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Unusual fungal infections

Prophylaxis

Prophylaxis alternatives

Examples of risk factors triggering targeted prophylaxis/pre-emptive therapy

Empirical Treatment of the Persistently Febrile Neutropenic Patient

Recommended empirical treatment

Current recommended initial strategy

Combination Treatment and Antifungals Under Development

Combination therapy: the issues

Antifungals under development

General references

Web sites

Abbreviations
Preface to the First Edition

This guide is intended as a unique resource for clinicians responsible for the management of patients with systemic fungal infections. Up-to-date information is combined with the authors’ extensive experience in the field and is presented in a clear, well-designed format.

The text focuses on three main areas and is displayed in the form of tables for easy accessibility:

- **Clinical and Laboratory Diagnosis** presents the essential examinations, investigations, and criteria for the diagnosis of systemic fungal infections

- **Antifungal Drugs** introduces currently available antifungal agents and provides details on their uses, typical dosages, adverse effects, and pharmaceutics/pharmacokinetics

- **Therapy of Specific Infections** describes preventative strategies and therapies against individual organisms and diseases.

Separate sections cover **Prophylaxis** and **Empirical Treatment of the Persistently Febrile Neutropenic Patient**, and a **General References** list is provided.

Dosage recommendations are based on the prescribing information for each antifungal agent and are accurate at the time of publication. The authors have made a special effort to ensure that the dosage recommendations are accurate and in agreement with the standards and collective opinion accepted at the time of publication. The formulations and usage described do not necessarily have specific approval by the regulatory authorities of all countries.

Since dosage regimens and contraindications may be regularly reviewed and revised, further editions of this guide are envisaged in order to keep this information updated.
Preface to the Third Edition

An even greater understanding of the benefits and limitations of old and new antifungal agents is reflected in this edition of *Therapeutic Guidelines in Systemic Fungal Infections*. Each table has been revised to present antifungal treatment as it is used today, taking into account evidence-based recommendations that have been made since the publication of the first and second editions. New diagnostic tests such as PCR and ELISA have been assessed in immunocompromised patients. These may assist in the choice of antifungal and may be used to monitor treatment success or failure. The number of oral and parenteral antifungal agents has increased significantly and new formulations of established agents have been licensed in many countries. Furthermore, antifungal susceptibility testing has been refined. Significant progress has been made in determining the applications of these tests in routine clinical practice. The use of these tests is indicated where appropriate. As previously, we have included the most relevant key publications and reviews at the ends of the tables. These provide a link to a far larger body of established literature.

We have made every effort to ensure that the dosage recommendations are accurate and in agreement with the standards and collective opinion accepted at the time of publication. The formulations and usage described do not necessarily have specific approval by the regulatory authorities of all countries. Since dosage regimens may be modified as new clinical research accumulates, readers are strongly advised to check the prescribing information to see whether changes have been made to the recommended dosages and/or contraindications for use. New antifungal agents are constantly being developed and evaluated. Some are close to being introduced into clinical practice. Significant changes in the guidelines and key publications will be available on Clinical Mycology Online (www.clinical-mycology.com).

Malcolm Richardson
Brian Jones
Clinical and Laboratory Diagnosis

1. Definitions of fungal infections
2. Categories of risk groups for systemic fungal infection
3. Essential clinical examination in neutropenic and solid organ transplant patients with suspected invasive fungal infection
4. Investigation of pulmonary infection in neutropenic and solid organ transplant patients
5. Essential investigations for the laboratory diagnosis of systemic fungal infections
6. Fungal species most commonly recovered from clinical specimens
7. Criteria for the diagnosis of systemic fungal infections: clinical features and laboratory parameters contributing to a definitive diagnosis
8. Assessment of the response to antifungal therapy – definitions
1 Definitions of fungal infections

PROVEN INVASIVE FUNGAL INFECTIONS

Deep tissue infections

Molds*

Histo/cytochemistry showing hyphae or spherules (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging)

OR

Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection

Yeasts*

Histo/cytochemistry showing yeast cells and/or pseudohyphae from a needle aspiration or biopsy excluding mucous membranes

OR

Positive culture obtained from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes by a sterile procedure

OR

Microscopy (India ink, mucicarmine stain) or antigen positivity for Cryptococcus in CSF

Fungemia

Molds*

Positive blood culture of fungi excluding Aspergillus species and Penicillium species, other than P. marneffei, accompanied by temporally related clinical signs and symptoms compatible with the relevant organism

Yeasts*

Positive blood culture of Candida and other yeasts in patients with temporally related clinical signs and symptoms compatible with the relevant organism

* Append identification at genus or species level if available
**Definitions of fungal infections**

<table>
<thead>
<tr>
<th>Endemic fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either systemic or only confined to lungs, must be proven by culture from the site affected, in a host with symptoms attributed to the fungal infection. If cultures are negative or unattainable, histopathological demonstration of the appropriate morphological forms must be combined with serological support.</td>
</tr>
</tbody>
</table>

**PROBABLE INVASIVE FUNGAL INFECTIONS**

- Defined as at least one criterion from host section (see next page)
- AND
- One microbiological criterion
- AND
- One major (or two minor) clinical criteria from an abnormal site consistent with infection

**POSSIBLE**

**INVASIVE FUNGAL INFECTIONS**

- Defined as at least one criterion from host section
- AND
- One microbiological OR one major (or two minor) clinical criteria from an abnormal site consistent with infection

**This category is NOT recommended for use in clinical trials on antifungal agents, but for use in studies on empirical treatment, epidemiological studies, and studies on health economics when needed.**

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**Clinical and laboratory diagnosis**
### Definitions of fungal infections

#### CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Microbiological criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Neutropenia: neutrophils &lt;500/mm³ for more than 10 days</td>
<td>1. Positive culture of a mold (including <em>Aspergillus</em> species, <em>Fusarium</em> species, zygomycetes, <em>Scedosporium</em> species) or <em>C. neoformans</em> from sputum, BAL</td>
</tr>
<tr>
<td>2. Persistent fever for &gt;96 h refractory to appropriate broad spectrum antibacterial treatment</td>
<td>2. Positive culture or cytology/direct microscopy for molds from sinus aspirate</td>
</tr>
<tr>
<td>3. Body temperature either &gt;38°C or &lt;36°C AND any of the following</td>
<td>3. Positive cytology/direct microscopy for a mold or <em>Cryptococcus</em> from sputum, BAL</td>
</tr>
<tr>
<td>a. Prolonged neutropenia (&gt;10 days) in the previous 60 days</td>
<td>4. Positive <em>Aspergillus</em> antigen in BAL, CSF or ≥ 2 blood samples</td>
</tr>
<tr>
<td>b. Recent or current use of significant immunosuppressive agents in the</td>
<td>5. Positive cryptococcal antigen in blood</td>
</tr>
<tr>
<td>previous 30 days</td>
<td>6. Positive cytology/direct microscopy for fungal elements other than</td>
</tr>
<tr>
<td>c. Invasive fungal infection in a previous episode</td>
<td><em>Cryptococcus</em> in sterile body fluids</td>
</tr>
<tr>
<td>d. Coexistence of AIDS</td>
<td>7. Two positive urine cultures of yeasts in the absence of urinary catheter</td>
</tr>
<tr>
<td>4. Signs and symptoms indicating GVHD</td>
<td>8. <em>Candida</em> casts in urine in the absence of urinary catheter</td>
</tr>
<tr>
<td>5. Prolonged use of corticosteroids (&gt;3 weeks)</td>
<td>9. Positive blood culture of <em>Candida</em> species</td>
</tr>
<tr>
<td></td>
<td>10. Pulmonary abnormality and negative bacterial cultures of any possible bacteria</td>
</tr>
<tr>
<td></td>
<td>from any specimen related to lower respiratory tract infection, including blood, sputum, BAL etc</td>
</tr>
</tbody>
</table>
**Clinical criteria**

Should be related to the site of microbiological criteria and temporally related to the current episode

### Lower Respiratory Tract Infection

**Major**

Any of the following new infiltrates on CT imaging: halo sign, air crescent sign, or cavity within an area of consolidation

**Minor**

1. Symptoms of LRTI (cough, chest pain, hemoptysis, dyspnea)
2. Physical finding of pleural rub
3. Any new infiltrate not fulfilling major criterion

### Sinonasal Infection

**Major**

Suggestive radiologic evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction)

**Minor**

1. Upper respiratory symptoms (nasal discharge, stuffiness etc)
2. Nose ulceration or eschar of nasal mucosa or epistaxis
3. Periorbital swelling
4. Maxillary tenderness
5. Black necrotic lesions or perforation of the hard palate

### Central Nervous System Infection

**Major**

Suggestive radiologic evidence of CNS infection (i.e. meningitis extending from a paranasal, auricular, or vertebral process; intracerebral abscesses or infarcts)

**Minor**

(CSF negative for other pathogens by culture, microscopy, and malignant cells)

1. Focal neurologic symptoms and signs (including focal seizures, hemiparesis, and cranial nerve palsies)
2. Mental changes
3. Meningeal irritation findings
4. Abnormalities in CSF biochemistry and cell count

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**Clinical and laboratory diagnosis**
1 Definitions of fungal infections

Disseminated Fungal Infection

1. Papular or nodular skin lesions without any other explanation
2. Intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis

Chronic Disseminated Candidosis

Small, peripheral, target-like abscesses (bull's eye) in liver and/or spleen demonstrated by CT or MRI

Possible Candidemia

No prominent signs or symptoms of infection in patient with positive blood culture of Candida

Key reference

### Categories of risk groups for systemic fungal infection

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Low**           | PBSC autologous BMT  
Childhood acute lymphoblastic leukemia (except for *P. carinii* pneumonia) |
| **Intermediate: low** | Moderate neutropenia $0.1-0.5 \times 10^9/l$ $<3$ weeks  
Lymphocytes $<0.5 \times 10^9/l$ + antibiotics, e.g. co-trimoxazole  
Older age/central venous catheter |
| **Intermediate: high** | Colonized $>1$ site or heavy at $1$ site  
Lymphocytes $<0.5$ to $>0.1 \times 10^9/l$ $>3$ to $<5$ weeks  
Acute myeloid leukemia/total body irradiation  
Allogeneic matched sibling donor BMT |
| **High**          | Neutropenia $<0.1 \times 10^9/l$ $>5$ weeks  
Colonized by *C. tropicalis*  
Allogeneic unrelated or mismatched donor BMT  
GVHD  
Neutropenia $<0.5 \times 10^9/l$ $>5$ weeks  
Corticosteroids $>1$ mg/kg and neutrophils $<1 \times 10^9/l$ $>1$ week  
Corticosteroids $>2$ mg/kg $>2$ weeks  
High-dose cytosine arabinoside  
Fludarabine? |

**Essential clinical examination in neutropenic and solid organ transplant patients with suspected invasive fungal infection**

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Features</th>
<th>Likely infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Scattered lesions, often on limbs; maculopapular, progressing to pustular lesions with central necrosis</td>
<td>Acute disseminated candidosis, disseminated aspergillosis, or <em>Fusarium</em> infection</td>
</tr>
<tr>
<td>Sinus</td>
<td>Upper respiratory tract symptoms with necrotic or ulcerated areas</td>
<td>Invasive aspergillosis or mucormycosis</td>
</tr>
<tr>
<td>Palate</td>
<td>Ulceration, including the hard palate</td>
<td>Rhinocerebral mucormycosis</td>
</tr>
<tr>
<td>Chest</td>
<td>Signs are few and non-specific: all should be investigated</td>
<td>Invasive pulmonary aspergillosis, PCP, or other fungal pneumonia</td>
</tr>
<tr>
<td>Eyes</td>
<td>Funduscropy may reveal ‘cotton-wool ball’ lesions of <em>Candida</em> choroidoretinitis — rare in neutropenic patients</td>
<td>Acute disseminated candidosis</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Headache, altered mental state, seizure, focal neurologic signs, and neck stiffness</td>
<td>Cryptococcal or candidal meningitis</td>
</tr>
</tbody>
</table>

Investigation of pulmonary infection in neutropenic and solid organ transplant patients

Respiratory signs or symptoms

Underlying condition?

Solid organ recipient

Chest X-ray

Diffuse shadowing?

Focal lesions?

Consider CT-guided biopsy

Consider needle/open biopsy

Yes

No

Focal lesions?

Yes

No

Yes

Cavitation?

Yes

Consider resection

Chest X-ray + CT scan

Diffuse shadowing?

Yes

BAL

No

Focal lesions?

Yes

Consider needle/open biopsy

No

Consider resection

### Essential investigations for the laboratory diagnosis of systemic fungal infections

#### Aspergillosis
- microscopy of sputum, BAL fluid (enhanced by Calcofluor white), and stained biopsy material
- culture of respiratory secretions and biopsy material
- twice weekly EIA for galactomannan (Platelia *Aspergillus*, Bio-Rad, FDA approval 2003) in ‘high risk’ and ‘intermediate risk’ patients (variable results between laboratories)
- detection of β-1,3-D-glucan (Glucatel, Associates of Cape Cod Inc)
- PCR screening twice weekly on whole blood in high/intermediate risk hematology patients (if available locally)

#### Blastomycosis
- microscopy of pus, sputum, bronchial washings, and urine
- culture of pus, sputum, bronchial washings, and urine
- detection of antibody by immunodiffusion

#### Candidosis
- microscopy of body fluids (enhanced by Calcofluor white) and stained biopsy material
- culture of blood and other body fluids
- culture of respiratory secretions
- culture of biopsy material
- detection of precipitins by CIE
- ELISA for *Candida* mannan (Bio-Rad) (variable results between laboratories)
- ELISA for *Candida* anti-mannan (limited value in immunocompromised patients)
- detection of β-1,3-D-glucan (Glucatel)
- PCR on whole blood (if available locally)
### Coccidioidomycosis
- microscopy of sputum, joint fluid, pus, and CSF sediment
- culture of sputum, joint fluid, CSF sediment, and pus
- coccidioidin or spherulin skin test
- detection of IgM in serum by latex agglutination, tube precipitin test, or immunodiffusion test
- detection of IgG in serum by classical complement fixation test or immunodiffusion
- detection of antibody in CSF if meningitis is suspected

### Cryptococcosis
- microscopy of CSF or other body fluids and secretions
- culture of CSF, blood, sputum, urine, and prostatic fluid
- detection of antigen in CSF, urine, and blood by latex agglutination
- (e.g. Immuno-Mycologics Inc; Meridian Diagnostics Inc; Bio-Rad) and ELISA (Meridian Diagnostics Inc)

### Histoplasmosis
- microscopy of stained smears of peripheral blood, sputum, bronchial washings, and pus
- culture of blood, sputum, bone marrow, pus, and tissue
- detection of antibody by immunodiffusion and complement fixation
- detection of antigen by radioimmunoassay in blood, urine, CSF, and BAL

