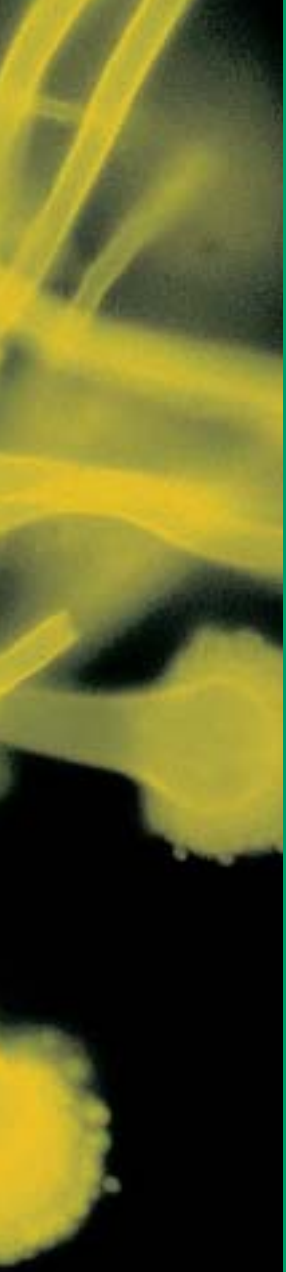

Therapeutic Guidelines in Systemic Fungal Infections

Third Edition

Malcolm D Richardson

Brian L Jones

Current Medical Literature

Therapeutic Guidelines in Systemic Fungal Infections

Third Edition

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Current Medical Literature

Contents

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(i) *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

Endemic fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis)

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

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

1(iii) *Definitions of fungal infections*

CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS

Host factors

1. Neutropenia: neutrophils <500/mm^3 for more than 10 days
2. Persistent fever for >96 h refractory to appropriate broad spectrum antibacterial treatment
3. Body temperature either >38°C or <36°C AND any of the following predisposing conditions:
   a. Prolonged neutropenia (>10 days) in the previous 60 days
   b. Recent or current use of significant immunosuppressive agents in the previous 30 days
   c. Invasive fungal infection in a previous episode
   d. Coexistence of AIDS
4. Signs and symptoms indicating GVHD
5. Prolonged use of corticosteroids (>3 weeks)

Microbiological criteria

1. Positive culture of a mold (including *Aspergillus* species, *Fusarium* species, zygomycetes, *Scedosporium* species) or *C. neoformans* from sputum, BAL
2. Positive culture or cytology/direct microscopy for molds from sinus aspirate
3. Positive cytology/direct microscopy for a mold or *Cryptococcus* from sputum, BAL
4. Positive *Aspergillus* antigen in BAL, CSF or ≥ 2 blood samples
5. Positive cryptococcal antigen in blood
6. Positive cytology/direct microscopy for fungal elements other than *Cryptococcus* in sterile body fluids
7. Two positive urine cultures of yeasts in the absence of urinary catheter
8. *Candida* casts in urine in the absence of urinary catheter
9. Positive blood culture of *Candida* species
10. Pulmonary abnormality and negative bacterial cultures of any possible bacteria from any specimen related to lower respiratory tract infection, including blood, sputum, BAL etc

Clinical criteria

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

Lower Respiratory Tract Infection

Major	*Minor*
Any of the following new infiltrates on CT imaging: halo sign, air crescent sign, or cavity within an area of consolidation	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	*Minor*
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)	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	*Minor*
Suggestive radiologic evidence of CNS infection (i.e. meningitis extending from a paranasal, auricular, or vertebral process; intracerebral abscesses or infarcts)	(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

1(v) *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

Ascioglu S, Rex JH, de Pauw B et al.
Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus.
Clinical Infectious Diseases 2002; 34: 7-14.

Categories of risk groups for systemic fungal infection 2

Low
PBSC autologous BMT
Childhood acute lymphoblastic leukemia (except for *P. carinii* pneumonia)
Intermediate: low
Moderate neutropenia 0.1–0.5×10^9/l <3 weeks
Lymphocytes <0.5×10^9/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 >0.1×10^9/l >3 to <5 weeks
Acute myeloid leukemia/total body irradiation
Allogeneic matched sibling donor BMT
High
Neutropenia <0.1×10^9/l >5 weeks
Colonized by *C. tropicalis*
Allogeneic unrelated or mismatched donor BMT
GVHD
Neutropenia <0.5×10^9/l >5 weeks
Corticosteroids >1 mg/kg and neutrophils <1×10^9/l >1 week
Corticosteroids >2 mg/kg >2 weeks
High-dose cytosine arabinoside
Fludarabine?

