. *Pediatr Blood Cancer* 2007;**48**:165–72.
87. White DA, Wong PW, Downey R. The utility of open lung biopsy in patients with hematologic malignancies. *Am J Respir Crit Care Med* 2000;**161**:723–9.
88. Hoffer FA, Gow K, Flynn PM, Davidoff A. Accuracy of percutaneous lung biopsy for invasive pulmonary aspergillosis. *Pediatr Radiol* 2001;**31**:144–52.
89. Patel NR, Lee PS, Kim JH, Weinhouse GL, Koziel H. The influence of diagnostic bronchoscopy on clinical outcomes comparing adult autologous and allogeneic bone marrow transplant patients. *Chest* 2005;**127**:1388–96.
90. Carrafiello G, Lagana D, Nosari AM, et al. Utility of computed tomography and of fine needle aspiration biopsy in early diagnosis of fungal pulmonary infections. *Radiol Med* 2006;**111**:33–41.
91. Clark BD, Vezza PR, Copeland C, Wilder AM, Abati A. Diagnostic sensitivity of bronchoalveolar lavage versus fine needle aspirate. *Mod Pathol* 2002;**15**:1259–65.
92. Hwang SS, Kim HH, Park SH, Jung JI, Jang HS. The value of CT-guided percutaneous needle aspiration in immunocompromised patients with suspected pulmonary infection. *Am J Roentgenol* 2000;**175**:235–8.
93. Kim K, Lee MH, Kim J, et al. Importance of open lung biopsy in the diagnosis of invasive pulmonary aspergillosis in patients with hematologic malignancies. *Am J Hematol* 2002;**71**:75–9.
94. Lass-Flörl C, Resch G, Nachbaur D, et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immuno-compromised patients. *Clin Infect Dis* 2007;**45**:e101–4.
95. Rickerts V, Mousset S, Lambrecht E, et al. Comparison of histopathological analysis, culture, and polymerase chain reaction assays to detect invasive mold infections from biopsy specimens. *Clin Infect Dis* 2007;**44**:1078–83.
96. Haynes K, Rogers TR. Retrospective evaluation of a latex agglutination test for diagnosis of invasive aspergillosis in immunocompromised patients. *Eur J Clin Microbiol Infect Dis* 1994;**13**:670–4.
97. Saugier-Veber P, Devergie A, Sulahian A, et al. Epidemiology and diagnosis of invasive pulmonary aspergillosis in bone marrow transplant patients. *Bone marrow transplant* 1993;**12**:121–4.
98. Becker MJ, Lugtenburg EJ, Cornelissen JJ, et al. Galactomannan detection in computerized tomography-based broncho-alveolar lavage fluid and serum in haematological patients at risk for invasive pulmonary aspergillosis. *Br J Haematol* 2003;**121**:448–57.
99. Bretagne S, Costa JM, Marmorat-Khuong A, et al. Detection of Aspergillus species DNA in bronchoalveolar lavage samples by competitive PCR. *J Clin Microbiol* 1995;**33**:1164–8.
100. Buchheidt D, Baust C, Skladny H, et al. Detection of aspergillus species in blood and bronchoalveolar lavage samples from immunocompromised patients by means of 2-step polymerase chain reaction: clinical results. *Clin Infect Dis* 2001;**33**:428–35.
101. Busca A, Locatelli F, Barbui A, et al. Usefulness of sequential Aspergillus galactomannan antigen detection combined with early radiologic evaluation for diagnosis of invasive pulmonary aspergillosis in patients undergoing allogeneic stem cell transplantation. *Transplant Proc* 2006;**38**:1610–3.
102. Einsele H, Hebart H, Roller G, et al. Detection and identification of fungal pathogens in blood by using molecular probes. *J Clin Microbiol* 1997;**35**:1353–60.
103. Maertens J, Verhaegen J, Demuynck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. *J Clin Microbiol* 1999;**37**:3223–8.
104. Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the Aspergillus double-sandwich enzyme immunoassay. *Clin Infect Dis* 2007;**44**:1329–36.
105. Spiess B, Buchheidt D, Baust C, et al. Development of a LightCycler PCR assay for detection and quantification of Aspergillus fumigatus DNA in clinical samples from neutropenic patients. *J Clin Microbiol* 2003;**41**:1811–8.
106. Verweij PE, Latgé JP, Rijs AJMM, et al. Comparison of antigen detection and PCR assay using bronchoalveloar lavage fluid for diagnosing invasive pulmonary aspergillosis in patients receiving treatment for hematologic malignancies. *J Clin Microbiol* 1995;**33**:3150–3.
107. Weisser M, Rausch C, Droll A, et al. Galactomannan does not precede major signs on a pulmonary computerized tomographic scan suggestive of invasive aspergillosis in patients with hematological malignancies. *Clin Infect Dis* 2005;**41**:1143–9.
108. Aubry A, Porcher R, Bottero J, et al. Occurrence and kinetics of false-positive Aspergillus galactomannan test results following treatment with beta-lactam antibiotics in patients with hematological disorders. *J Clin Microbiol* 2006;**44**:389–94.
109. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1→3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis* 2005;**41**:654–9.
110. Ruhnke M, Böhme A, Buchheidt D, et al. Diagnosis of invasive fungal infections in hematology and oncology. *Ann Hematol* 2003;**82**(Suppl. 2):S141–8.
111. Lass-Flörl C, Gunsilius E, Gastl G, et al. Diagnosing invasive aspergillosis during antifungal therapy by PCR analysis of blood samples. *J Clin Microbiol* 2004;**42**:4154–7.