### Mucormycosis
- microscopy of material from necrotic lesions, sputum, and BAL
- culture of nasal and palatal scrapings, biopsy material, and sputum
- PCR on whole blood (if available locally)
<table>
<thead>
<tr>
<th><strong>Paracoccidioidomycosis</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• microscopy of pus, sputum, and crusts from granulomatous lesions</td>
<td></td>
</tr>
<tr>
<td>• culture of pus, sputum, and crusts from granulomatous lesions</td>
<td></td>
</tr>
<tr>
<td>• detection of antibody by complement fixation</td>
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<table>
<thead>
<tr>
<th><strong>Penicillium marneffei infection</strong></th>
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<tbody>
<tr>
<td>• microscopy of Wright-stained bone marrow smears, touch smears of skin, or lymph node biopsies</td>
<td></td>
</tr>
<tr>
<td>• culture of skin biopsies, lymph node biopsies, blood, pus, bone marrow</td>
<td></td>
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<tr>
<td>• aspirates, sputum, and BAL</td>
<td></td>
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<tr>
<td>• detection of antibody by ELISA (under development)</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Sporotrichosis</strong></th>
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<tbody>
<tr>
<td>• microscopy of stained pus and tissue</td>
<td></td>
</tr>
<tr>
<td>• culture of pus and tissue</td>
<td></td>
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<table>
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<th><strong>Unusual fungal infections</strong></th>
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<table>
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<tr>
<th><strong>HYALOHYPOMYCOSIS</strong></th>
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<tbody>
<tr>
<td>• <em>Fusarium</em></td>
<td></td>
</tr>
<tr>
<td>• culture of blood and biopsies of cutaneous lesions</td>
<td></td>
</tr>
<tr>
<td>• <em>Scedosporium</em></td>
<td></td>
</tr>
<tr>
<td>• culture of respiratory secretions and CSF</td>
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<table>
<thead>
<tr>
<th><strong>PHAEOHYPOMYCOSIS</strong></th>
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<tbody>
<tr>
<td>• paranasal infection (<em>Alternaria, Bipolaris, Curvularia, Exserohilum</em>)</td>
<td></td>
</tr>
<tr>
<td>• microscopy of sinus mucus, pus, scrapings, and stained tissue sections</td>
<td></td>
</tr>
<tr>
<td>• culture of sinus mucus, pus, and scrapings</td>
<td></td>
</tr>
<tr>
<td>• cerebral phaeohyphomycosis (<em>Cladophialophora [Xylohypha] bantiana</em>)</td>
<td></td>
</tr>
<tr>
<td>• culture of sinus material and respiratory secretions</td>
<td></td>
</tr>
</tbody>
</table>
Unusual fungal infections (continued)

**YEAST INFECTIONS**

- trichosporonosis
  - microscopy of smears and histopathologic sections of cutaneous lesions
  - culture of blood and biopsies of cutaneous lesions
- systemic *Malassezia (Pityrosporum)* infection
  - microscopy of stained blood smears
  - culture of blood, with subculture onto lipid-rich media
  - culture of catheter tip in lipid-containing broth
**Clinical and laboratory diagnosis of systemic fungal infections**

**Key references**


Essential investigations for the laboratory diagnosis of systemic fungal infections

Hebart H, Loffler J, Meisner C et al.
Early detection of Aspergillus infection after allogeneic stem cell transplantation by polymerase chain reaction screening.

Hendolin PH, Paulin L, Koukila-Kähkölä P et al.
Panfungal PCR and multiplex liquid hybridization for detection of fungi in tissue specimens.

Herbrecht R, Letscher-Bru V, Oprea C et al.
Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients.

Bronchoalveolar lavage in the diagnosis of pulmonary complications of bone marrow transplantation patients.
Bone Marrow Transplantation 2000; 25: 975-979.

Iwen PC, Hinrichs SH, Rupp ME.
Utilization of the internal transcribed spacer regions as molecular targets to detect and identify human fungal pathogens.

Jensen HE, Schonheyder HC, Hotchi M, Kaufman L.
Diagnosis of systemic mycoses by specific immunohistochemical tests.
APMIS 1996; 104: 241-258.

Klont RR, Meis JF, Verweij PE.
Critical assessment of issues in the diagnosis of invasive aspergillosis.
 Clinical Microbiology and Infection 2001; 7 (Suppl. 2): 32-37.

Lass-Florl C, Aigner J, Gunsilius E et al.
Screening for Aspergillus spp. using polymerase chain reaction of whole blood samples from patients with haematological malignancies.
British Journal of Haematology 2001; 113: 180-184

Lin M-T, Lu H-C, Chen W-L.
Improving efficacy of antifungal therapy by polymerase chain reaction-based strategy among febrile patients with neutropenia and cancer.
Clinical Infectious Diseases 2001; 33: 1621-1627

Mamon RL, Rossi CL, Camargo ZP, Blotta MH.
Capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in sera of patients with paracoccidioidomycosis.

Maertens J, Verhaegen J, Demuyck 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.

Maertens J, Verhaegen J, Lagrou K et al.
Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation.

Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients.
Journal of Infectious Diseases 2002; 186: 1297-1306.

Muller FM, Trusen A, Weig M.
Clinical manifestations and diagnosis of invasive aspergillosis in immunocompromised children.

Nair M, Kapila K, Verma K.
Fine-needle aspiration: another diagnostic modality for rhinocerebral mucormycosis.
Diagnostic Cytopathology 1999; 21: 300-301.

National Committee for Clinical Laboratory Standards.

Patel RG, Patel B, Petrini MF, Carter RR, Griffith J.
Clinical presentation, radiographic findings, and diagnostic methods of pulmonary blastomycosis: a review of 100 consecutive cases.
5

Essential investigations for the laboratory diagnosis of systemic fungal infections


Fungal species most commonly recovered from clinical specimens

### Blood
- Candida
- Cryptococcus
- Histoplasma
- filamentous fungi: rarely isolated from blood with the exception of Fusarium

### Cerebrospinal fluid
- Candida
- Coccidioides
- Cryptococcus
- Histoplasma

### Pus and other exudates (abscesses, wounds, and ulcers)
- Blastomyces
- Coccidioides
- Cryptococcus
- Fusarium
- Histoplasma
- Sporothrix

### Respiratory secretions (sputum, bronchial lavage, bronchial brushings, and transtracheal aspirates)
- Aspergillus
- Blastomyces
- Candida
- Coccidioides
- Cryptococcus
- Histoplasma
- Mucor
- Paracoccidioides
- Scedosporium
- Rhizopus
- Sporothrix
(ii) Fungal species most commonly recovered from clinical specimens

<table>
<thead>
<tr>
<th>Swabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aspergillus</td>
</tr>
<tr>
<td>• Candida</td>
</tr>
<tr>
<td>• Fusarium</td>
</tr>
<tr>
<td>• Rhizopus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous body fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>URINE</td>
</tr>
<tr>
<td>• Candida</td>
</tr>
<tr>
<td>• Cryptococcus</td>
</tr>
</tbody>
</table>

| CHEST, ABDOMINAL, AND SYNOVIAL |
|• Aspergillus                |
|• Candida                     |

| VITREOUS                      |
|• Candida                     |

| BONE MARROW                   |
|• Candida                     |
|• Cryptococcus                |
|• Histoplasma                 |
Criteria for the diagnosis of systemic fungal infections: clinical features and laboratory parameters contributing to a definitive diagnosis

<table>
<thead>
<tr>
<th>Esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• endoscopically visualized plaques in the esophagus are clinically suggestive of fungal infection</td>
</tr>
<tr>
<td>• positive fungal culture</td>
</tr>
<tr>
<td>• pseudohyphae seen on Gram or other appropriate stain, or biopsy demonstrating invasive fungal elements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proof of Candida pneumonia requires:</strong></td>
</tr>
<tr>
<td>• chest radiographs with acute infiltrate are clinically compatible with fungal pneumonia</td>
</tr>
<tr>
<td>• acceptable lower respiratory tract culture(s) with positive fungal growth;</td>
</tr>
<tr>
<td>• acceptable lower respiratory cultures include transthoracic needle aspiration, transbronchial biopsy, open lung biopsy, or thoroscopically directed biopsy</td>
</tr>
<tr>
<td>• pseudohyphae in appropriately stained biopsy sections</td>
</tr>
</tbody>
</table>

| **Proof of Aspergillus, Pseudallescheria, and Fusarium pneumonia requires:** |
| • persistent or progressive pulmonary infiltrate resistant to antibacterial therapy |
| • recovery of one of the above organisms from induced sputum or BAL fluid |
| • clinical evidence of pneumonia (cough, dyspnea, pleuritic pain, rales, and bronchial or pleural rub) |
| • characteristic findings on chest X-ray or imaging, such as: |
| • subpleural radiologic densities, nodules, and wedge-shaped or cavitating lesions |
| • ‘halo sign’ on CT scan |
| • progression of lesions from infiltrates to cavity or crescent lesions |
| • BAL fluid negative for other agents known to cause observed pneumonic process |
| • persistent *Aspergillus* antigenemia in blood (*Platelia Aspergillus*, Bio-Rad Laboratories Inc) |
Criteria for the diagnosis of systemic fungal infections: clinical features and laboratory parameters contributing to a definitive diagnosis

Sinusitis
- symptomatic and radiographic evidence suggesting acute sinusitis
- sinus needle aspirate or biopsy culture positive for fungus

Urinary tract infection
- clean catch or catheterized urine sediment containing $\geq 1 \times 10^3$ cfu/ml of fungi

Fungemia
- at least one positive blood culture yielding fungus during a febrile episode
- persistent \textit{Candida} antigenemia or high titers of anti-\textit{Candida} antibody (Platelia \textit{Candida} antigen ELISA; Platelia \textit{Candida} antibody ELISA)

Acute disseminated candidosis
- fungemia plus culture or histologic evidence of deep tissue infection (including subcutaneous nodules)
- persistent \textit{Candida} antigenemia or high titers of anti-\textit{Candida} antibody

Endophthalmitis
- ophthalmoscopic examination suggestive of endophthalmitis
- positive fungal culture from either the eye, blood, or other sites of dissemination

Abscess or osteomyelitis
- radiographic, nuclear medicine, or nuclear magnetic resonance evidence of inflammatory focus
- biopsy or aspiration culture positive for fungus
### Criteria for the diagnosis of systemic fungal infections: clinical features and laboratory parameters contributing to a definitive diagnosis

#### Meningitis

- abnormal CSF findings suggesting inflammation, direct microscopic evidence of fungus (e.g. India ink), or positive cryptococcal antigen test
- positive fungal culture or *Cryptococcus, Candida, or Aspergillus* antigen in CSF

#### Chronic disseminated candidosis (hepatosplenic candidosis)

**PROVEN**

- persistent fever after recovery from neutropenia associated with lesions of the liver, spleen, or kidney identified by diagnostic imaging. Diagnosis requires recovery of *Candida* species from blood culture or culture or histologic confirmation from biopsy of an involved organ

**POSSIBLE**

- persistent or intermittent fever after recovery from neutropenia associated with characteristic lesions of the liver, spleen, or kidney
### Assessment of the response to antifungal therapy – definitions

<table>
<thead>
<tr>
<th><strong>Complete response</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of all clinical signs and symptoms attributable to a systemic fungal infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Partial response</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major improvement or resolution of the attributable clinical signs and symptoms and at least 50% improvement in radiologic findings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Good response</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Denotes both complete and partial responses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Stable response</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• intermediate responses (some improvement but &lt;50% radiologic improvement)</td>
</tr>
<tr>
<td>• short courses of therapy with little assessment of response other than that the patient is alive, or death due to another documented cause</td>
</tr>
<tr>
<td>• some indication that the infection was improving, but not enough to reach a partial response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Failure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression and death due to systemic fungal infection</td>
</tr>
</tbody>
</table>
Antifungal Drugs

9 Amphotericin B
10 Regimen for rapid escalation of amphotericin B dosage
11 Regimen for gradual escalation of amphotericin B dosage
12 Liposomal amphotericin B (AmBisome®)
13 Amphotericin B colloidal dispersion (Amphotec®, Amphotec®)
14 Amphotericin B lipid complex (Abelcet®)
15 Pharmacokinetic comparisons of amphotericin B formulations
16 Polyene comparisons: infusion-related reactions
17 Polyene comparisons: nephrotoxicity
18 Caspofungin
19 Fluconazole
20 Flucytosine (5-fluorocytosine)
21 Regimens for administration of flucytosine in renal impairment
22 Itraconazole
23 Voriconazole

Antifungal drugs
Amphotericin B

(i)

Spectrum of activity

- Aspergillus species
- Blastomyces dermatitidis
- Candida species
- Coccioides immitis
- Cryptococcus neoformans
- Fusarium species
- Sporothrix shenckii
- Histoplasma capsulatum
- Paracoccidioides brasiliensis
- ineffective against Scedosporium and Trichosporon

Uses

- aspergillosis
- candidosis
- blastomycosis
- coccidioidomycosis
- cryptococcosis
- fusariosis
- histoplasmosis
- paracoccidioidomycosis
- sporotrichosis
- certain forms of mucormycosis, hyalohyphomycosis, and phaeohyphomycosis
- reduced effectiveness in aspergillosis and candidosis in neutropenic patients

Pharmaceutics

- oral suspension 100 mg/ml
- lozenge 10 mg
- powder for injection 50 mg per vial
### Pharmacokinetics
- no mucosal or cutaneous absorption
- minimal absorption from GI tract
- extensively bound to plasma lipoproteins
- enters serous cavities
- crosses placental barrier
- plasma half-life 24 h
- renal excretion very slow

### Dosage
- all dosages suitable for adults and children
- 0.5–1.0 mg/kg per day i.v. for 10–14 days
- up to 1.5 mg/kg per day for disseminated infections

### Contraindications
- known sensitivity to amphotericin B

### Precautions
- to avoid precipitation do not reconstitute or dilute with saline, do not mix with other drugs
- renal function and serum potassium concentrations should be closely monitored
- maintain high fluid and sodium intake
- potassium supplements may be required to compensate for urinary losses
- dosage must be reduced if renal function deteriorates substantially, particularly if serum creatinine levels rise by more than 50% – infusion of an osmotic diuretic such as mannitol may then be of value
- monitor blood count at weekly intervals
Amphotericin B

Adverse effects

- chills, fever, and vomiting
- anaphylaxis, flushing, and muscle and joint pains
- deterioration of renal function must be anticipated
- progressive normochromic anemia is indicative of bone marrow depression

Drug interactions

- concomitant administration of other nephrotoxic drugs should be avoided
- corticosteroids may worsen hypokalemia due to amphotericin B
- action of flucytosine is potentiated

Key references


Ellis D. Amphotericin B: spectrum and resistance. Journal of Antimicrobial Chemotherapy 2002; 49(suppl 1); 7-10.