Adapted with permission from: Prentice HG, Kibbler CC, Prentice AG. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. British Journal of Haematology 2000; 110: 273-284.

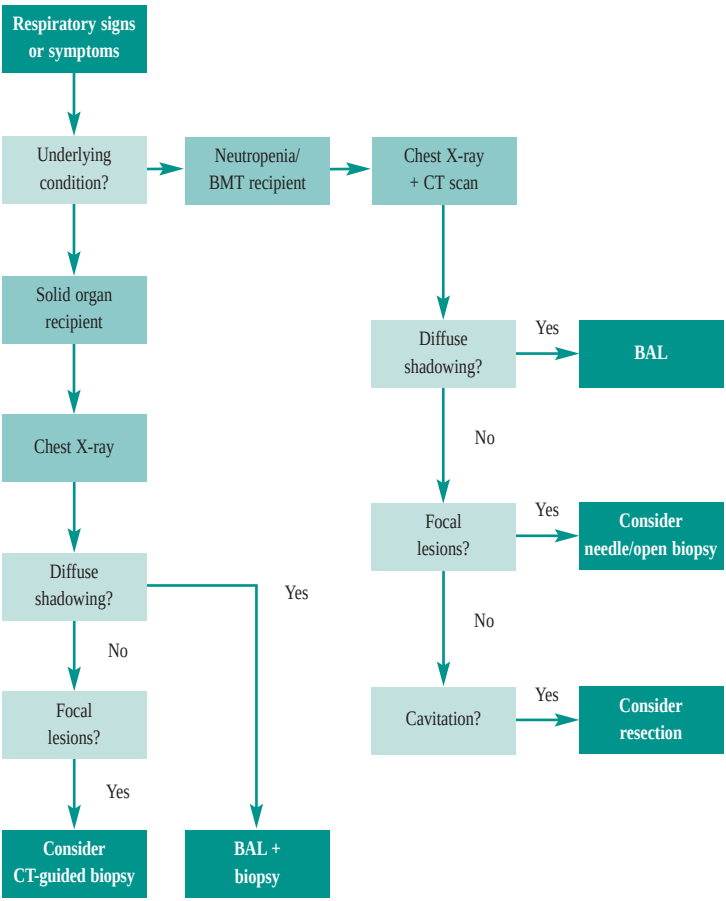
3 *Essential clinical examination in neutropenic and solid organ transplant patients with suspected invasive fungal infection*

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

Adapted with permission from: Denning DW *et al*. Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. European Journal of Clinical Microbiology and Infectious Diseases 1997; 16: 424-436.

Investigation of pulmonary infection in neutropenic and solid organ transplant patients

4



Adapted with permission from: Denning DW *et al*. Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. European Journal of Clinical Microbiology and Infectious Diseases 1997; 16: 424-436.

5 (i) *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)

5 (iii) *Essential investigations for the laboratory diagnosis of systemic fungal infections*

Paracoccidioidomycosis

- microscopy of pus, sputum, and crusts from granulomatous lesions
- culture of pus, sputum, and crusts from granulomatous lesions
- detection of antibody by complement fixation

Penicillium marneffei infection

- microscopy of Wright-stained bone marrow smears, touch smears of skin, or lymph node biopsies
- culture of skin biopsies, lymph node biopsies, blood, pus, bone marrow
- aspirates, sputum, and BAL
- detection of antibody by ELISA (under development)

Sporotrichosis

- microscopy of stained pus and tissue
- culture of pus and tissue

Unusual fungal infections

HYALOHYPHOMYCOSIS

- *Fusarium*
  - culture of blood and biopsies of cutaneous lesions
- *Scedosporium*
  - culture of respiratory secretions and CSF

PHAEOHYPHOMYCOSIS

- paranasal infection *(Alternaria, Bipolaris, Curvularia, Exserohilum)*
  - microscopy of sinus mucus, pus, scrapings, and stained tissue sections
  - culture of sinus mucus, pus, and scrapings
- cerebral phaeohyphomycosis *(Cladophialophora [Xylohypha] bantiana)*
  - culture of sinus material and respiratory secretions

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

5 (v) *Essential investigations for the laboratory diagnosis of systemic fungal infections*

Key references

Areno JP, Campbell GD, George RB.
Diagnosis of blastomycosis.
Seminars in Respiratory Infections 1997; 12: 252-262.

