Lung Infiltrates in Patients with Febrile Neutropenia

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases
Publisher

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V.
Alexanderplatz 1
D-10178 Berlin

Executive chairman: Prof. Dr. med. Lorenz Trümper

Phone: +49 (0)30 27 87 60 89 - 0
Fax: +49 (0)30 27 87 60 89 - 18

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

www.onkopedia-guidelines.info

The information of the DGHO Onkopaedia Web Site is not intended or implied to be a substitute for professional medical advice or medical care. The advice of a medical professional should always be sought prior to commencing any form of medical treatment. To this end, all component information contained within the web site is done so for solely educational purposes. DGHO Deutsche Gesellschaft für Hämatologie und Onkologie and all of its staff, agents and members disclaim any and all warranties and representations with regards to the information contained on the DGHO Web Site. This includes any implied warranties and conditions that may be derived from the aforementioned web site information.
Lung Infiltrates in Patients with Febrile Neutropenia

Date of document: January 2012

Compliance rules:
- Guideline
- Conflict of interests

Authors: Georg Maschmeyer, Thomas Beinert, Dieter Buchheidt, Oliver A. Cornely, Hermann Einsele, Werner Heinz, Claus Peter Heußel, Herbert Hof, Christoph Kahl, Michael Kiehl, Joachim Lorenz, Gloria Mattiuzzi

on behalf of the AGIHO Infectious Diseases Working Party of the DGHO

1 Definition and Basic Information

Febrile neutropenia with lung infiltrates is one of most common complications after intensive chemotherapy. The guideline was developed by the Infectious Disease Working Party AGIHO of the DGHO for these patients [1]. This guideline does not refer to patients undergoing allogenic hematopoietic stem cell transplantation. These patients are subject to a separate guideline.

Categories are based on the evaluation of study results and the recommendations developed by the Infectious Diseases Society of America, ISDA, see Table 1.

Table 1: Categories of Evidence

<table>
<thead>
<tr>
<th>Category, grade Strength of Recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation for use</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence to support a recommendation against use</td>
</tr>
<tr>
<td>E</td>
<td>Good evidence to support a recommendation against use</td>
</tr>
</tbody>
</table>

Quality of Evidence                                      Definition
I    Evidence from ≥1 properly randomized, controlled trial
II   Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferable 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 studies, or reports from expert committees

2 Epidemiology

Lung infiltrates (LIs) emerge in 15-28% of patients with profound neutropenia following intensive chemotherapy. As compared with other types of infections, treatment of LIs in neutropenic patients is more difficult and costly. These infiltrates may have numerous different causes including multi-resistant bacteria, filamentous fungi, *Pneumocystis jiroveci* und viruses. Differential diagnosis includes alveolar bleeding, infiltration by the underlying malignancy, crypto-
genic organising pneumonia, immune reconstitution syndrome and lesions caused by chemotherapy or radiation.

Clinical trials, microbiological and histological results along with autopsy studies indicate that the majority of LIs in febrile neutropenic patients is caused by filamentous fungi. Clinical outcome of proven invasive aspergilliosis in neutropenic patients is poor, 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 and a with CT scan not typical for pneumocystis pneumonia (B-II).

3 Diagnostics

The algorithm for rational diagnostics is depicted in Figure 1.

Figure 1: Algorithm for Clinical Management in Patients with Febrile Neutropenia and Lung Infiltrates

Clinical Suspect
(Fever and/or signs and/or symptoms of LRTI)

Chest Radiograph

CT Scan

pathologic normal / unclear

pathologic pathologic

BAL not feasible normal

negative

Pre-emptive Therapy

No Response Response

Targeted Therapy

No Response Response

Invasive Diagnostics

CT Follow-up Control

Legend:
1 CT - Computer Tomography;
2 BAL - Bronchoalveolar Lavage;
3 LI - Lung Infiltrate;
4 Invasive Diagnostics: e.g. open lung biopsy or fine needle biopsy;
‒ ‒ ‒ dotted lines indicate exceptions from recommended procedure

3.1 Imaging

Patients with fever of unknown origin (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 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 technique (B-II).