Regimen for rapid escalation of amphotericin B dosage

<table>
<thead>
<tr>
<th>Time infusion started (h)</th>
<th>Duration of infusion (h)</th>
<th>Dosage (mg)</th>
<th>Volume of solution 1 (ml)</th>
<th>Volume of solution 2 (ml)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>40</td>
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<td>4</td>
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<td>24</td>
<td>240</td>
<td>760</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>25</td>
<td>250</td>
<td>750</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>50</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

(then at 24 h intervals; dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is the lesser, although doses up to 1.5 mg/kg are used)

<table>
<thead>
<tr>
<th>Time infusion started (h)</th>
<th>Duration of infusion (h)</th>
<th>Dosage (mg)</th>
<th>Volume of solution 1 (ml)</th>
<th>Volume of solution 2 (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>9</td>
<td>90</td>
<td>360</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>10</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>20</td>
<td>200</td>
<td>300</td>
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<tr>
<td>48</td>
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<td>30</td>
<td>300</td>
<td>700</td>
</tr>
<tr>
<td>72</td>
<td>6</td>
<td>40</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>96</td>
<td>6</td>
<td>50</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

(then at 24 h intervals; dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is the lesser, although doses up to 1.5 mg/kg are used)

Solution 1: amphotericin B at 100 mg/l in 5% dextrose solution
Solution 2: 5% dextrose solution

### Regimen for gradual escalation of amphotericin B dosage*

<table>
<thead>
<tr>
<th>Time infusion started (h)</th>
<th>Duration of infusion (h)</th>
<th>Dosage (mg)</th>
<th>Volume of solution 1 (ml)</th>
<th>Volume of solution 2 (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>9</td>
<td>90</td>
<td>360</td>
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<tr>
<td>24</td>
<td>6</td>
<td>10</td>
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<td>400</td>
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<tr>
<td>48</td>
<td>6</td>
<td>20</td>
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<td>300</td>
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<td>72</td>
<td>6</td>
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<td>96</td>
<td>6</td>
<td>40</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>120</td>
<td>6</td>
<td>50</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

(then at 24 h intervals; dose not to exceed 50 mg or 1.0 mg/kg per infusion, whichever is the lesser)

Solution 1: amphotericin B at 100 mg/l in 5% dextrose solution  
Solution 2: 5% dextrose solution


*Little need for this regimen except in rare circumstances
**Liposomal amphotericin B (AmBisome®)**

### Spectrum of activity

- *Aspergillus* species
- *Blastomyces dermatitidis*
- *Candida* species
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Fusarium* species
- *Histoplasma capsulatum*
- *Paracoccidioides brasiliensis*
- *Sporothrix schenckii*
- agents of systemic and subcutaneous zygomycosis

### Uses

- empirical treatment of febrile neutropenia
- treatment (primary or secondary) of serious fungal infections, e.g., *Candida*, *Aspergillus* and other filamentous fungi, and *Cryptococcus* species
- patients who have developed side effects to cAMB
- patients in whom cAMB is contraindicated because of renal impairment

### Pharmaceutics

- powder for injection 50 mg per vial
  - reconstitute in 12 ml sterile water (final drug concentration ~4 mg/ml)
  - dilute with 1–19 parts of 5% dextrose to give final concentration of 0.2–2.0 mg/ml amphotericin B
  - filter sterilize
  - reconstituted drug in water can be stored in refrigerator (2–8°C) for up to 4 h prior to dilution with dextrose
  - commence infusion within 6 h of dilution with 5% dextrose
**Liposomal amphotericin B (AmBisome®)**

### Pharmacokinetics
- non-linear
- different increases in serum concentrations when dose increased to 1 to 5 mg/kg per day
- serum level of 10–35 mg/l measured after 3 mg/kg dose
- serum level of 25–60 mg/l measured after 5 mg/kg dose
- serum level of 5–10 mg/l detected 24 h after 5 mg/kg dose
- highest drug levels found in liver and spleen
- levels higher than MIV found in lung
- low levels present in kidneys
- terminal half-life 100–150 h

### Dosage
- initial dose of 1 mg/kg per day, increasing to 3–5 mg/kg per day or higher
- recommended dosage for empiric therapy 3 mg/kg per day
- recommended dosage for confirmed infection 3 or 5 mg/kg per day
- infuse over 2 h period, if well tolerated reduce to 1 h
- typical cumulative dosage 1–3 g over 3–4 weeks, maximum tolerated dose not determined
- cumulative dosage of 30 g possible without significant toxicity
- in neonates/children 1–5 mg/kg per day

### Contraindications
- known hypersensitivity to amphotericin B

### Precautions
- to avoid precipitation do not reconstitute or dilute with saline, do not mix with other drugs
- monitor renal function even though nephrotoxicity is minimal
- monitor electrolytes
### Liposomal amphotericin B (AmBisome®)

#### Adverse effects
- fever, chills, and anaphylaxis (rare)
- renal impairment (defined as twice baseline serum creatine concentrations) but markedly reduced compared with conventional amphotericin B; generally transient and not associated with long-term functional impairment

#### Drug interactions
- same as those seen with cAMB
- augmentation of nephrotoxic effects of aminoglycoside antibiotics, cyclosporine, and certain anti-neoplastic agents
- augmentation of corticosteroid potassium loss – resulting hypokalemia increases toxicity of digitalis glycosides
Liposomal amphotericin B (AmBisome®)

Key references

Adler-Moore J, Proffitt RT.
Effect of tissue penetration on AmBisome efficacy.

Adler-Moore J, Proffitt RT.
AmBisome: liposomal formulation, structure, mechanism of action and pre-clinical experience.

Barrett JP, Vardulaki KA, Conlon C et al.
A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations.
Clinical Therapeutics 2003; 25: 1293-1320.

Bekersky I, Fielding RM, Dressler DE et al.
Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans.

Boswell GW, Buell D, Bekersky I.
AmBisome (liposomal amphotericin B): a comparative review.

Coukell AJ, Brogan RN.
Liposomal amphotericin B. Therapeutic use in the management of fungal infections and visceral leishmaniasis.

De Marie S.
New developments in the diagnosis and management of invasive fungal infections.
Haematologia 2000; 85: 88-93.

Leenders ACAP, Daenen S, Jansen RLH et al.
Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections.

Martin MT, Gavaldon J, Lopez P et al.
Efficacy of high doses of liposomal amphotericin B in the treatment of experimental aspergillosis.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.

Scarcella A, Pasquariello MB, Giugliano B, Vendemmi M, de Lucia A.
Liposomal amphotericin B for neonatal fungal infections.
Pediatric Infectious Diseases 1998; 17: 146-148.

Walsh TJ, Goodman JL, Pappas P et al.
Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with Aspergillus species and other filamentous fungi: maximum tolerated dose study.
Antimicrobial Agents and Chemotherapy 2001; 45: 3487-3496.

Wingard JR.
Liposomal amphotericin B for fever and neutropenia.

Wong-Beringer A, Jacobs RA, Guglielmo BJ.
Lipid formulations of amphotericin B: clinical efficacy and toxicities.
Clinical Infectious Diseases 1998; 27: 603-618.
### Spectrum of activity

- *Aspergillus* species
- *Blastomyces dermatitidis*
- *Candida* species
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Fusarium* species
- *Histoplasma capsulatum*
- *Paracoccidioides brasiliensis*
- *Sporothrix schenckii*
- agents of systemic and subcutaneous zygomycosis

### Uses

- serious fungal infections unresponsive to cAMB
- patients who have developed side effects to cAMB
- patients in whom cAMB is contraindicated because of renal impairment

### Pharmaceutics

- powder for injection, 50 mg and 100 mg per vial
  - reconstitute in 10 or 20 ml sterile water to give a drug concentration of 5 mg/ml
  - dilute 8-fold with 5% dextrose to give a final concentration of 0.625 mg/ml amphotericin B
- reconstituted drug in water can be stored in refrigerator (2–8°C) for up to 24 h prior to dilution with 5% dextrose solution
- after final dilution, store in refrigerator (2–8°C) and use within 24 h
Amphotericin B colloidal dispersion
(Amphocil®, Amphotec®)

Pharmacokinetics
- serum level of 2 mg/l measured after 1 mg/kg dose
- rapid distribution in tissues
- highest drug levels seen in liver and spleen
- levels in renal tissue much lower compared with cAMB

Dosage
- initial dose 1 mg/kg, increasing to 3–4 mg/kg, infused at a rate of 1–2 mg/kg/h
- infusion time may be extended if acute reactions are experienced or infusion volume cannot be tolerated
- dosages of up to 6 mg/kg have been used
- median cumulative doses of 30 g can be administered
- median treatment duration 16 days
- in children daily dosages (mg/kg) as for adults

Contraindications
- known hypersensitivity to amphotericin B or other components of Amphocil®

Precautions
- to avoid precipitation do not reconstitute or dilute with saline, do not mix with other drugs
- in the treatment of renal dialysis patients, Amphocil® should be administered at the end of each dialysis period
- potassium and magnesium should be monitored regularly
- monitor renal function, especially where nephrotoxic drugs are given concomitantly
Amphotericin B colloidal dispersion
(Advancan®, Amphotec®)

### Adverse effects

- renal impairment (defined as twice baseline serum creatine concentrations) but markedly reduced compared with conventional amphotericin B; generally transient and not associated with long-term functional impairment
- fever and chills
- anaphylactoid reactions including hypotension, tachycardia, bronchospasm, dyspnea, hypoxia, and hyperventilation have been reported
- acute reactions successfully treated by reducing rate of infusion and prompt administration of antihistamines and adrenal corticosteroids
- serious anaphylactoid effects may necessitate discontinuation of Advancan®

### Drug interactions

- augmentation of nephrotoxic aminoglycoside antibiotics, cisplatin, and pentamidine
- corticosteroids
- corticotropin (ACTH)
- use of Advancan® in combination with flucytosine has not been studied
Amphotericin B colloidal dispersion (Amphocil®, Amphotec®)

Key references

Bohme A, Karthaus M.
Systemic fungal infections in patients with hematological malignancies: indications and limitations of the antifungal armamentarium.
Chemotherapy 1999; 45: 315-324.

Barrett JP, Vardulaki KA, Conlon C et al.
A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations.
Clinical Therapeutics 2003; 25: 1293-1320.

Noskin GA, Pietrelli L, Coffey G, Gurwith M, Liang LJ.
Amphotericin B colloidal dispersion for treatment of candidemia in immunosuppressed patients.
Clinical Infectious Diseases 1998; 26: 461-467.

Noskin G, Pietrelli L, Gurwith M, Bowden R.
Treatment of invasive fungal infections with amphotericin B colloidal dispersion in bone marrow transplantation recipients.
Bone Marrow Transplantation 1999; 23: 697-703.

Patel R.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.

Roland WE.
Amphotericin B colloidal dispersion versus amphotericin B in the empirical treatment of fever and neutropenia.
Clinical Infectious Diseases 1999; 28: 935-936.

Viscoli C, Castagnola E.
Emerging fungal pathogens, drug resistance and the role of lipid formulations of amphotericin B in the treatment of fungal infections in cancer patients: a review.

Wong-Beringer A, Jacobs RA, Guglielmo BJ.
Lipid formulations of amphotericin B: clinical efficacy and toxicities.
Clinical Infectious Diseases 1998; 27: 603-618.
Amphotericin B lipid complex (Abelcet®)

### Spectrum of activity

- *Aspergillus fumigatus*
- *Blastomyces dermatitidis*
- *Candida* species
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Fusarium* species
- *Histoplasma capsulatum*
- *Sporothrix schenckii*
- agents of mucormycosis

### Uses

- primary therapy of confirmed systemic candidosis
- serious fungal infections unresponsive to cAMB
- patients who have developed side effects to cAMB
- patients in whom cAMB is contraindicated because of renal impairment

### Pharmaceutics

- sterile suspension 50 mg and 100 mg in vial
- dilute with 5% dextrose for a final infusion volume of 500 ml. For pediatric patients and patients with cardiovascular disease, dilute the drug with 5% dextrose to a final infusion volume of approximately 250 ml
- diluted suspension can be refrigerated (2–8°C) for up to 24 h before infusion

### Pharmacokinetics

- serum level lower than for cAMB due to rapid distribution in tissues
- maximum serum level of 1–2 mg/l for a 5 mg/kg dose
- human tissue distribution not studied in detail
Amphotericin B lipid complex (Abelcet®)

Dosage

- 5 mg/kg infused over 2 h period for minimum of 2 weeks
- cumulative dosage of 73 g administered without significant toxicity

Contraindications

- Abelcet® is contraindicated in patients who have shown hypersensitivity to cAMB or any other formulation component

Precautions

- to avoid precipitation do not reconstitute or dilute with saline, do not mix with other drugs
- anaphylaxis has been reported
- if severe respiratory distress occurs, infusion should be discontinued immediately

Adverse effects

- renal impairment (defined as twice baseline serum creatine concentrations) but markedly reduced compared with conventional amphotericin B; generally transient and not associated with long-term functional impairment
- transient fever and chills 1–2 h after initiation of infusion
- increase in azotemia, and hypokalemia
- rare instances of hypertension, bronchospasm, arrhythmias, and shock

Drug interactions

- none seen to date, but potential exists when administered concomitantly with nephrotoxic drugs
Amphotericin B lipid complex (Abelcet®)

Key references

Barrett JP, Vardulaki KA, Conlon C et al.
A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations.
Clinical Therapeutics 2003; 25: 1293-1320.

Bohme A, Karthaus M.
Systemic fungal infections in patients with hematological malignancies: indications and limitations of the antifungal armamentarium.
Chemotherapy 1999; 45: 315-324.

Boyle JA, Swenson CE.
ABELCET treatment.

Linden P, Lee L, Walsh TJ.
Retrospective analysis of the dosage of amphotericin B lipid complex for treatment of invasive fungal infections.

Martino R, Subira M, Sureda A, Sierra J.
Amphotericin B lipid complex at 3 mg/kg/day for treatment of invasive fungal infections in adults with haematological malignancies.

Martino R, Subira M, Domingo-Albos A, Sureda A, Brunet S, Sierra J.
Low-dose amphotericin B lipid complex for the treatment of persistent fever of unknown origin in patients with hematologic malignancies and prolonged neutropenia.
Chemotherapy 1999; 45: 205-212.

Patel R.
Antifungal agents. Part I. Amphotericin B preparations and flucytosine.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.

Sallah S, Semelka RC, Sallah W, Vainright JR, Philips DL.
Amphotericin B lipid complex for the treatment of patients with acute leukemia and hepatosplenic candidiasis.
Leukemia Research 1999; 23: 995-999.

Viscoli C, Castagnola E.
Emerging fungal pathogens, drug resistance and the role of lipid formulations of amphotericin B in the treatment of fungal infections in cancer patients: a review.

Walsh TJ, Seibel NL, Arndt C et al.
Amphotericin B lipid complex in pediatric patients with invasive fungal infections.

Wong-Beringer A, Jacobs RA, Guglielmo BJ.
Lipid formulations of amphotericin B: clinical efficacy and toxicities.
Clinical Infectious Diseases 1998; 27: 603-618.
Pharmacokinetic comparisons of amphotericin B formulations

<table>
<thead>
<tr>
<th></th>
<th>AmBisome®</th>
<th>ABCD</th>
<th>Amphotericin B</th>
<th>ABLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong> mg/kg</td>
<td>3</td>
<td>1.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><strong>Peak blood level</strong> µg/ml</td>
<td>29</td>
<td>2.5</td>
<td>3.6</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>AUC</strong> µg/ml/h</td>
<td>423</td>
<td>56.8</td>
<td>34.2</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Clearance</strong> ml/h/kg</td>
<td>22.2</td>
<td>28.4</td>
<td>40.2</td>
<td>211</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong> l</td>
<td>25.9</td>
<td>553</td>
<td>111</td>
<td>2286</td>
</tr>
<tr>
<td><strong>Half-life (elimination)</strong> h</td>
<td>23</td>
<td>235</td>
<td>34</td>
<td>173.4</td>
</tr>
</tbody>
</table>

2nd phase 3rd phase 2nd phase
Polyene comparisons: infusion-related reactions

Comments

- The figure above summarizes the incidence of infusion-related reactions associated with polyenes.
- Infusion-related reactions (e.g., fever, chills/rigors) are typically defined as events that occur during or within 1 h after study drug infusion.
- Walsh et al conducted a randomized, double-blind trial comparing AmBisome® 3 mg/kg/day versus conventional amphotericin B (CAB) 0.6 mg/kg/day as empiric antifungal therapy in patients with febrile neutropenia.
- No premedication was administered on day 1 for prevention of infusion-related reactions, per protocol.
- AmBisome®-treated patients had significantly ($P < 0.001$) fewer episodes of fever (increase ± 1.0°C) and chills compared with patients treated with CAB.
- AmBisome® has a reduced risk for infusion-related reactions compared with CAB.
- Wingard et al reported the results of a randomized, double-blind trial comparing AmBisome® 3 or 5 mg/kg/day versus Abelcet® 5 mg/kg/day as empiric antifungal therapy in 244 patients with persistent fever and neutropenia.
- No premedication was administered on day 1 for the prevention of infusion-related events.
- AmBisome® treatment at either dose level resulted in significantly ($P < 0.001$) fewer reports of infusion-related reactions compared with Abelcet®.