112. Ljungman P, von Dobeln L, Ringholm L, et al. The value of CMV and fungal PCR for monitoring for acute leukaemia and autologous stem cell transplant patients. *Scand J Infect Dis* 2005;**37**:121–7.
113. Musher B, Fredricks D, Leisenring W, Balajee SA, Smith C, Marr KA. Aspergillus galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *J Clin Microbiol* 2004;**42**:5517–22.
114. Donnelly JP. Polymerase chain reaction for diagnosing invasive aspergillosis: getting closer but still a ways to go. *Clin Infect Dis* 2006;**42**:487–9.
115. White PL, Linton CJ, Perry MD, Johnson EM, Barnes RA. The evolution and evaluation of a whole blood polymerase chain reaction assay for the detection of invasive aspergillosis in hematology patients in a routine clinical setting. *Clin Infect Dis* 2006;**42**:479–86.
116. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, et al. Markers of bacteremia in febrile neutropenic patients with haematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. *Eur J Clin Microbiol Infect Dis* 2004;**23**:539–44.
117. Ostermann H, Rothenburger M, Mesters RM, van de Loo J, Kienast J. Cytokine response to infection in patients with acute myelogenous leukaemia following intensive chemotherapy. *Br J Haematol* 1994;**88**:332–7.
118. Monneret G, Doche C, Durand DV, Lepape A, Bienvenu J. Procalcitonin as a specific marker of bacterial infection in adults. *Clin Chem Lab Med* 1998;**36**:67–8.
119. Kiehl MG, Ostermann H, Thomas M, Birkfellner T, Kienast J. Inflammatory mediators in BAL fluid as markers of evolving

pneumonia in leukocytopenic patients. *Chest* 1997;**112**:1214–20.
120. Allaouchiche B, Coronel B, Gagnieu MC, Chassard D, Mercatello A. Cytokine levels in bronchoalveolar lavage fluid and blood of neutropenic patients with pneumonia. *Bull Cancer* 2004;**91**:E77–80.
121. Link H, Böhme A, Cornely OA, et al. Antimicrobial therapy of unexplained fever in neutropenic patients. *Ann Hematol* 2003;**82**(Suppl. 2):S105–17.
122. Schoepf UJ, Bruening RD, Hong C, et al. Multislice helical CT of focal and diffuse lung disease: comprehensive diagnosis with reconstruction of contiguous and high-resolution CT sections from a single thin-collimation scan. *Am J Roentgenol* 2001;**177**:179–84.
123. Herbrecht R, Denning DW, Patterson TF. Et al; Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;**347**:408–15.
124. Slobbe L, Polinder S, Doorduijn JK, et al. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia–myelodysplastic syndrome treated with intensive chemotherapy: an observational study. *Clin Infect Dis* 2008;**47**:1507–12.
125. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing. *Clin Infect Dis* 2007;**44**:1289–97.
126. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004;**351**:1391–402.
127. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003;**326**:1111–9.
128. Pagano L, Caira M, Nosari A, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study. *Clin Infect Dis* 2007;**45**:1161–70.
129. Reich G, Mapara MY, Reichardt P, Dörken B, Maschmeyer G. Infectious complications after high-dose chemotherapy and autologous stem cell transplantation. *Bone Marrow Transpl* 2001;**27**:525–9.
130. Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients. *Transpl Infect Dis* 2007;**9**:189–95.
131. Holmberg LA, Boeckh M, Hooper H, et al. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. *Blood* 1999;**94**:4029–35.
132. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker WB, Lautenbach E. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing enterobacteriaceae: variability by site of infection. *Arch Intern Med* 2005;**165**:1375–80.
133. Böhme A, Ruhnke M, Buchheidt D, et al. Treatment of invasive fungal infections in cancer patients. *Ann Hematol* 2009;**88**:97–110.
134. Maschmeyer G, Haas A. Defining clinical failure for salvage studies. *Med Mycol* 2006;**44**:S315–8.
135. Nahimana A, Rabodonirina M, Zanetti G, et al. Association between a specific Pneumocystis jiroveci dihydropteroate synthase mutation and failure of pyrimethamine/sulfadoxine prophylaxis in human immunodeficiency virus-positive and -negative patients. *J Infect Dis* 2003;**188**:1017–23.
136. Thomas Jr CF, Limper AH. Pneumocystis pneumonia. *N Engl J Med* 2004;**350**:2487–98.
137. Smego Jr RA, Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med* 2001;**161**:1529–33.
138. Hilbert G, Gruson D, Vargas F, et al. Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med* 2000;**28**:3185–90.
139. Delclaux C, Zahar JR, Amraoui G, et al. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in non-human immunodeficiency virus-infected patients. *Clin Infect Dis* 1999;**29**:670–2.
140. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. *Chest* 1998;**113**:1215–24.
141. Cherif H, Martling CR, Hansen J, Kalin M, Björkholm M. Predictors of short and long-term outcome in patients with hematological disorders admitted to the intensive care unit for a life-threatening complication. *Support Care Cancer* 2007;**15**:1393–8.
142. Maschmeyer G, Bertschat FL, Moesta KT, et al. Outcome analysis of 189 consecutive cancer patients referred to the intensive care unit as emergencies during a 2-year period. *Eur J Cancer* 2003;**39**:783–92.
143. Owczuk R, Wujtewicz MA, Sawicka W, Wadrzyk A, Wujtewicz M. Patients with haematological malignancies requiring invasive mechanical ventilation: differences between survivors and non-survivors in intensive care unit. *Support Care Cancer* 2005;**13**:332–8.
144. Sculier JP. Intensive care and oncology. *Support Care Cancer* 1995;**3**:93–105.