In patients with pathologic findings on chest radiographs additional thoracic CT scan is recommended for a more detailed imaging of the lung infiltrates.

### 3.2 Bronchoscopy

In patients with LIs, a fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) of the affected region is recommended (B-III). The maximum period between sampling and start of laboratory work-up should be less than 4 h. Samples should be transported under cooling conditions (+4°C) (A-III). The recommended program for microbiological work-up is shown in Tables 2 and 3.

**Table 2: Processing of Bronchoalveolar Lavage (BAL) Material (B-III). - Recommended Program**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytospin preparations</td>
<td>Distinction between intracellular from extracellular pathogens and identifying infiltration by underlying malignancy</td>
</tr>
<tr>
<td>Gram stain</td>
<td></td>
</tr>
<tr>
<td>Giemsa / May - Grünwald - Giemsa stain</td>
<td>Assessment of macrophages, ciliated epithelium, leukocytes)</td>
</tr>
<tr>
<td>Calcofluor-white or equivalent</td>
<td>Assessment of fungi and <em>Pneumocystis jiroveci</em></td>
</tr>
<tr>
<td>Direct immunofluorescence test for <em>Pneumocystis jiroveci</em></td>
<td>Confirmatory</td>
</tr>
<tr>
<td>Direct immunofluorescence for <em>Legionella</em> spp.</td>
<td></td>
</tr>
<tr>
<td>Ziehl-Neelsen / Auramin stain</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> – Antigen</td>
<td>Galactomannan Sandwich ELISA</td>
</tr>
<tr>
<td>Quantitative cultures</td>
<td>Dilutions of $10^{-2}$ to $10^{-4}$; Culture media: blood, McConkey / Endo, Levinthal / Blood (bacterial culture), <em>Legionella</em> - BCYE α or equivalent (<em>Legionella</em> spp.), Löwenstein-Jensen or equivalent (mycobacteria), Sabouraud / Kimmig or equivalent (fungal culture)</td>
</tr>
</tbody>
</table>

**Table 3: Processing of Bronchoalveolar Lavage (BAL) Material (B-III)- Optional Program**

<table>
<thead>
<tr>
<th>Method</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrichment culture</td>
<td>Brain-Heart Infusion, dextrose broth</td>
</tr>
<tr>
<td>Direct immunofluorescence test for <em>Chlamydia pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Culture for <em>Chlamydia pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Legionella</em> PCR</td>
<td></td>
</tr>
<tr>
<td>Shell vial technique and PCR for influenza, parainfluenza and adenovirus</td>
<td></td>
</tr>
<tr>
<td>Culturing or antigen detection of Herpes simplex and Varicella zoster virus</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus early antigen; rapid culture</td>
<td></td>
</tr>
<tr>
<td>CMV antibody</td>
<td>ELISA, IgG/IgM</td>
</tr>
<tr>
<td>HSV antibody (ELISA, IgG/IgM)</td>
<td>ELISA, IgG/IgM</td>
</tr>
<tr>
<td>VZV antibody (ELISA, IgG/IgM/IgA)</td>
<td>ELISA, IgG/IgM/IgA</td>
</tr>
<tr>
<td>Respiratory syncytial virus (PCR, ELISA)</td>
<td>PCR, ELISA</td>
</tr>
<tr>
<td>Panfungal/Aspergillus PCR</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood cultures 1 h after bronchoscopy</td>
<td>Diagnosis of transient bacteremia</td>
</tr>
</tbody>
</table>
Microbiological findings from neutropenic patients must be interpreted critically with respect to their etiological significance.

Etiologically significant are:

- *Pneumocystis jiroveci*, Gram-negative aerobic pathogens, pneumococci, *Mycobacterium tuberculosis* or *Aspergillus* spp. or *Aspergillus*-Galactomannan or zygomycetes obtained from BAL or sputum samples; positive rapid culture for CMV or detection of CMV “immediate early antigen”
- Isolation of pneumococci, alpha-haematolytic 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

Etiologically insignificant for lung infiltrates are

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

*Note*: Detection of these pathogens may indicate other infections.