Antifungal drugs
Polyene comparisons: infusion-related reactions

Comments (continued)

- Although both agents are lipid formulations of amphotericin B, AmBisome® demonstrates a reduced incidence of infusion-related adverse events compared with Abelcet®, with or without premedication.
- In a randomized, controlled trial in invasive aspergillosis, infusion-related reactions occurred more often in patients treated with Amphotec® 6 mg/kg/day compared with CAB 1.0–1.5 mg/kg/day.
- Overall, Amphotec® has a higher incidence of infusion-related toxicities compared with CAB.

Key references


Polyene comparisons: nephrotoxicity

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
<td>34%–60%</td>
</tr>
<tr>
<td>AmBisome</td>
<td>10%–20%</td>
</tr>
<tr>
<td>Abelcet</td>
<td>42%–63%</td>
</tr>
<tr>
<td>Amphotec</td>
<td>25%–40%</td>
</tr>
</tbody>
</table>

- CAB nephrotoxicity is dose dependent and cumulative
- CAB nephrotoxicity is dose dependent and cumulative
- Randomized trials demonstrate less nephrotoxicity than CAB
- No randomized trials showing Abelcet® to be less nephrotoxic than CAB

CAB = Conventional amphotericin B.
Increase in serum creatinine ≥2 × baseline or 1.0 mg/dl or 50% decrease in calculated

Comments

- This table summarizes the incidence of nephrotoxicity for the amphotericin B formulations
- Nephrotoxicity is a frequent occurrence with conventional amphotericin B
- Comparing the incidence of nephrotoxicity of the amphotericin B lipid formulations, AmBisome® is markedly less nephrotoxic compared with Abelcet® and Amphotec®

Key references


Antifungal drugs 43
### Caspofungin

**Spectrum of activity**

**Potent fungicidal activity against:**
- *Candida albicans*
- *C. tropicalis*
- *C. glabrata*
- *C. krusei* (less susceptible)
- *C. parapsilosis* (less susceptible)
- *C. dubliniensis*
- *C. lusitaniae*

**Variable activity against:**
- *Aspergillus* species
- *Histoplasma*
- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Coccidioides immitis*
- *Sporothrix schenckii*
- dematiaceous fungi

**No activity against:**
- *Cryptococcus neoformans*
- *Trichosporon beigeli*
- *Fusarium* species
- Agents of zygomycosis
- Dermatophytes

**Potential synergy with:**
- Amphotericin B (*C. neoformans*)
- Fluconazole (*C. neoformans*)
- acquired resistance not reported
- animal models:
  - Disseminated candidosis: prolonged survival
  - Disseminated cryptococcosis: ineffective
  - Invasive aspergillosis: prolonged survival
  - Acute pneumocystis infection: elimination of cyst forms
Caspofungin

**Uses**

- *invasive forms of candidosis* – comparable activity compared with amphotericin B: intraperitoneal abscesses, peritonitis, pleural space infections. Not studied in endocarditis, osteomyelitis or meningitis due to *Candida*
- *candidemia*
- *invasive aspergillosis* – in patients who have failed to respond to, or who are intolerant to, other antifungal agents. Has not been studied as initial therapy for invasive aspergillosis

**Pharmaceutics**

- only available for parenteral administration
- supplied in lyophilized form in 50 and 70 mg amounts
- reconstituted in 10.5 ml 0.9% sodium chloride
- reconstituted drug solution further diluted by adding 10 ml to 250 ml 0.9% sodium chloride
- use infusion solution within 24 h, store at <25°C

**Pharmacokinetics**

- dose-proportional pharmacokinetics
- poor oral bioavailability
- excretion by hepatic and renal routes
- serum concentrations of ~10 mg/l reached after single 70 mg parenteral dose, administered over 1 h
- 70 mg/day maintains trough plasma levels above MIC of most susceptible fungi
- blood concentrations increase in proportion to dosage
- less than 10% of dose remains in blood 36–48 h after administration
- protein binding >96%
- about 92% of dose distributed to tissues – highest concentration in liver
- CSF level negligible
- little excretion or metabolism during first 30 h after administration
- initial half-life ~9–11 h
- elimination half-life 40–50 h
- not cleared by hemodialysis

*Antifungal drugs*
### Dosage

- invasive aspergillosis
- once-daily dosing
- 70 mg on day 1 followed by 50 mg daily
- infusion over 1 h period
- duration patient dependent
- systemic candidosis, including candidemia
- i.v. loading dose 70 mg then 50 mg/day
- infusion over 1 h period
- esophageal candidosis: HIV infected adults: 50 and 70 mg/day: 14 days
- caspofungin: 85.1% response
- amphotericin B: 66.7% response

### Adverse effects

- well tolerated, but can cause:
  - fever
  - rash
  - nausea
  - vomiting
  - transient elevations of liver function tests reported in some patients
  - potential to cause histamine release
  - no serious adverse effects in HIV infected patients

### Drug interactions

- does not inhibit cytochrome P450 enzyme system
- does not induce P450-3A4 metabolism of other drugs
- co-administration with cyclosporin frequently results in transaminase elevations of 2–3 fold upper limit of normal but resolves when both drugs are discontinued. Also, caspofungin serum concentrations increase, but no effect on cyclosporin pharmacokinetics.
- no other interactions reported
Antifungal drugs

Caspofungin

Key references

Arikan S, Lozano-Chiu M, Paetznick V, Rex JH. 
In vitro synergy of caspofungin and amphotericin B against Aspergillus and Fusarium spp. 

Denning DW. 
Echinocandin antifungal drugs. 

Deresinski SC, Stevens DA. 
Caspofungin. 
Clinical Infectious Diseases 2003; 36: 1445-1457.

Georgopapadakou NH. 
Update on antifungals targeted to the cell wall: focus on beta-1,3-glucan synthase inhibitors. 

Groll AH, Walsh TJ. 
Caspofungin: pharmacology, safety and therapeutic potential in superficial and invasive fungal infections. 

Kartsonis N, DiNubile MJ, Bartízal K, Hicks PS, Ryan D, Sable CA. 
Efficacy of caspofungin in the treatment of esophageal candidiasis resistant to fluconazole. 

Keating G, Figgitt D. 
Caspofungin: a review of its use in oesophageal candidiasis, invasive candidiasis and invasive aspergillosis. 
Drugs 2003; 63: 2235-2263.

Mora-Duarte J, Betts R, Rotstein C et al. 
Comparison of caspofungin and amphotericin B for invasive candidiasis. 

Morrison VA. 
The role of caspofungin and the echinocandins in the antifungal armamentarium. 

Pacetti SA, Gelone SP. 
Caspofungin acetate for treatment of invasive fungal infections. 

Stone JA, Holland SD, Wickensham PJ et al. 
Antimicrobial agents and Chemotherapy 2002; 46: 739-745.

Ullmann AJ. 
Review of the safety, tolerability, and drug interactions of the new antifungal agents caspofungin and voriconazole. 

Villanueva A, Gotuzzo E, Arathon EG et al. 
A randomised double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. 

Walsh TJ. 
Echinocandins – an advance in the primary treatment of invasive candidiasis. 

Wiederhold NP, Lewis RE. 
The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. 
## Fluconazole

### Spectrum of activity

- *Candida* species (reduced activity against *C. glabrata*, virtually no activity against *C. krusei*)
- Cryptococcus neoformans
- ineffective against *Aspergillus* species

### Uses

- mucosal and cutaneous candidosis
- recalcitrant oropharyngeal candidosis in HIV-positive patients
- deep forms of candidosis in non-neutropenic patients
- acute cryptococcal meningitis in AIDS
- in combination with amphotericin B in treatment of cryptococcosis and deep forms of candidosis (urinary tract and peritoneum)
- maintenance treatment to prevent relapse of cryptococcosis in patients with AIDS
- prophylaxis against candidosis; ineffective against aspergillosis

### Pharmaceutics

- capsule: either 50 mg, 150 mg, or 200 mg
- powder for oral suspension available as 50 mg, 100 mg, or 200 mg in 5 ml and 35 ml packs
- intravenous infusion – 2 mg/ml in 0.9% sodium chloride solution
### Fluconazole

**Pharmacokinetics**

- rapid and almost complete absorption after oral administration
- identical serum concentrations attained after both oral and parenteral administration
- blood concentrations increase in proportion to dosage over wide range of dose levels
- serum concentrations in the region of 1 mg/l achieved 2 h after single 50 mg oral dose
- after repeated dosing, serum level increases to 2–3 mg/l
- administration with food does not affect absorption
- rapid and widespread distribution after both oral and parenteral administration
- protein binding low
- elimination by renal excretion
- serum half-life 20–30 h, prolonged in renal failure
- removed during hemodialysis

**Dosage**

- oropharyngeal candidosis, 50–100 mg per day for 1–2 weeks
- esophageal and mucocutaneous candidosis, 100–200 mg per day for 2–4 weeks
- lower urinary tract candidosis, 50–100 mg per day for 14–30 days
- cryptococcosis, 200–400 mg per day for 6–8 weeks
- systemic candidosis, 200–400 mg per day for 6–8 weeks
- use in renal impairment – fluconazole is excreted predominantly in the urine as unchanged drug – no adjustments in single-dose therapy are required; in patients with impaired renal function who will receive multiple doses of fluconazole, the normal recommended dose (according to indication) should be given on day 1, followed by a daily dose based on the following information:
  - for creatinine clearance >50 ml/min, use 100% recommended dose
  - for creatinine clearance 11–50 ml/min, use 50% recommended dose
  - for patients receiving regular dialysis, use one dose after each session
- maintenance in cryptococcosis in AIDS, 100–200 mg per day
### Dosage (continued)

- prophylaxis for candidosis, 50–400 mg per day; use 400 mg per day in high-risk patients several days before anticipated neutropenia, and continue for 1 week after recovery of neutrophil count to $1 \times 10^9/\text{l}$
- children
  - mucosal candidosis, 3 mg/kg per day
  - systemic candidosis and cryptococcosis, 6–12 mg/kg per day
  - prophylaxis, 3–12 mg/kg per day

### Contraindications

- hypersensitivity to azole derivatives
- co-administration of terfenadine and cisapride

### Precautions

- hepatic function should be monitored when treatment is prolonged
- women of child-bearing age should take effective contraceptive precautions
- during treatment and for several weeks thereafter

### Adverse effects

- generally well tolerated
- nausea most frequently reported adverse effect, seldom necessitates discontinuation of treatment
- vomiting, abdominal distention, and discomfort reported
- elevation of hepatic enzyme levels occurs in small percentage of individuals, readily reversible in early stages
- treatment should be discontinued if signs develop that are suggestive of hepatic disease
- fatal exfoliative skin rashes (Stevens–Johnson syndrome) in AIDS or cancer, although causal relationship not established
- discontinue drug if bullous lesions or erythema multiforme develop
Fluconazole

### Drug interactions

- hepatic metabolism of cyclosporine, phenytoin, sulfonylureas, theophylline, and warfarin is inhibited
- rifampicin accelerates clearance of fluconazole
- concomitant administration of terfenadine should be avoided, since it has been associated with serious, sometimes fatal, cardiac dysrhythmias
- fluconazole prolongs serum half-life of chlorpropamide, glibenclamide, glipizide, and tolbutamide
- prothrombin time in patients receiving concomitant treatment with fluconazole and anticoagulants should be monitored
- fluconazole increases plasma zidovudine concentrations
- fluconazole increases plasma rifabutin concentrations
- tacrolimus
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Fluconazole

Key references


## Flucytosine (5-fluorocytosine)

### Spectrum of activity
- *Candida* species
- *Cryptococcus neoformans*
- *Cladophialophora (Cladosporium) carrionii*
- *Fonsecaea* species
- *Phialophora verrucosa*

### Uses
- seldom used as single drug
- used in combination with amphotericin B for cryptococcosis and forms of systemic candidosis

### Pharmaceutics
- oral tablets
- infusion for parenteral administration of 250 ml fractions containing 10 mg/ml in aqueous saline solution

### Pharmacokinetics
- rapid and almost complete absorption following oral administration
- identical serum concentrations obtained after oral and parenteral administration
- in adults with normal renal function, oral dose of 25 mg/kg at 6 h intervals
- produces peak serum concentrations of 30–40 mg/l
- absorption is lower in patients with impaired renal function but peak serum concentrations are higher
- slight accumulation of drug during first 4 days of treatment, then peak serum concentrations remain constant
- low protein binding (12%)
- wide tissue distribution
- elimination by renal excretion of unchanged drug (about 90% of administered dose)
- serum half-life 2.5–5.0 h; much longer in renal failure, necessitating modification of dose
Flucytosine (5-fluorocytosine)

### Dosage
- Oral administration preferred, i.v. solution if oral route contraindicated
- i.v. solution administered through venous catheter or as intraperitoneal infusion over 20–40 min, monitor blood counts twice weekly
- If renal function normal, initial dose 50–150 mg/kg given in four divided doses at 6 h intervals
- If renal function impaired, initial dose 25 mg/kg but subsequent doses and intervals adjusted to achieve peak serum concentrations of 70–80 mg/l (trough 30–40 mg/l)
- Half-life prolonged in small infants – administer at 12 or 24 h intervals

### Contraindications
- Known hypersensitivity to flucytosine
- Severe renal or hepatic insufficiency
- Thrombocytopenia and other blood dyscrasias

### Precautions
- Monitor serum creatinine twice weekly and adjust dosage where appropriate
- Measure serum levels repeatedly, especially in patients with renal insufficiency – withdraw samples shortly before subsequent dose is scheduled
- Caution when flucytosine is administered in combination with amphotericin B: amphotericin B may lead to reduced clearance of flucytosine
- Caution when flucytosine is administered in combination with other myelosuppressive drugs
- Blood counts and hepatic function tests should be performed at regular intervals in all patients
### Flucytosine (5-fluorocytosine)

#### Key references

Patel R.  
Antifungal agents. Part I. Amphotericin B preparations and flucytosine.  

Vermes A, van Der Sijs H, Guchelaar HJ.  
Flucytosine: correlation between toxicity and pharmacokinetic parameters.  

Vermes A, Guchelaar HJ, Dankert J.  
Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions.  

#### Adverse effects

- transient rashes, nausea, vomiting, and diarrhea
- diarrhea can become protracted if flucytosine is continued
- mild changes in liver function tests occur in around 10% of patients
- rare cases of leukopenia and potentially fatal thrombocytopenia

#### Drug interactions

- action of amphotericin B is potentiated
Regimens for administration of flucytosine in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Individual dosage (mg/kg)</th>
<th>Dosage interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>25.0–37.5</td>
<td>6</td>
</tr>
<tr>
<td>40–20</td>
<td>25.0–37.5</td>
<td>12</td>
</tr>
<tr>
<td>10–20</td>
<td>25.0–37.5</td>
<td>&gt;24*</td>
</tr>
</tbody>
</table>

Renal function is considered to be normal when creatinine clearance is greater than 40–50 ml/min or concentration of creatinine in serum is less than 180 µmol/l; concentration of creatinine in serum is not reliable unless renal function is stable.

*Dosage interval must be based on frequent serum drug concentration measurements.

