

Lung Infiltrates in Patients with Febrile Neutropenia

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

Publisher

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Table of contents

1 Definition and Basic Information	2
2 Epidemiology	2
3 Diagnostics	3
3.1 Imaging.....	3
3.2 Bronchoscopy	4
4 Therapy	5
4.1 Pre-emptive Antimicrobial Therapy.....	5
4.2 Targeted Antimicrobial Therapy	6
4.3 Respiratory Failure	6
9 References	7
10 Antimicrobial Drugs and Dose	7
15 Links	8
16 Authors' Affiliations	8
17 Disclosures	9

Lung Infiltrates in Patients with Febrile Neutropenia

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- [Guideline](#)
- [Conflict of interests](#)

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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

Category, grade Strength of Recommendation	Definition
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 for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
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

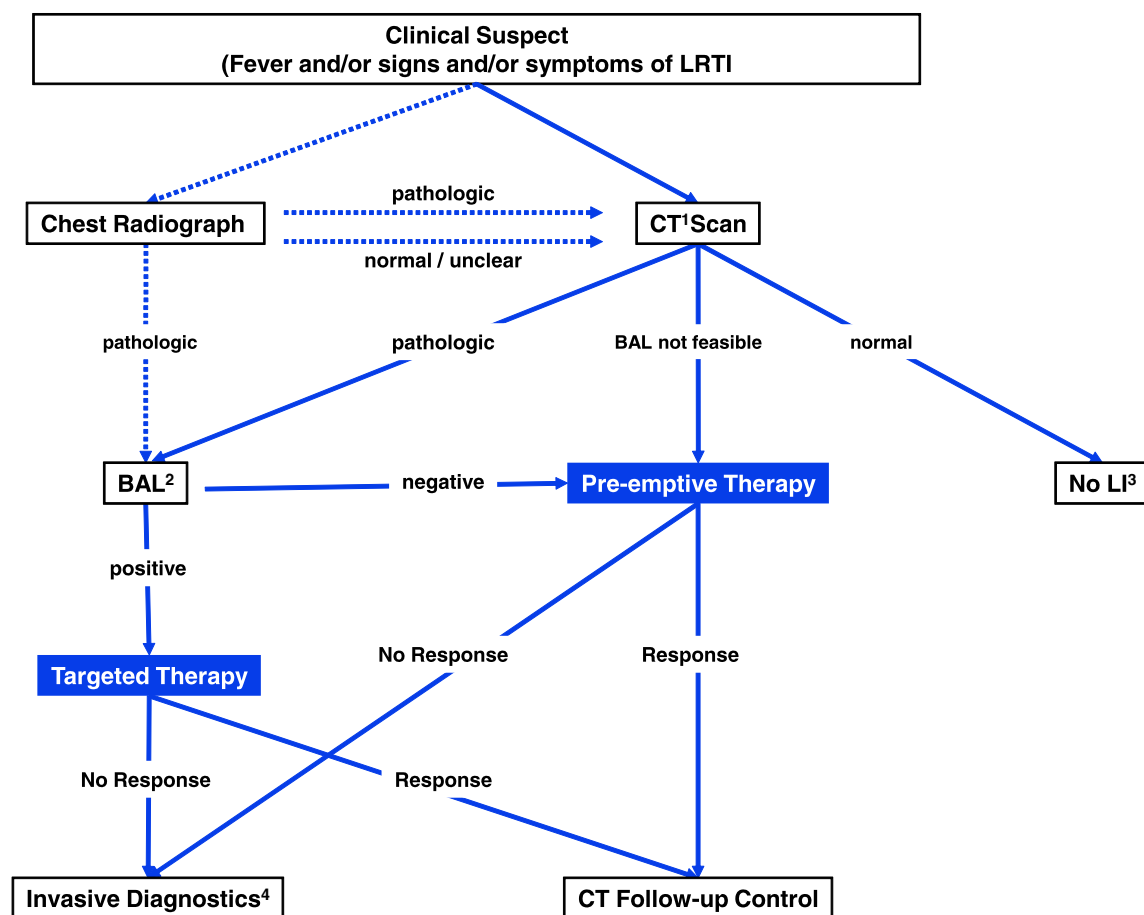
Lung infiltrates (LIs) emerge in 15-28% of patients with profound neutropenia following intensive chemotherapy. As compared with other types of infections, treatment of LIs in neutropenic patients is more difficult and costly. These infiltrates may have numerous different causes including multi-resistant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



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

Methods	Notes
Cytospin preparations	Distinction between 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 <i>Pneumocystis jiroveci</i>
Direct immunofluorescence test for <i>Pneumocystis jiroveci</i>	Confirmatory
Direct immunofluorescence for <i>Legionella</i> spp.	
Ziehl-Neelsen / Auramin stain	
<i>Aspergillus</i> - Antigen	Galactomannan Sandwich ELISA
Quantitative cultures	Dilutions of 10 ⁻² to 10 ⁻⁴ ; Culture media: blood, McConkey / Endo, Levinthal / Blood (bacterial culture), Legionella - BCYE α or equivalent (<i>Legionella</i> spp.), Löwenstein-Jensen or equivalent (mycobacteria), Sabouraud / Kimmig or equivalent (fungal culture)

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

Method	Note
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)	ELISA, IgG/IgM
VZV antibody (ELISA, IgG/IgM/IgA)	ELISA, IgG/IgM/IgA
Respiratory syncytial virus (PCR, ELISA)	PCR, ELISA
Panfungal/Aspergillus PCR	
Peripheral blood cultures 1 h after bronchoscopy	Diagnosis of transient bacteremia
Throat swab	Assessment of oral flora in comparison with BAL
<i>Pneumocystis jiroveci</i> PCR	

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.