### 4 Therapy

#### 4.1 Pre-emptive Antimicrobial Therapy

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.

In patients with acute leukemia or other aggressive hematological malignancies and severe neutropenia lasting for more than 10 days and LIIs, initial antimicrobial therapy should consist of an anti-pseudomonal beta-lactam antibacterial agent plus voriconazole (6 mg/kg every 12 h on day 1, followed by 4 mg/kg every 12 Stunden) or liposomal amphotericin B (3 mg/kg daily) (B-II), see Figure 2. Recommendations on dosage are summarized in the Addendum Antimicrobial Therapy, see Tables 4, 5, 6 and 7.
Figure 2: Pre-emptive Antimicrobial Therapy

Legend:

1 ASCT - autologous Stem Cell Transplantation

Liposomal amphotericin B is preferred in patients in whom a pulmonary zygomycosis is considered and in those patients who have recently been treated with voriconazole or posaconazole (B-III). The antifungal therapy should be continued until hematopoetic recovery and regression of clinical and radiological signs of infection (B-III).

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

Patients after autologous stem cell transplantation (ASCT) have a very low risk of fungal pneumonia. Therefore, pre-emptive antifungal therapy should be restricted to individual patients with febrile neutropenia and lung infiltrates (B-II). In patients with LIs of unknown origin after CD34-selected ASCT, bronchoscopy with BAL should be considered to eventually diagnose CMV infection (B-III). In case of a positive rapid culture or detection of ‘immediate early antigen’, pre-emptive ganciclovir treatment is indicated (B-III).

4.2 Targeted Antimicrobial Therapy

Voriconazole or liposomal amphotericin B is the agent of choice for primary treatment of invasive pulmonary aspergillosis, 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).

Patients with proven *Pneumocystis jiroveci* (PcP) pneumonia should be treated primarily with trimethoprim-sulfamethoxazole (cotrimoxazole) at a daily dosage of TMP 15-20mg/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. In case of confirmed resistance or TMP/SMX intolerance, second-line therapy with clindamycin plus primaquine is an alternative (C-III).

4.3 Respiratory Failure

Non-invasive CPAP with mask is recommended in patients with progressive respiratory failure (B-II). The value of glucocorticoids in this setting is unclear. Neutropenic cancer patients with respiratory failure caused by LIs may have a favorable outcome under intensive care, including
mechanical ventilation. 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).

5 References


6 Antimicrobial Drugs and Dose

Table 4: Betalactam Antibiotics (in alphabetical order)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose¹</th>
<th>Application</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipemem - Cilastatin</td>
<td>3 x 1 g oder 4 x 0,5 g</td>
<td>IV</td>
<td>until afebrile for at least 72 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3 x 1 g</td>
<td>IV</td>
<td>until afebrile for at least 72 h</td>
</tr>
<tr>
<td>Piperacillin - Tazobactam</td>
<td>3 - 4 x 4,5 g</td>
<td>IV</td>
<td>until afebrile for at least 72 h</td>
</tr>
</tbody>
</table>

Legend:
¹ Dose for patients with normal renal function

Table 5: Antimycotics (in alphabetic order)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose¹</th>
<th>Application</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin, liposomal</td>
<td>3 mg / kg</td>
<td>IV</td>
<td>until hematological recovery and resolution of clinical and radiological signs of infection</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Day 1: 2 x 6 mg / kg From Day 2: 2 x 4 mg / kg</td>
<td>IV</td>
<td>until hematological recovery and resolution of clinical and radiological signs of infection</td>
</tr>
</tbody>
</table>

Legend:
¹ Dose for patients with normal renal function; ² recommended in patients with pulmonary zygomycosis and in patients after treatment with voriconazole or posaconazole