## Itraconazole

### Spectrum of activity

- *Aspergillus* species
- *Blastomyces dermatitidis*
- *Candida* species
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Penicillium marneffei*
- *Paracoccidioides brasiliensis*
- *Scedosporium apiospermum*
- *Sporothrix schenckii*
- dermatophytes
- *Malassezia* species
- *dematiaceous molds*
- less active against *Fusarium* species
- ineffective against *Zygomycetes*
- acquired resistance is rare, occasional strains of *Candida albicans* and *Aspergillus fumigatus* following treatment

### Uses

- various superficial infections including dermatophytoses, pityriasis versicolor, and mucosal and cutaneous forms of candidosis
- various subcutaneous infections including chromoblastomycosis, sporotrichosis, and certain forms of phaeohyphomycosis
- blastomycosis
- histoplasmosis
- useful alternative to amphotericin B for invasive aspergillosis
- prophylaxis against *Aspergillus* and *Candida*
- maintenance to prevent relapse in AIDS patients with histoplasmosis or cryptococcosis
- Inadequate evaluation in systemic candidosis
Itraconazole

**Pharmaceutics**
- oral capsules
- oral solution
- intravenous formulation
- Supplied as 25ml solution containing 250 mg itraconazole and 400 mg hydroxypropyl-β-cyclodextrin
- Dilute with 50 ml 0.9% sodium chloride solution prior to infusion
- After reconstitution can be stored at +4°C maximum 48 h

**Pharmacokinetics**
- variable absorption (capsule formulation)
- incomplete absorption (55%) from GI tract
- absorption improved if given with food (capsules)
- single 100 mg capsule produces peak serum concentration of 0.1–0.2 mg/l 2–4 h after administration
- oral solution 5 mg/kg for 1–2 weeks achieves levels of 1.0-1.5 mg/l in AIDS and neutropenic patients
- higher concentrations achieved after repeated dosing
- serum concentrations markedly lower when gastric acid reduced (capsules); no effect of reduced gastric acid with liquid formulation
- absorption of liquid formulation enhanced if given without food
- 5 mg/kg oral solution results in 1.0–1.5 mg/l blood concentration after 1–2 weeks, absorption adequate and predictable
- 99% protein binding
- CSF concentrations minimal
- concentrations in lung, liver, kidney, stomach, spleen, muscle, and bone 2–3 times higher than in serum
- using the i.v. dosage schedule of 200 mg twice daily on days 1–2, followed by 200 mg once daily from day 3 onwards, steady-state plasma concentrations of itraconazole are attained after 2 days
- extensive metabolism by hepatic cytochrome P450 enzyme system
- major metabolite – hydroxyitraconazole – bioactive
- serum half-life: 20–30 h, increasing to 40 h after prolonged dosing
**Dosage**

**Oral**
- oropharyngeal candidosis in non-immunocompromised patients, 10 mg per day for 2 weeks
- oropharyngeal candidosis in neutropenic patients and those with AIDS, 200–400 mg per day
- oral solution in oropharyngeal candidosis, 200–400 mg per day for 1–2 weeks
- deep fungal infection, 200–400 mg per day
- loading dose of 600 mg per day for life-threatening infections
- maintenance in AIDS patients with histoplasmosis or cryptococcosis, 200 mg b.d.
- prophylaxis in neutropenic patients, 400 mg per day, ideally 5–7 days before anticipated neutropenia or at start of chemotherapy (required in *de novo* presentation of acute leukemia)

**Intravenous**
- first line for histoplasmosis, second line for aspergillosis, candidosis, and cryptococcal meningitis
  - day 1 and 2: 1 h infusion 200 mg twice daily
  - from day 3 on: one 1 h infusion 200 mg each day. Safety for periods longer than 14 days has not been established

**Contraindications**
- known hypersensitivity to azole derivatives
- severe hepatic impairment
- pregnancy, except for therapy of life-threatening infections
- terfenadine, astemizole, quinidine, pimozide, CYP3A4-metabolized HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam and triazolam are contraindicated with itraconazole
- itraconazole i.v. cannot be used when administration of sodium chloride is indicated
- hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration, therefore, patients with renal impairment, defined as creatinine clearance below 30 ml/min, should not be treated with itraconazole i.v.
Itraconazole

### Precautions

- dosage should be reduced in accordance with creatinine clearance rate in patients with renal impairment
- hepatic function should be monitored when treatment is prolonged
- women of child-bearing age should take effective contraceptive precautions during treatment and for several weeks thereafter
- Do not infuse i.v. formulation with other drugs
- Should not be used in patients who have had heart failure

### Adverse effects

- well tolerated, but can cause:
  - vomiting
  - abdominal discomfort and epigastric pain
  - constipation
  - headache (rare)
  - dizziness
  - pruritus
  - allergic rashes
- avoid use in patients with liver disease
- avoid use in patients with previous hepatotoxic drug reactions
- hypokalemia possible during long-term therapy at high doses (400 mg per day)
- hypertension possible at higher dosages
- Isolated cases of Stevens–Johnson syndrome
- Discontinue if signs of congestive heart failure
Itraconazole

Drug interactions

- drugs affecting the metabolism of itraconazole:
  - enzyme-inducing drugs such as rifampicin, rifabutin, carbamazepine, isoniazid, and phenytoin significantly reduce the bioavailability of itraconazole
  - as itraconazole is metabolized mainly through CYP3A4, potent inhibitors of this enzyme may increase the bioavailability of itraconazole. Examples are ritonavir, indinavir, and clarithromycin
- effect of itraconazole on the metabolism of other drugs:
  - itraconazole can inhibit the metabolism of drugs metabolized by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects
- drugs which should not be used with itraconazole:
  - terfenadine
  - astemizole
  - triazolam
  - oral midazolam
  - quinidine
  - pimozide
  - CYP3A4-metabolized HMG-CoA reductase inhibitors
- drugs whose plasma levels, effects, or side effects should be monitored. Their dosage, if co-administered with itraconazole, should be reduced if necessary:
  - oral anticoagulants
  - anti-HIV protease inhibitors such as ritonavir, indinavir, and saquinavir
  - certain antineoplastic agents: vinca alkaloids, busulfan, docetaxel, and trimetrexate
  - CYP3A4-metabolized calcium channel blockers such as dihydropyridines and verapamil
  - certain immunosuppressive agents: cyclosporine, tacrolimus, and rapamycin
  - others: digoxin, carbamazepine, buspirone, alfentanil, alprazolam, midazolam i.v., rifabutin, and methylprednisolone
Itraconazole

**Key references**


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**Antifungal drugs**
Itraconazole


Antifungal drugs
### Voriconazole

**Spectrum of activity**

- broad spectrum of activity (largely on basis of in vitro studies; only limited number of in vivo studies available)
  - Candida species
  - Cryptococcus neoformans
  - Aspergillus species
  - Fusarium species
  - Penicillium marneffei
  - Scedosporium apiospermum
  - Blastomyces dermatitidis
  - Coccidioides immitis
  - Histoplasma capsulatum
  - dermatophyte species
  - dematiaceous fungi
- ineffective against Zygomycetes
- acquired resistance not reported
- may be active against fluconazole and itraconazole resistant Candida species, and itraconazole and amphotericin B resistant Aspergillus, depending on mechanism of resistance

**Uses**

- treatment of serious fungal infection in immunocompromised patients
- acute invasive aspergillosis – in USA approved as first-line treatment. 53% complete or partial response
- invasive candidosis due to fluconazole-resistant Candida species (including Candida krusei): 71% complete or partial response
- infections due to Fusarium and Scedosporium – in USA approved for salvage treatment
- cryptococcosis: variable response
- Fusarium infections: 43% response
Voriconazole

**Pharmaceutics**
- supplied for i.v. administration in lyophilized form in 200 mg amounts
- reconstitute in 19 ml sterile water to give an extractable volume of 20 ml concentrated solution containing 10 mg/ml voriconazole
- dilute further with 5% dextrose or 0.9% sodium chloride
- can be stored at refrigerator temperature for maximum of 24 h

**Pharmacokinetics**
- oral administration leads to rapid and almost complete absorption
- 2 h after single 400 mg dose, serum concentrations of ~2 mg achieved but variable levels seen in certain demographic groups
- disproportionate increase in blood levels with increasing oral and parenteral dosage
- non-linear pharmacokinetics in high-risk patients: may indicate monitoring levels
- absorption reduced with high fat meals but is not affected by changes in gastric pH
- mean time to maximum plasma concentration: 1–2 h post-dose
- variation in metabolism (rapid vs. slow metabolizers)
- grapefruit juice markedly increases blood levels in mice. Effect of grapefruit juice in humans is unknown
- bioavailability >96%
- multiple dosing in presence of food reduces systemic exposure by 22% compared to the fasting state
- best when not administered within 1 h of food intake
- widely distributed throughout tissues
- protein binding 58%
- large volume of distribution: 4.6 l/kg
- metabolites:
  - one major (N-oxide)
  - several minor
  - not active
- elimination by metabolic clearance
- extensively metabolized by cytochrome P450 isoenzymes: may affect delivery across intestinal mucosa
- elimination half-life is dose-dependent: 6–9 h after a 3 mg/kg parenteral dose or 200 mg oral dose
Voriconazole

Dosage

- loading dose: i.v formulation 6 mg/kg every 12 h for two doses: steady state reached
  - infusion rate: maximum 3 mg/kg/h over a 1–2 h period
  - infusion concentration should not exceed 5 mg/ml
- maintenance dose: 4 mg/kg every 12 h
- oral therapy:
  - 200 mg every 12 h >40 kg
  - 100 mg every 12 h <40 kg
  - if patient response inadequate, increase to 300 mg every 12h (or 150 mg every 12 h for patients <40 kg)
  - 1 h before or 1 h following a meal
- treatment intolerance:
  - reduce i.v. maintenance dose to 3 mg/kg every 12 h.
  - reduce oral dose in 50 mg steps to a minimum of 200 mg every 12 h
    (100 mg every 12 h for patients <40 kg)
- no adjustment required in patients with abnormal liver function tests (up to 5-fold upper limit of normal) but continued monitoring is recommended
- no adjustment of oral dose required for patients with renal impairment
- hemodialysis (4 h session) does not remove a sufficient amount of drug – no dosage adjustment required

Precautions

- Avoidance of strong direct sunlight

Do not use i.v. formulation in patients with moderate renal impairment (creatinine clearance <50 ml/min), due to cyclodextrin excipient
Voriconazole

Adverse effects

- >30% transient visual disturbances, but no anatomical correlates of the disturbances
- headache
- gastrointestinal upset
- rare cases of severe exfoliative cutaneous reactions, eg. Stevens–Johnson syndrome
- elevation in liver function tests in ~13% patients
  - associated with higher serum concentrations or dosages
  - reversible on discontinuation
  - isolated cases of hepatitis, cholestasis and fulminant hepatic failure
  - monitoring of liver function essential when used in patients with severe hepatic impairment
  - cases of torsades de pointes reported

Drug interactions

- similar to those seen with itraconazole
- absorption not reduced if given concomitantly with drugs that reduce gastric acid secretion
- increase in serum concentration may be seen of:
  - sirolimus
  - terfenadine
  - astemizole
  - cisapride
  - pimozide
  - quinidine
  - cyclosporin – monitor levels
  - tacrolimus – monitor levels
  - warfarin – monitor prothrombin time
  - lovastatin and midazolam – adjust dose
  - tolbutamide and glipizide – monitor blood glucose levels
- inhibition of anti-HIV protease inhibitors
- marked reduction in blood level if given with inducers of P450 enzyme system:
  do not administer together with:
  - carbamazepine
  - phenobarbital
  - rifampicin
Voriconazole

Key references

Jeu LA, Piacenti FJ, Lyakhovetskiy AG, Fung HB.
Voriconazole.
Clinical Therapeutics 2003; 25: 1321-1381.

Maxwell MJ, Messer SA, Hollis RJ, Diekema DJ,
Pfaller MA.
Evaluation of Etest method for determining voriconazole and amphotericin B MICs for 162 clinical isolates of Cryptococcus neoformans.

Muijsers RBR, Goa KL, Scott LJ.
Voriconazole in the treatment of invasive aspergillosis.
Drugs 2002; 62: 2655-2664.

Pfaller MA, Diekema DJ, Messer SA, Boyken L, Hollis RJ, Jones RN.
In vitro activities of voriconazole, posaconazole, and four licensed systemic antifungal agents against Candida species infrequently isolated from blood.
Journal of Clinical Microbiology 2003; 41: 78-83.

Potoski BA, Brown J.
The safety of voriconazole.
Clinical Infectious Diseases 2002; 35: 1273-1275.

Purkins L, Wood N, Ghahramani P et al.
Pharmacokinetics and safety of voriconazole following intravenous-to oral oral-dose escalation regimens.

Ullmann AJ.
Review of the safety, tolerability, and drug interactions of the new antifungal agents caspofungin and voriconazole.
Therapy of Specific Infections

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25  Prevention of invasive aspergillosis
26  Blastomycosis
27  Candidosis
28  Coccidioidomycosis
29  Cryptococcosis
30  Histoplasmosis
31  Mucormycosis
32  Paracoccidioidomycosis
33  Penicillium marneffei infection
34  Sporotrichosis
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Therapy of specific infections
### Aspergillosis

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic (ABPA)</strong></td>
<td>Designed for acute asthmatic exacerbations and for avoiding end-stage fibrosis. Mild disease may not require treatment. Indications for steroids: increasing serum concentrations, new or worsening infiltrates on chest radiographs. Prednisolone 1.0 mg/kg per day until radiographs are clear, then 0.5 mg/kg per day for 2 weeks followed by alternate-day dosing for 3–6 months. Bronchodilators and postural drainage may help to reduce mucus plugging. Itraconazole 200 mg/day 16 weeks.</td>
</tr>
<tr>
<td><strong>Aspergilloma</strong></td>
<td>Surgical resection with perioperative amphotericin B. Intracavitary instillation of amphotericin B 10–20 mg in 10–20 ml distilled water.</td>
</tr>
<tr>
<td><strong>Chronic necrotizing</strong></td>
<td>Surgical resection. Itraconazole 200–400 mg per day. Parenteral and local amphotericin B.</td>
</tr>
<tr>
<td></td>
<td>- Chronic indolent invasive in immunocompetent: Surgical debridement and drainage combined with amphotericin B 1.0 mg/kg/day. Long-term suppressive treatment with itraconazole may prevent recurrence. In chronic granulomatous sinusitis surgical removal of paranasal granuloma.</td>
</tr>
</tbody>
</table>
### Acute invasive in immuno-compromised

- Surgical debridement but increased mortality associated with neutropenia
- Amphotericin B sinonasal lavage or spray after debridement, or AmBisome® 3–5 mg/kg per day or higher, or Abelcet® 5 mg/kg per day, or itraconazole 400–600 mg per day

### Paranasal granuloma

- Surgical debridement and itraconazole 200–400 mg per day

### Acute invasive

- Poor response rate, especially if neutrophil count does not recover
- Minimum 2 wk treatment
- Amphotericin B 1.0–1.5 mg/kg per day
- AmBisome® 3–5 mg/kg per day or higher
- Amphocil® (Amphotec®) 3–4 mg/kg per day, up to 6 mg/kg per day
- Abelcet® 5 mg/kg per day
- Itraconazole: oral 400–600 mg per day for 4 days then 200 mg twice daily without food, or i.v. 200 mg 12 h intervals for 4 doses then 200 mg/day for up to 2 wk. Infuse over 1 h
- Voriconazole: i.v.: 6 mg/kg 12 h intervals, 2 doses, then 4 mg/kg 12 h intervals, then p.o. 200 mg 12 h intervals when oral medication tolerated
- Caspofungin
  - Use in patients who have failed to tolerate, or are intolerant of other antifungal drugs
  - i.v. 70 mg loading dose first day
  - 50 mg/day subsequent days
  - Infuse over 1 h
- Variable duration of treatment
- Granulocyte transfusions, CSFs and interferon not recommended for routine clinical use
## Aspergillosis

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>Poor prognosis&lt;br&gt;AmBisome® 3–5 mg/kg and higher&lt;br&gt;Itraconazole 600 mg/day and higher</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Amphotericin B 1.0 mg/kg/day, 2–3 months’ duration&lt;br&gt;Replace infected valves 1–2 weeks after treatment started</td>
</tr>
<tr>
<td>Bone infection</td>
<td>Surgical debridement&lt;br&gt;Amphotericin B 1.0 mg/kg/day&lt;br&gt;Itraconazole i.v.</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Usefulness controversial&lt;br&gt;Itraconazole oral solution 400 mg per day or&lt;br&gt;Amphotericin B 0.5 mg/kg per day</td>
</tr>
<tr>
<td>Empirical</td>
<td>Amphotericin B 1 mg/kg per day&lt;br&gt;AmBisome® 3 mg/kg per day</td>
</tr>
</tbody>
</table>
Aspergillosis

Key references

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.