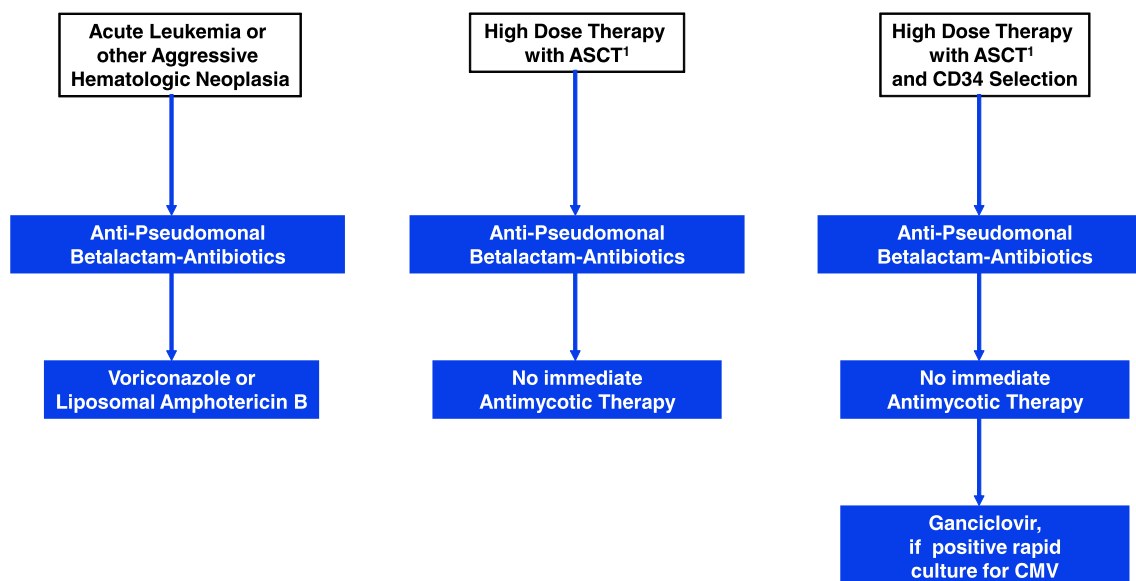
4 Therapy

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 LIs, 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 antimycotic therapy should be continued until hematopoietic 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).

9 References

1. Maschmeyer G, Beinert T, Buchheidt D, Cornely OA, Einsele H, Heinz W, Heussel CP, Kahl C, Kiehl M, Lorenz J, Hof H, Mattiuzzi G. Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients. 2008 updated guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology. Eur J Cancer 45:2462-72, 2009.

10 Antimicrobial Drugs and Dose

Table 4: Betalactam Antibiotics (in alphabetical order)

Drug	Daily Dose ¹	Application	Duration
Imipemem - Cilastatin	3 x 1 g oder 4 x 0,5 g	IV	until afebrile for at least 72 h
Meropenem	3 x 1 g	IV	until afebrile for at least 72 h
Piperacillin - Tazobactam	3 - 4 x 4,5 g	IV	until afebrile for at least 72 h

Legend:

¹ Dose for patients with normal renal function

Table 5: Antimycotics (in alphabetic order)

Drug	Dose ¹	Application	Duration
Amphotericin, liposomal ²	3 mg / kg	IV	until hematological recovery and resolution of clinical and radiological signs of infection
Voriconazole	Day 1: 2 x 6 mg / kg From Day 2: 2 x 4 mg / kg	IV	until hematological recovery and resolution of clinical and radiological signs of infection

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

Drug	Dose ¹	Application	Duration
Cotrimoxazole (Trimethoprim - Sulfamethoxazole)	3 - 4 x 30 - 40 mg/kg or 3 - 4 x 2400 mg	IV	2 - 3 weeks and until hematological recovery and resolution of clinical and radiological signs of infection
Clindamycin plus Primaquine	3 - 4 x 600 mg plus 30 mg	IV PO	2 - 3 weeks and until hematological recovery and resolution of clinical and radiological signs of infection

Legend:

¹ Dose for patients with normal renal function

Table 7: Antiviral Therapy in Patients with CMV Pneumonia

Drug	Dose ¹	Application	Duration
Ganciclovir	2 x 5 mg / kg	IV	2 weeks and until hematological recovery and resolution of clinical and radiological signs of infection

Legend:

¹ Dose for patients with normal renal function;

15 Links

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

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17 Disclosures

according to the rules of the responsible Medical Societies.