Table 6: Antibiotics in Patients with Pneumocystis - Pneumonia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose¹</th>
<th>Application</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole (Trimethoprim - Sulfamethoxazole)</td>
<td>3 - 4 x 30 - 40 mg/kg or 3 - 4 x 2400 mg</td>
<td>IV</td>
<td>2 - 3 weeks and until hematological recovery and resolution of clinical and radiological signs of infection</td>
</tr>
<tr>
<td>Clindamycin plus Primaquine</td>
<td>3 - 4 x 600 mg plus 30 mg</td>
<td>IV PO</td>
<td>2 - 3 weeks and until hematological recovery and resolution of clinical and radiological signs of infection</td>
</tr>
</tbody>
</table>

Legend:
¹ Dose for patients with normal renal function

Table 7: Antiviral Therapy in Patients with CMV Pneumonia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose¹</th>
<th>Application</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>2 x 5 mg / kg</td>
<td>IV</td>
<td>2 weeks and until hematological recovery and resolution of clinical and radiological signs of infection</td>
</tr>
</tbody>
</table>
7 Links

https://www.agiho.de/ueber-die-agiho

8 Authors’ Affiliations

Prof. Dr. med. Georg Maschmeyer
Klinikum Ernst von Bergmann
Zentrum für Innere Medizin
Klinik für Hämatologie, Onkologie
und Palliativmedizin
Charlottenstr. 72
14467 Potsdam
georg.maschmeyer@klinikumevb.de

PD Dr. med. Thomas Beinert
Paracelsus-Kliniken
Klinik am See
Dehneweg 6
37581 Bad Gandersheim
thomas.beinert@paracelsus-kliniken.de

Prof. Dr. med. Dieter Buchheidt
Klinikum Mannheim GmbH
Medizinische Fakultät Mannheim
Ill. Medizinische Klinik
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
dieter.buchheidt@umm.de

Prof. Dr. med. Oliver A. Cornely
Uniklinik Köln, Klinik I für Innere Med.
Zentrum für Klinische Studien
Infektiologie-Hämatologie-Onkologie
Kerpener Str. 62
50937 Köln
oliver.cornely@uk-koeln.de

Prof. Dr. med. Hermann Einsele
Universitätsklinikum Würzburg
Medizinische Klinik und Poliklinik II
Oberdürrbacher Str. 6
97080 Würzburg
einsele_h@ukw.de

PD Dr. med. Werner Heinz
Kliniken Nordoberpfalz AG
Klinikum Weiden
Med. Klinik I
Söllnerstr.16
92637 Weiden
werner.heinz@kliniken-nordoberpfalz.ag
Prof. Dr. med. Claus Peter Heußel
Thoraxklinik am Universitätsklinikum Heidelberg
Abteilung für Diagnostische & Interventionelle Radiologie
Amalienstr. 5
69126 Heidelberg
clauspeter.heussel@med.uni-heidelberg.de

Prof. Dr. med. Herbert Hof
Labor Dr. Limbach und Kollegen
Medizinisches Versorgungszentrum
Im Breitspiel 15
69126 Heidelberg
herbert.hof@labor-limbach.de

Prof. Dr. med. Christoph Kahl
Klinikum Magdeburg gGmbH
Klinik für Hämatologie, Onkologie und Palliativmedizin
Birkenallee 34
39130 Magdeburg
christoph.kahl@klinikum-magdeburg.de

Prof. Dr. med. Michael Kiehl
Klinikum Frankfurt (Oder) GmbH
Medizinische Klinik I
Müllroser Chaussee 7
15236 Frankfurt (Oder)
michael.kiehl@klinikumffo.de

Prof. Dr. med. Joachim Lorenz
Märkische Kliniken GmbH
Klinikum Lüdenscheid
Pneumologie und Internistische Intensivmedizin
Paulmannshöher Str. 14
58515 Lüdenscheid
joachim.lorenz@kkh-luedencheid.de

Gloria Mattiuzzi
M.D. Anderson Cancer Center Houston
Department of Leukemia
Hematologic Malignancies
Supportive Care Program
Houston, Texas