Centers for Disease Control and Prevention.
Guidelines for prevention of nosocomial pneumonia.

Centers for Disease Control and Prevention.
Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients.

Denning DW.
Chronic forms of pulmonary aspergillosis.

Herbrecht R, Denning DW, Patterson TF et al.
Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis.

Ellis M.
Amphotericin B and invasive aspergillosis – how do the data guide us?

Habicht JM, Passweg J, Kuhne T et al.
Successful local excision and long-term survival for invasive pulmonary aspergillosis during neutropenia after bone marrow transplantation.

Ikemoto H.
Medical treatment of pulmonary aspergilloma.

Kawamura S, Maesaki S, Tomono K et al.
Clinical evaluation of 61 patients with pulmonary aspergilloma.

Klont RR, Meis JF, Verweij PE.
Critical assessment of issues in the diagnosis of invasive aspergillosis.

Kuhn FA, Javer AR.
Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents.

Leon EE, Craig TJ.
Antifungals in the treatment of allergic bronchopulmonary aspergillosis.
Annals of Allergy, Asthma, and Immunology 1999; 82: 511-516.

Lin SJ, Schranz J, Teutsch SM.
Aspergillosis case fatality rate: systematic review of the literature.

Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients.
Journal of Infectious Diseases 2002; 186: 1297-1306.

Marr KA, Carter RA, Boechk M et al.
Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors.
Blood 2002; 100: 4358-4366.

Marr KA, Patterson T, Denning D.
Aspergillosis. Pathogenesis, clinical manifestations, and therapy.

Perea S, Patterson TF.
Invasive Aspergillus infections in hematologic malignancy patients.

Therapy of specific infections


### Prevention of invasive aspergillosis

<table>
<thead>
<tr>
<th>Preventative strategy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of exposure to <em>Aspergillus</em> conidia</td>
<td>Heavily contaminated areas including compost heaps, grain silos, moldy hay, and marijuana. Consider water as a source of bioaerosols in hospitals</td>
</tr>
<tr>
<td>Implement surveillance program</td>
<td>Air sampling, dust sampling, water analysis, and patient surveillance</td>
</tr>
<tr>
<td>Remove all environmental sources in hospital environments</td>
<td>Potted plants, flowers, food items such as spices and tea, thorough cleaning</td>
</tr>
<tr>
<td>High-efficacy particulate air (HEPA) filters or laminar air-flow (LAF)</td>
<td>Expensive, but HEPA or LAF should be considered for patients at very high risk for invasive aspergillosis</td>
</tr>
<tr>
<td>Prophylaxis: itraconazole, low-dose amphotericin B, amphotericin B inhalation</td>
<td>Efficacy data conflicting, should be considered in high-risk group</td>
</tr>
<tr>
<td>Administration of colony-stimulating factors to neutropenic patients</td>
<td>Expensive, considered as part of overall strategy</td>
</tr>
<tr>
<td>Empirical cAMB</td>
<td>Strongly recommended – shown to reduce mortality – 0.6 mg/kg per day</td>
</tr>
<tr>
<td>Empirical AmBisome®</td>
<td>Reduces emerging infections</td>
</tr>
<tr>
<td>Secondary prophylaxis (antifungal treatment to prevent recrudescence of proven invasive aspergillosis treated during a prior episode of immunosuppression)</td>
<td>Relapse rates greater than 50% without prophylaxis. Amphotericin B 0.6–1.0 mg/kg per day given at onset of chemotherapy or neutropenia Consider surgical resection of localized disease</td>
</tr>
</tbody>
</table>
Key references


Anaissie EJ, Costa SF. Nosocomial aspergillosis is waterborne. Clinical Infectious Diseases 2001; 33: 1546-1548.


Foot ABM, Veys PA, Gibson BES. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. Bone Marrow Transplantation 1999; 24: 1089-1093.


Prevention of invasive aspergillosis

Perfect JR, Cox GM, Lee JY et al.
The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis.
Clinical Infectious Diseases 2001; 32: 1824-1833.

Richardson MD.
The effective prevention of systemic fungal infection: precluding the risk of environmental exposure.

Richardson MD, Rennie S, Marshall I et al.
Fungal surveillance of an open haematology ward.

Warnock DW, Hajjeh RA, Lasker BA.
Epidemiology and prevention of invasive aspergillosis.
Current Infectious Disease Reports 2001; 3: 507-516.

Warris A, Gaustad P, Meis JFGM et al.
Recovery of filamentous fungi from water in a paediatric bone marrow transplantation unit.
# 26

**Blastomycosis**

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary: mild/moderate disease</td>
<td>Itraconazole, oral, 200 mg per day up to 6 months, or up to 3 months if lesions resolve; if no improvement, increase to 400 mg per day</td>
</tr>
<tr>
<td></td>
<td>Oral ketoconazole 400 mg per day, increasing to 600–800 mg/kg as required</td>
</tr>
<tr>
<td></td>
<td>Fluconazole 400–800 mg/kg if itraconazole not absorbed</td>
</tr>
<tr>
<td>Pulmonary: life threatening</td>
<td>Amphotericin B 0.7–1.0 mg/kg/d. If good response itraconazole 200–400 mg/d.</td>
</tr>
<tr>
<td></td>
<td>Little experience with lipid formulations of amphotericin B</td>
</tr>
<tr>
<td>Disseminated: mild/moderate disease</td>
<td>If no CNS involvement:</td>
</tr>
<tr>
<td></td>
<td>– itraconazole 200–400 mg/d for at least 6 months</td>
</tr>
<tr>
<td></td>
<td>– fluconazole 400–800 mg/d if itraconazole not tolerated</td>
</tr>
<tr>
<td></td>
<td>CNS involvement: amphotericin B 0.7–1.0 mg/kg/d to a total dose of 2 g</td>
</tr>
<tr>
<td>Disseminated: life-threatening</td>
<td>Amphotericin B 0.7–1.0 mg/kg per day to a total dose of 1.5–2.5 g</td>
</tr>
<tr>
<td>Disseminated: osteomyelitis</td>
<td>Amphotericin B 0.5–0.7 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>Itraconazole 12 months</td>
</tr>
</tbody>
</table>
Blastomycosis

Key references


### Candidosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **Mucosal**     | Reversal of known risk factors  
Antifungals  
• topical  
• nystatin suspension, 4–6 ml 4 times daily, 7–14 days  
• nystatin pastilles, 4–5 times daily, 7–14 days  
• clotrimazole troches, one 10 mg troche 5 times daily  
• itraconazole oral solution, 200 mg per day, 7–14 days  
• amphotericin B oral suspension, 1 ml 4 times daily, 100 mg/ml suspension in azole-refractory disease  
• systemic: fluconazole, itraconazole |

**Oropharyngeal**  
Improvement of host defenses  
Topical antifungals  
• nystatin suspension  
• clotrimazole troche  
• fluconazole 100–200 mg, two divided doses, or 3 mg/kg, two divided doses in children  
• itraconazole oral solution 200 mg/day, preferably in two intakes for 1 week. If no response, continue for further week  
• amphotericin B 0.5 mg/kg, 3–7 days  
Antifungal susceptibility testing not generally indicated but useful in refractory infections |

| **Esophageal** | Fluconazole 200 mg per day orally, 14–21 days  
Itraconazole oral solution 200 mg per day  
Fluconazole-refractory disease: itraconazole oral solution ≥ 200 mg/day, or amphotericin B i.v. 0.3–0.7 mg/kg per day  
Caspofungin 50 mg/d 7–21 days  
Antifungal susceptibility testing not generally indicated but useful in refractory infection |
<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Therapy not generally required in asymptomatic candiduria</td>
</tr>
<tr>
<td></td>
<td>Catheter removal</td>
</tr>
<tr>
<td></td>
<td>Fluconazole 200 mg per day, 7–14 days; if <em>C. glabrata</em> or <em>C. krusei</em> is causal agent use i.v. amphotericin B (0.3–1.0 mg/kg 1–7 d)</td>
</tr>
<tr>
<td>Candidemia</td>
<td></td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>Removal of all existing central venous catheters</td>
</tr>
<tr>
<td></td>
<td>Fluconazole 800 mg loading dose, followed by 400 mg per day for 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 0.5 mg/kg per day, 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 0.75–1 mg/kg per day – less sensitive yeasts</td>
</tr>
<tr>
<td></td>
<td>Abelcet® 5 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>AmBisome® 1–3 mg/kg per day or higher</td>
</tr>
<tr>
<td></td>
<td>Amphotec® 2–6 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>Caspofungin 70 mg loading dose, followed by 50 mg/day. Infuse over 1 h</td>
</tr>
<tr>
<td>Persistent neutropenia</td>
<td>Catheter removal</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 1 mg/kg per day plus flucytosine</td>
</tr>
<tr>
<td></td>
<td>AmBisome® 1–3 mg/kg per day or higher</td>
</tr>
<tr>
<td></td>
<td>Neonates Amphotericin B</td>
</tr>
<tr>
<td>Candida glabrata infection</td>
<td>Amphotericin B ≥ 0.7 mg/kg per day</td>
</tr>
<tr>
<td>Candida krusei infection</td>
<td>Amphotericin B 1.0 mg/kg per day</td>
</tr>
<tr>
<td>Candida lusitaniae infection</td>
<td>Fluconazole 400 mg per day</td>
</tr>
</tbody>
</table>
### Candidosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated</td>
<td></td>
</tr>
<tr>
<td>• acute</td>
<td>Amphotericin B 1 mg/kg per day plus flucytosine</td>
</tr>
<tr>
<td></td>
<td>Fluconazole 800 mg per day or higher in less critically ill patients, dependent on species</td>
</tr>
<tr>
<td></td>
<td>AmBisome® 1–3 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>Caspofungin 70 mg/d followed by 50 mg/d. Infuse over 1 h</td>
</tr>
<tr>
<td>• chronic</td>
<td>Fluconazole 400 mg per day in stable patients</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 1 mg/kg per day plus flucytosine</td>
</tr>
<tr>
<td></td>
<td>AmBisome® 3–5 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 0.6–0.7 mg/kg per day, followed by fluconazole (follow-up out-patient therapy – 6 months to 1 year)</td>
</tr>
<tr>
<td><strong>Candida peritonitis</strong></td>
<td>Re-exploration of abdominal cavity</td>
</tr>
<tr>
<td></td>
<td>Drainage of infection</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
</tr>
<tr>
<td><strong>CAPD and catheter-related peritonitis</strong></td>
<td>Catheter removal</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B or fluconazole</td>
</tr>
<tr>
<td><strong>Candida meningitis</strong></td>
<td>Amphotericin B 0.7–1.0 mg/kg per day plus flucytosine</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg 4 times daily</td>
</tr>
<tr>
<td></td>
<td>Removal of ventricular prosthetic devices</td>
</tr>
<tr>
<td><strong>Candida endocarditis</strong></td>
<td>Valve resection</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B 0.7 mg/kg per day plus flucytosine</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg 4 times daily</td>
</tr>
<tr>
<td><strong>Candida endophthalmitis</strong></td>
<td>Amphotericin B plus flucytosine, followed by fluconazole 400–800 mg, 6–12 weeks</td>
</tr>
</tbody>
</table>
### Candidosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| *Candida* osteomyelitis and arthritis | Amphotericin B 0.7–1.0 mg/kg/d 6–10 weeks with or without flucytosine 100 mg/kg/d  
                   Debridement of necrotic bone if extensive vertebral destruction is present  
                   Infected non-prosthetic joints  
                   – amphotericin B 1.0 mg/kg/d 6–10 wk  
                   If no improvement after 1 week, add flucytosine 100 mg/kg/d  
                   Open drainage essential |
| Infected prosthetic joints       | Remove all foreign material and necrotic bone tissue  
                   Treatment as for infected, non-prosthetic joints  
                   Replace with new prosthesis when infection eradicated |
Candidosis

Key references


Candidosis

Rex JH, Walsh TJ, Sobel JD et al.
Practice guidelines for the treatment of candidiasis.
Clinical Infectious Diseases 2000; 30: 662-678.

Saiman L, Ludington E, Pfaller MA et al.
Risk factors for candidemia in neonatal intensive care unit patients.

Saag MS, Fessel WJ, Kaufman CA et al.
Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients.

Sallah S, Semelka RC, Webbie R, Sallah W, Nguyen NP, Vos P.
Hepatosplenic candidiasis in patients with acute leukemia.
British Journal of Haematology 1999; 106: 697-701.

Schwarze R, Penk A, Pitrow L.
Treatment of candidal infections with fluconazole in neonates and infants.

Sobel JD, Kaufman CA, McKinsey D et al.
Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group.

Taillandier J, Estnault Y, Alemanni M.
Age and Ageing 2000; 29: 117-123.

Trick WE, Fridkin SF, Edwards JR et al.
Clinical Infectious Diseases 2002; 35: 627-630.

Villanueva A, Gotuzzo E, Arathoon EG et al.
A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis.

Wise GJ, Talluri GS, Marella VK.

Worthington HV, Clarkson JE.
Prevention of oral mucositis and oral candidiasis for patients with cancer treated with chemotherapy: Cochrane systematic review.

Therapy of specific infections
## Coccidioidomycosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>• no dissemination risk</td>
<td>Observe, or fluconazole 400 mg per day for 3–6 months</td>
</tr>
<tr>
<td>• dissemination risk</td>
<td>Amphotericin B 0.5–0.7 mg/kg per day, followed by fluconazole 400 mg for 6 months</td>
</tr>
<tr>
<td><strong>Pulmonary cavity</strong></td>
<td></td>
</tr>
<tr>
<td>(uncomplicated) or fibronodular disease</td>
<td>Surgical resection or closure</td>
</tr>
<tr>
<td></td>
<td>Fluconazole 400 mg per day or itraconazole 200 mg b.d. for at least 12 months. If no response, amphotericin B 0.5–0.7 mg/kg/d</td>
</tr>
<tr>
<td><strong>Progressive pulmonary or disseminated (non-meningeal)</strong></td>
<td></td>
</tr>
<tr>
<td>• immediately life-threatening</td>
<td>Amphotericin B 1.0–1.5 mg/kg per day, to achieve a total dose of 2500–3000 mg; switch to fluconazole when disease is under control</td>
</tr>
<tr>
<td>• slowly progressive or stable</td>
<td>Fluconazole 400–800 mg/kg per day, or itraconazole 200 mg b.d.</td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td>Fluconazole 600–1200 mg per day</td>
</tr>
<tr>
<td></td>
<td>Itraconazole 400–600 mg per day</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B directly into CSF together with systemic therapy followed by oral fluconazole 600–1200 mg/kg/day</td>
</tr>
<tr>
<td><strong>HIV-infected</strong></td>
<td>Control infection, followed by lifelong therapy with fluconazole 400 mg per day, or itraconazole 200 mg b.d. In meningitis fluconazole 800 mg/d</td>
</tr>
</tbody>
</table>
Coccidioidomycosis

Key references

Blair JE, Logan JL.
Coccidioidomycosis in solid organ transplantation.
Clinical Infectious Diseases 2001; 33: 1536-1544.

Deresinski SC.
Current Opinion in Infectious Diseases 2001; 14: 693-696.

Galgiani JN, Ampel NM, Catanzaro A et al.
Practice guidelines for the treatment of coccidioidomycosis.
Clinical Infectious Diseases 2000; 30: 658-661.

Goldman M, Johnson PC, Sarosi GA.
Fungal pneumonias. The endemic mycoses.

Kauffman CA.
Endemic mycoses in patients with hematologic malignancies.
Seminars in Respiratory Infections 2002; 17: 106-112.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.

Panackal AA, Hajjeh RA, Cetron MS, Warnock DW.
Fungal infections among returning travelers.
Clinical Infectious Diseases 2002; 35: 1088-1095.

Rivitti EA, Aoki V.
Deep fungal infections in tropical countries.
Clinical Dermatology 1999; 17: 171-190.

Torres HA, Rivero GA, Kontoyiannis DP.
Endemic mycoses in a cancer hospital.
Medicine (Baltimore) 2002; 81: 201-212.
### Meningitis in normal hosts

- amphotericin B 0.7–1.0 mg/kg, plus flucytosine 37.5 mg/kg every 6 h for 4 weeks, or for 6–10 weeks in patients with risk factors that correlate with a high frequency of relapse
- amphotericin B 0.7–1.0 mg/kg per day, plus flucytosine 100 mg/kg per day for 2 weeks, followed by fluconazole 400 mg per day for a minimum of 10 weeks, then fluconazole maintenance for 6–12 months
- lipid formulations of amphotericin B

### Meningitis in AIDS

- amphotericin B 0.7–1.0 mg/kg per day plus flucytosine 100 mg/kg per day for 2–3 weeks, followed by fluconazole 400 mg per day for a minimum of 10 weeks, then fluconazole 200 mg per day for life
- liposomal amphotericin B (AmBisome®) 4 mg/kg per day or itraconazole 200–400 mg/kg per day
- maintenance therapy with fluconazole 200 mg per day for life
- combination of fluconazole 400–800 mg/day plus flucytosine 100 mg/kg per day but high incidence of side effects
- if CD4 T-lymphocyte count increases above 100–200 cells per µl following highly active antiretroviral therapy (HAART), maintenance treatment can be discontinued

### Pulmonary – normal hosts

- usually none, observation only
- asymptomatic: if treatment considered fluconazole 200–400 mg per day for 3–6 months
- symptomatic infection:
  - fluconazole 200–400 mg per day for 3–6 months
  - itraconazole 200–400 mg per day for 6–12 months
  - amphotericin B 0.4–0.7 mg/kg per day up to a total dose of 1000–2000 mg
### Cryptococcosis

#### Pulmonary – progressive and/or HIV-infected patients
- amphotericin B 0.7–1.0 mg/kg per day
- fluconazole 200–400 mg/kg per day for life
- itraconazole 200 mg b.d.

#### Extrapulmonary – non-meningeal
- amphotericin B 0.3–0.6 mg/kg per day plus flucytosine 100–150 mg/kg per day
- fluconazole 400 mg per day for 3–6 months
- itraconazole 200 mg twice daily for 6–12 months

#### Management of elevated intracranial pressure
- percutaneous lumbar drainage

#### Maintenance
- fluconazole 200–400 mg p.o. 4 times daily, lifelong
- itraconazole 200 mg p.o. 2 times daily, lifelong
- amphotericin B 1 mg/kg i.v. 1–3 times per week, lifelong
Key references


# Histoplasmosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pulmonary</td>
<td>Spontaneous improvement in most cases, observe; where required, amphotericin B 0.5–0.7 mg/kg per day with steroids, or oral itraconazole 200 mg per day for 6–12 weeks. If hypoxic, amphotericin B 0.7 mg/kg/d, or lipid formulation 3 mg/kg/d followed by itraconazole 200–400 mg/d for 12 weeks.</td>
</tr>
<tr>
<td>Chronic pulmonary</td>
<td>Oral itraconazole 400 mg per day for 12–24 months. Amphotericin B 0.7 mg/kg per day for 10 weeks or AmBisome® 3 mg/kg per day in renal impairment. 12-month follow-up after discontinuation of treatment.</td>
</tr>
<tr>
<td>Disseminated</td>
<td><strong>• non-immunosuppressed</strong> Oral itraconazole 200–400 mg per day for 6–18 months, but fluconazole 400 mg/d if itraconazole not tolerated. Amphotericin B 0.7–1.0 mg/kg per day for 10 weeks in severe disease, infants 1.0 mg/kg for minimum of 6 weeks.</td>
</tr>
<tr>
<td></td>
<td><strong>• AIDS</strong> For severe disease: amphotericin B 0.7–1.0 mg/kg per day induction treatment, followed by itraconazole 400 mg/d to complete 12 week total induction period. In itraconazole intolerance, fluconazole 800 mg/d. Relapse common once drug discontinued. For milder disease: oral itraconazole 600 mg per day for 3 days, then 200 mg twice daily. For maintenance: amphotericin B 50 mg weekly or twice weekly highly effective but inconvenient; itraconazole 200–400 mg per day, or fluconazole 100–400 mg per day if itraconazole not absorbed, for life.</td>
</tr>
</tbody>
</table>
### Histoplasmosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal infections</td>
<td>CNS: amphotericin B 0.7–1.0 mg/kg/d, total dose 35 mg/kg over 3–4 months, followed by fluconazole 800 mg/d for another 9–12 months. In amphotericin B failure or intolerance, liposomal amphotericin B 3–5 mg/kg/d for 3–4 months. Bone/joint/skin: itraconazole 200 mg 4 times daily for variable periods. Mediastinal fibrosis Itraconazole 200 mg 4 times daily for 6 months. Surgical resection if progressive life-threatening obstruction. Surgical mortality is 20%</td>
</tr>
</tbody>
</table>
**Histoplasmosis**

**Key references**

Bamberger DM.
Successful treatment of multiple cerebral histoplasmosas with itraconazole.
Clinical Infectious Diseases 1999; 28: 915-916.

Corti ME, Cendoya CA, Soto I et al.
Disseminated histoplasmosis and AIDS: clinical aspects and diagnostic methods for early detection.
Aids and Patient Care STDs 2000; 14: 149-154.

Goldman M, Johnson PC, Sarosi GA.
Fungal pneumonias. The endemic mycoses.

Kauffman CA.
Management of histoplasmosis.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.

Odio CM, Navarrete M, Carrillo JM et al.
Disseminated histoplasmosis in infants.

Practice guidelines for the management of patients with histoplasmosis.
Clinical Infectious Diseases 2000; 30: 688-695.

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**Therapy of specific infections**

---
## Mucormycosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Rhinocerebral  | Control of diabetic acidosis  
Aggressive surgical debridement of all necrotic tissue  
Amphotericin B 1.0–1.5 mg/kg per day, total dose  
30–40 mg/kg, if contraindicated AmBisome® 5 mg/kg per day or higher  
Optimal duration and total dose of amphotericin B not determined |
| Pulmonary      | Reversal of predisposing conditions  
Restitution of neutrophils – spontaneously or with colony-stimulating factors – and reduction of glucocorticosteroid dose  
Amphotericin B: rapid escalation to 1.0–1.5 mg/kg per day  
Following stabilization, resection of necrotic lung tissue |
**Key references**

Eucker J, Sezer O, Graf B, Possinger K. 
Mucormycoses. 

Ferguson BJ. 
Mucormycosis of the nose and paranasal sinuses. 

Gonzalez CE, Rinaldi MG, Sugar AM. 
Zygomycosis. 

Hendrickson RG, Olshaker J, Duckett O. 
Rhinocerebral mucormycosis: a case of a rare, but deadly disease. 

Kontoyiannis DP, Wessel VC, Bodey GP et al. 
Zygomycosis in the 1990s in a tertiary-care cancer centre. 
Clinical Infectious Diseases 2000; 30: 851-856.

Lee FY, Mossad SB, Adal KA. 
Pulmonary mucormycosis: the last 30 years. 
Archives of Internal Medicine 1999; 159: 1301-1309.

Leleux X, Sendid B, Fruit J et al. 
Combined anti-fungal therapy and surgical resection as treatment of pulmonary zygomycosis in allogeneic bone marrow transplantation. 
Bone Marrow Transplantation 1999; 24: 417-420.

Losee JE, Selber J, Vega S et al. 
Primary cutaneous mucormycosis: guide to surgical management. 

Mondy KE, Haughey B, Custer PL et al. 
Rhinocerebral mucormycosis in the era of lipid-based amphotericin B: case report and literature review. 

Oh D, Notrica D. 
Primary cutaneous mucormycosis in infants and neonates: case report and review of the literature. 

Ribes JA, Vanover-Sams CL, Baker DJ. 
Zygomycosis in human disease. 

Talmi YP, Goldschmied-Reouven A, Bakon M et al. 
Rhino-orbital and rhino-orbito-cerebral mucormycosis. 

Van Steenwegen S, Maertens J, Boogaerts M, Deneffe G, Verheken E, Nackaerts K. 
Mucormycosis, a threatening opportunistic mycotic infection. 

Warwar RE, Bullock JD. 
Rhino-orbital-cerebral mucormycosis: a review. 
32

Paracoccidioidomycosis

- Long-term treatment required
- Assess response to treatment regularly, as relapses are common
- Oral itraconazole 100 mg per day for 6 months is preferred treatment
- Ketoconazole 200–400 mg per day for up to 12 months almost as effective
- Oral or parenteral fluconazole 200–400 mg per day for 6 months, if itraconazole or ketoconazole not absorbed
- Amphotericin B 1.0 mg/kg per day for 4–8 weeks, followed by sulfadiazine 500–1000 mg at 4 h intervals for 6–12 months; children, 60–100 mg/kg per day in divided doses

Key references


Therapy of specific infections
## Penicillium marneffei infection

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Preferred treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Itraconazole 200–400 mg per day or ketoconazole 400 mg per day</td>
</tr>
<tr>
<td>Severe</td>
<td>Amphotericin B 1 mg/kg per day for 2 weeks, then itraconazole 200–400 mg per day or ketoconazole 400 mg per day for a further 6 weeks provided improvement is seen with amphotericin B. Long-term maintenance for patients with AIDS, itraconazole 200 mg per day – relapse common if treatment discontinued</td>
</tr>
</tbody>
</table>

### Key references


## Sporotrichosis

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Preferred therapy</th>
</tr>
</thead>
</table>
| Pulmonary       | Difficult to treat, relapse common  
CDC outcome improved by lobectomy and concomitant amphotericin B 1 mg/kg per day, substituted by itraconazole 400 mg per day upon improvement  
For less severe disease, itraconazole 400 mg per day from outset |
| CNS             | Refractory to antifungal therapy |
| Osteoarticular  | Itraconazole 400 mg per day for 12 months or longer: shorter courses lead to relapse  
Fluconazole 400–800 mg per day is less effective; use where there is itraconazole intolerance |
| Disseminated    | Amphotericin B 1 mg/kg per day, continue until total dose of 1–2 g administered  
For less acute disease, itraconazole 400 mg per day  
For AIDS patients, lifelong itraconazole to prevent relapse |

### Key references

- Bustamante B, Campos PE. 
Endemic sporotrichosis. 
Current Opinion in Infectious Diseases 2001; 14: 145-149.

- Kauffman CA. 
Sporotrichosis. 
Clinical Infectious Diseases 1999; 29: 231-236.

- Morris-Jones R. 
Sporotrichosis. 

- Rivitti EA, Aoki V. 
Deep fungal infections in tropical countries. 
Clinical Dermatology 1999; 17: 171-190.

- Kauffman CA, Hajjeh R, Chapman SW. 
Practice guidelines for the management of patients with sporotrichosis. 
Clinical Infectious Diseases 2000; 30: 684-687.
Unusual fungal infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusariosis ( <em>Fusarium</em> species)</td>
<td>Correct neutropenia Amphotericin B 1.0–1.5 mg/kg per day, or liposomal amphotericin B 5 mg/kg per day Flucytosine 25 mg/kg every 6 h for non-responders (reversal of neutropenia necessary for recovery)</td>
</tr>
<tr>
<td>Pseudallescheriosis ( <em>Pseudallescheria boydii</em>, <em>Scedosporium apiospermum</em>)</td>
<td>Surgical removal if possible Miconazole 600 mg every 6 h i.v. usually best initial treatment for seriously ill patients (amphotericin B not effective) Itraconazole 400 mg per day for other patients</td>
</tr>
<tr>
<td>Phaeohyphomycosis</td>
<td>Skin and subcutaneous tissue disease Occasional dissemination: surgical excision Itraconazole (oral solution) 400 mg per day</td>
</tr>
<tr>
<td>Trichosporonosis ( <em>Trichosporon species</em>)</td>
<td>Correct neutropenia Amphotericin B 1.0–1.5 mg/kg per day</td>
</tr>
<tr>
<td>Paecilomyces lilacinus</td>
<td>Itraconazole 200 mg per day 3 months</td>
</tr>
<tr>
<td>Malassezia ( <em>Pityrosporum</em>) septicemia</td>
<td>Remove intravascular catheter Fluconazole 1 g i.v. per day if fungemia exists</td>
</tr>
</tbody>
</table>

Key references


35 (ii)  

**Unusual fungal infections**

Clancy CJ, Wingard JR, Hong Nguyen M.  
Subcutaneous phaeohyphomycosis in transplant recipients: review of the literature and demonstration of in vitro synergy between antifungal agents.  
Medical Mycology 2000; 38: 169-175.

Ere R, Galimberti M, Lucarelli G et al.  
Trichosporon beigelii: a life-threatening pathogen in immunocompromised hosts.  
Bone Marrow Transplantation 2000; 25: 745-749.

Fleming RV, Walsh TJ, Anaissie EJ.  
Emerging and less common fungal pathogens.  

Garcia-Diaz JB, Baumgarten K.  
Phaeohyphomycotic infections in solid organ transplant patients.  
Seminars in Respiratory Infections 2002; 17: 303-309.

Groll AH, Walsh TJ.  
Uncommon opportunistic fungi: new nosocomial threats.  

Guarro J, Gene J.  
Opportunistic fusarial infections in humans.  

Husain S, Alexander BD, Munoz P et al.  
Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi.  
Clinical Infectious Diseases 2003; 37: 221-229.

Jahagirdar BN, Morrison VA.  
Emerging fungal pathogens in patients with hematologic malignancies and marrow/stem-cell transplant recipients.  
Seminars in Respiratory Infection 2002; 17: 113-120.

Gutiérrez-Rodero F, Moragón M, Ortiz de la Tabla V et al.  
Cutaneous hyalohyphomycosis caused by Paecilomyces lilacinus in an immunocompromised host successfully treated with itraconazole: case report and review.  

LaRocco MT, Burgert SJ.  
Infection in the bone marrow transplantation recipient and role of the microbiology laboratory in clinical transplantation.  

Marr KA, Carter RA, Crippa F et al.  
Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients.  
Clinical Infectious Diseases 2002; 34: 909-917.

Musa MO, Al Eisa A, Halim M et al.  
The spectrum of Fusarium infection in immunocompromised patients with haematological malignancies and in non-immunocompromised patients: a single institution experience over 10 years.  

Nelson PE, Dignani MC, Anaissie EJ.  
Taxonomy, biology, and clinical aspects of Fusarium species.  
Clinical Microbiology Reviews 1994; 7: 479-504.

Nesky MA, Mcdougal EC, Peacock JE.  
Pseudallescheria boydii brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis.  
Clinical Infectious Diseases 2000;31:673-7.

Nucci M, Anaissie E.  
Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management.  
Clinical Infectious Diseases 2002; 35: 909-920.

Rossmann SN, Cernoch PL, Davis JR.  
Dematiaceous fungi are an increasing cause of human disease.  

Singh N, Chang FY, Gayowski T, Marino IR.  
Infections due to dematiaceous fungi in organ transplant recipients: case report and review.  
Clinical Infectious Diseases 1997; 24: 369-374.

Walsh TJ, Groll AH.  
Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century.  

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**Therapy of specific infections**
Prophylaxis

36 Prophylaxis alternatives

37 Examples of risk factors triggering targeted prophylaxis/pre-emptive therapy
### Prophylaxis alternatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>100–400 mg per day High-risk patients, 400 mg/kg per day</td>
<td>Effective for prevention of candidosis in immunocompromised patients Does not prevent emergence of <em>Candida glabrata</em> and <em>C. krusei</em> infections Offers no protection against aspergillosis or mucormycosis</td>
</tr>
<tr>
<td>Itraconazole (capsule)</td>
<td>400 mg per day</td>
<td>Has reduced incidence of candidosis and IPA; higher dose (600 mg/kg) given 2 weeks before chemotherapy Absorption highly variable, routine monitoring of serum levels required</td>
</tr>
<tr>
<td>Itraconazole (oral solution)</td>
<td>2.5 mg/kg twice daily</td>
<td>Benefit in reducing emergent IPA and <em>non-albicans</em> species of <em>Candida</em>; reliable absorption Start immediately prior to cytostatic treatment and generally 1 week before transplant procedure</td>
</tr>
<tr>
<td>Amphotericin B (i.v.)</td>
<td>0.15–0.25 mg/kg per day</td>
<td>Higher dose (0.25 mg/kg per day) has shown benefit</td>
</tr>
<tr>
<td>Amphotericin B (aerosol)</td>
<td>10 mg 3 times daily</td>
<td>Problems with tolerance: nausea and vomiting Caution in asthmatics — monitor peak flow and use bronchodilators prior to inhalation, benefits uncertain</td>
</tr>
</tbody>
</table>
Prophylaxis alternatives

Key references


Foot ABM, Veys PA, Gibson BES. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. Bone Marrow Transplantation 1999; 24: 1089-1093.


Prophylaxis alternatives

Nucci M, Biasoli I, Akiti T et al.  
A double-blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients.  
Clinical Infectious Diseases 2000; 30: 300-305.

Patel R.  
Prophylactic fluconazole in liver transplant recipients: a randomized, double-blind, placebo-controlled trial.  

Singh N, Yu VL.  
Prophylactic fluconazole in liver transplant recipients.  

U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA).  
1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus.  
Infectious Diseases in Obstetrics and Gynecology 2000; 8: 5-74.

Winston DJ, Busuttil RW.  
Randomized control trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients.  

Wolff SN, Fay J, Stevens D et al.  
Fluconazole vs low-dose amphotericin B for the prevention of fungal infections in patients undergoing bone marrow transplantation: a study of the North American marrow transplant group.  
Bone Marrow Transplantation 2000; 25: 853-859.
### Examples of risk factors triggering targeted prophylaxis/pre-emptive therapy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Suggested prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteremia</td>
<td>Fluconazole + p.o. amphotericin B</td>
</tr>
<tr>
<td>Heavy colonization with <em>C. albicans</em> at 2 or more sites</td>
<td>Fluconazole + p.o. amphotericin B</td>
</tr>
<tr>
<td>Heavy colonization with non-<em>albicans</em> species at 2 or more sites</td>
<td>Itraconazole + p.o. amphotericin B</td>
</tr>
<tr>
<td>Colonization with <em>C. tropicalis</em></td>
<td>i.v. amphotericin B</td>
</tr>
<tr>
<td>Unexpected neutropenia &gt;21 days</td>
<td>Itraconazole + p.o. amphotericin B</td>
</tr>
<tr>
<td>GVHD</td>
<td>Itraconazole + p.o. amphotericin B</td>
</tr>
<tr>
<td>Relapsed/refractory leukemia</td>
<td>Itraconazole + p.o. amphotericin B</td>
</tr>
</tbody>
</table>

Empirical Treatment of the Persistently Febrile Neutropenic Patient

Recommended empirical treatment

Current recommended initial strategy
Recommended empirical treatment

- Lack of definitive diagnosis
- Persistent fever 72–96 h duration
- Resistance to antibacterial drugs
- Conventional amphotericin B
  - test dose 1 mg
  - reach full therapeutic level (1.0 mg/kg) within 24 h
- If cAMB contraindicated, use AmBisome®
- AmBisome® 1–3 mg/kg until resolution

Key references

Bennett J.
Editorial response: Choosing amphotericin B formulations – Between a rock and a hard place.
Clinical Infectious Diseases 2000; 31: 1164-1165.

Hamacher J, Spiliopoulos A, Kurt AM et al.

Jones BL, McLintock LA.
Impact of diagnostic markers on early antifungal therapy

Marr KA.
Empirical antifungal therapy: new options, new tradeoffs.

Roland WE.
Amphotericin B colloidal dispersion versus amphotericin B in the empirical treatment of fever and neutropenia.
Clinical Infectious Diseases 1999; 28: 935-936.

Silling G, Fegeler W, Roos N, Essink M, Buchner T.
Early empiric antifungal therapy of infections in neutropenic patients comparing fluconazole with amphotericin B/lucycytosine.
Mycoses 1999; 43 (suppl 2): 101-104.

Walsh TJ, Finberg RW, Arradt C et al.
Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia.

Wingard JR.
Liposomal amphotericin B for fever and neutropenia.

Wingard JR, White MH, Anaissie E et al.
A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia.
Clinical Infectious Diseases 2000; 31: 1155-1163.
Current recommended initial strategy

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Prophylaxis</th>
<th>Pre-emptive treatment</th>
<th>Empirical treatment</th>
<th>Targeted treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Low (not colonized, HEPA filtration)</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>• High (Colonized)</td>
<td>Yes</td>
<td>NR**</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>NR**</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**NR: Not relevant


Key reference

Combination Treatment and Antifungals Under Development

40 Combination therapy: the issues

41 Antifungals under development
Combination therapy: the issues

- *in vitro* data suggest additive or synergistic activity
- predicting whether synergy or antagonism will predominate is extremely difficult
- no consensus regarding which combinations are synergistic or antagonistic
- limited experimental data
- extrapolation from *in vitro* or animal studies is, at best, tenuous
- limited clinical data
- is sequential therapy combination therapy?

Key references


Vazquez JA. Combination antifungal therapy against Candida species: the new frontier – are we there yet? Medical Mycology 2003; 41: 355-368.
Posaconazole

Trade and generic names
• formerly known as SCH 56592, developed by Schering-Plough pharmaceuticals

Pharmaceutics
• oral tablet and suspension

Mechanism of action
• structurally related to itraconazole
• inhibition of cytochrome P450
• compared to itraconazole, posaconazole is a significantly more potent inhibitor of sterol C14 demethylation, particularly in Aspergillus

Susceptibility patterns
• broad spectrum of activity
• Candida species
• Cryptococcus neoformans
• Aspergillus species
• Rhizopus species
• Blastomyces dermatitidis
• Coccidioides immitis
• histoplasmosis
• dermatophyte species
• dematiaceous species
• little activity against fluconazole- and itraconazole-resistant Candida species

Usual doses
• no detailed data are currently available and typical doses are not yet known

Side effects
• no side effects have been observed in phase I study in healthy volunteers

Current status
• phase III clinical trials

Antifungals under development
**Ravuconazole**

**Trade and generic names**
- formerly known as BMS-207147 and ER-30346
- developed by Bristol-Myers Squibb
- brand name not announced

**Mechanism of action**
- oral route of administration only
- triazole structurally related to fluconazole and itraconazole
- inhibition of cytochrome P450
- similar potency to itraconazole in inhibition of sterol C14 demethylation

**Susceptibility patterns**
- Activity against:
  - *Candida albicans*
  - *Cryptococcus neoformans*
  - *Aspergillus fumigatus*
  - dermatophytes
  - dematiaceous fungi
- Limited activity against:
  - *Sporothrix schenckii*
  - *Scedosporium* species
  - *Fusarium*
  - zygomycetes

**Usual doses**
- no data available from phase I and ongoing phase II clinical trials
- typical doses are not yet known

**Side effects**
- results of clinical trials not yet reported

**Current status**
- phase II trials
Micafungin

- Developed by Fujisawa Pharmaceutical Co.
- Water soluble echinocandin-like lipopeptide
- Inhibits 1,3-β-D-glucan synthase

Pharmacology
- Potent fungicidal activity against Candida species: C. albicans, C. glabrata, C. krusei
- Reduced activity against C. parapsilosis, C. guilliermondii
- No cross-resistance to fluconazole-resistant isolates of C. albicans
- No activity against Cryptococcus neoformans and Trichosporon cutaneum
- Inhibitory activity against Aspergillus fumigatus
- No inhibitory activity against Fusarium species, Scedosporium, zygomycetes
- Potent activity against mycelial forms of Histoplasma capsulatum, Blastomyces dermatitidis, Coccioidioides immitis
- No activity against yeast-like forms of Histoplasma capsulatum and Blastomyces dermatitidis
- Prolonged activity in experimental infections of candidosis and invasive aspergillosis

Metabolism and pharmacokinetics
- half-life: approximately 4 to 6 h
- dose-proportional increase in AUC
- 99% serum binding
- toxicity: no data are currently available

Clinical development
- Phase 1
  - doses of 2.5, 5, 12.5, 25 or 50 mg i.v. well tolerated in volunteers
  - steady state reached after 4 days
  - in haematopoetic stem cell transplant patients dose levels 12.5–200 mg/day well tolerated
  - no increase in serum creatinine
  - no increase in liver function tests

Combination treatment and antifungals under development
<table>
<thead>
<tr>
<th>Micafungin (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phase II – HIV-infected patients with <em>Candida</em> esophagitis</td>
</tr>
<tr>
<td>• Doses up to 50 mg/day evaluated</td>
</tr>
<tr>
<td>• Resolution/improvement in 100% patients after 8 days at 50 mg/day</td>
</tr>
<tr>
<td>• Phase III: no data currently available</td>
</tr>
<tr>
<td>• may be useful as empirical treatment in patients with PUO based on broad antifungal activity in experimental infection</td>
</tr>
<tr>
<td>• ‘fungistatic’ activity against <em>Aspergillus</em> species indicates further evaluation</td>
</tr>
<tr>
<td>• may be useful in combination with amphotericin B and antifungal triazoles</td>
</tr>
</tbody>
</table>

**Key references**

Adis International Ltd.
Posaconazole: SCH 56592.
*Drugs in R & D* 2003; 4: 258-263.

Arikan S, Rex JH.
Ravuconazole Eisai/Bristol-Myers Squibb.
*Current Opinion in Investigational Drugs* 2002; 3: 555-561.

Denning DW.
Echinocandin antifungal drugs.

Deresinski SC, Stevens DA.
Caspofungin.
*Clinical Infectious Diseases* 2003; 36: 1445-1457.

Fromling RA.
Micafungin sodium (FK-463).
*Drugs Today (Barc)* 2002; 38: 245-57.

Groll AH, Walsh TJ.
FK-463.
*Current Opinion in Anti-infective Investigational Drugs* 2000; 2: 405-412.

Gupta AK, Tomas E.
New antifungal agents.

Wiederhold NP, Lewis RE.
The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy.


Groll AH, Walsh TJ.
Antifungal chemotherapy: advances and perspectives.
Swiss Medical Weekly 2002; 132: 303-311.

Jones BL, McIntlock LA.
Impact of diagnostic markers on early antifungal therapy.

Loeffler J, Stevens DA.
Antifungal drug resistance.
Clinical Infectious Diseases 2003; suppl 1: S31-S41.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.

Luna B, Drew RH, Perfect JR.
Agents for treatment of invasive fungal infections.

Marty F, Mylonakis E.
Antifungal use in HIV infection.

Muller FM, Groll AH, Walsh TJ.
Current approaches to diagnosis and treatment of fungal infections in children infected with human immunodeficiency virus.

Perea S, Patterson TF.
Antifungal resistance in pathogenic fungi.
Clinical Infectious Diseases 2002; 35: 1073-1080.

Prentice HG, Kibbler CC, Prentice AG.
Towards a targeted, risk based, antifungal strategy in neutropenic patients.

Rex JH, Pfaffer MA.
Has antifungal susceptibility testing come of age?
Clinical Infectious Diseases 2002; 35: 982-989.

Rex JH, Pfaffer MA, Walsh TJ.
Antifungal susceptibility testing: practical aspects and current challenges.
Clinical Microbiology Reviews 2001; 14: 643-658.

Richardson MD, Warnock DW.
Fungal Infection: Diagnosis and Management, Third Edition.

Sugar A, Lyman CA.
A practical guide to medically important fungi and the diseases they cause.

Valgus JM.
What’s new in antifungals?

Wheat LJ, Goldman M, Sarosi G.
State-of-the-art review of pulmonary fungal infections.

Wong-Beringer A, Kriengikuykit J.
Systemic antifungal therapy: new options, new challenges.
Pharmacotherapy 2003; 23: 1441-1462.

Richardson MD, Johnson EM.
Pocket Guide to Fungal Infection.
Web sites

Please note that this list is by no means exhaustive!

FUNGAL INFECTIONS, GENERAL

http://www.clinical-mycology.com
(University of Helsinki)

http://www.mycology.adelaide.edu.au
(University of Adelaide)

http://www.doctorfungus.org
(An on-line reference to all things mycological)

http://www.aspergillus.man.ac.uk

SOCIETIES

http://www.asm.org/
(American Society for Microbiology)

http://www.isham.org
(International Society for Human and Animal Mycology and links to affiliated societies)

PUBLISHERS

http://www.currentmedicalliterature.com
(Current Medical Literature)

http://www.blackwellpublishing.co.uk
(medical mycology books and journals from Blackwell Publishing)

http://www.tandf.co.uk/journals/titles/13693786.asp
(Medical Mycology. The journal of the International Society for Human and Animal Mycology)

http://www.reviberoamnicol.com/
(ejournal: Revista Iberoamericana de Micología)

MYCOLOGY DISCUSSION FORUMS

http://www.fungalforum.com
(Forum for Deep Fungal Infections)
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABCD</td>
<td>Amphotericin B colloidal dispersion</td>
</tr>
<tr>
<td>ABLC</td>
<td>Amphotericin B lipid complex</td>
</tr>
<tr>
<td>ABPA</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>BAL</td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td>BMT</td>
<td>Bone marrow transplant</td>
</tr>
<tr>
<td>cAMB</td>
<td>Conventional amphotericin B</td>
</tr>
<tr>
<td>CAPD</td>
<td>Continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CIE</td>
<td>Counterimmunoelectrophoresis</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EIA</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GVHD</td>
<td>Graft versus host disease</td>
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<tr>
<td>IPA</td>
<td>Invasive pulmonary aspergillosis</td>
</tr>
<tr>
<td>LRTI</td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PBSC</td>
<td>Peripheral blood stem cell</td>
</tr>
<tr>
<td>PCP</td>
<td><em>Pneumocystis carinii</em> pneumonia</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PUO</td>
<td>Pyrexia of unknown origin</td>
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