Bougnoux M-E, Dupont C, Mateo J et al.
Serum is more suitable than whole blood for diagnosis of systemic candidiasis by nest PCR.
Journal of Clinical Microbiology 1999; 37: 925-930.

Boutboul F, Alberti C, Leblanc T et al.
Invasive aspergillosis in allogeneic stem cell transplant recipients: increasing antigenemia is associated with progressive disease.
Clinical Infectious Diseases 2002; 34: 939-943.

Bretagne S, Costa JM, Bart-Delabesse E et al.
Comparison of serum galactomannan antigen detection and competitive polymerase chain reaction for diagnosing invasive aspergillosis.
Clinical Infectious Diseases 1998; 26: 1407-1412.

Buchheidt D, Spiess B, Hehlmann R.
Systemic infections with Aspergillus species in patients with hematological malignancies: current serological and molecular diagnostic approaches.
Onkologie 2001; 24: 531-536.

Caillot D, Couaillier JF, Bernard A et al.
Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia.
Journal of Oncology 2001; 19: 253-259.

Caillot D, Mannone L, Cuisenier B et al.
Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients.
Clinical Microbiology and Infection 2001; Suppl 2: 54-61.

Chen SC, Halliday CL, Meyer W.
A review of nucleic-acid based diagnostic tests for systemic mycoses with an emphasis on polymerase chain reaction-based assays.
Medical Mycology 2002; 40: 333-357.

Christensson B, Sigmundsdottir G, Larsson L.
D-arabinitol – a marker for invasive candidiasis.
Medical Mycology 1999; 37: 391-396.

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

Del Negro GM, Pereira CN, Andrade HF et al.
Evaluation of tests for antibody response in the follow-up of patients with acute and chronic forms of paracoccidioidomycosis.
Journal of Medical Microbiology 2000; 49: 37-46.

Denning DW.
Early diagnosis of invasive aspergillosis.
Lancet 2000; 355: 423-424.

Desakorn V, Simpson AJ, Wuthiekanun V et al.
Development and evaluation of rapid urinary antigen detection tests for diagnosis of penicilliosis marneffei.
Journal of Clinical Microbiology 2002; 40: 3179-3183.

Do Valle AC, Costa RL, Fialho Monteiro PC et al.
Interpretation and clinical correlation of serological tests in paracoccidioidomycosis.
Medical Mycology 2001; 39: 373-377.

Einsele H, Hebart H, Roller G et al.
Detection and identification of fungal pathogens in blood by molecular probes.
Journal of Clinical Microbiology 1997; 35: 1353-1360.

Elias Costa MR, Da Silva Lacaz C, Kawasaki M, De Camargo ZP.
Conventional versus molecular diagnostic tests.
Medical Mycology 2000; Suppl 1: 139-145.

Glazer M, Nusair S, Breuer R, Lafair J, Sherman Y, Berkman N.
The role of BAL in the diagnosis of pulmonary mucormycosis.
Chest 2000; 117: 279-282.

GomezGM, Cisalpino PS, Taborda CP, de Camargo ZP.
PCR for diagnosis of paracoccidioidomycosis.
Journal of Clinical Microbiology 2000; 38: 3478-3480.

Hamilton AJ.
Serodiagnosis of histoplasmosis, paracoccidioidomycosis and penicilliosis marneffei; current status and future trends.
Medical Mycology 1998; 36: 351-364.

Hebart H, Loffler J, Meisner C et al.
Early detection of Aspergillus infection after allogeneic stem cell transplantation by polymerase chain reaction screening.
Journal of Infectious Diseases 2000; 181: 1713-1719.

Hendolin PH, Paulin L, Koukila-Kähkölä P et al.
Panfungal PCR and multiplex liquid hybridization for detection of fungi in tissue specimens.
Journal of Clinical Microbiology 2000; 38: 4186-4192.

Herbrecht R, Letscher-Bru V, Oprea C et al.
Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients.
Journal of Clinical Oncology 2002; 20: 1898-1906.

Huaringa AJ, Leyva FJ, Signes-Costa J et al.
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.
Medical Mycology 2002; 40: 87-109.

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

Mamoni RL, Rossi CL, Camargo ZP, Blotta MH.
Capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in sera of patients with paracoccidioidomycosis.
American Journal of Tropical Medicine and Hygiene 2001; 65: 237-241.

Maertens J, Verhaegen J, Demuynck H et al.
Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis.
Journal of Clinical Microbiology 1999; 37: 3223-3228.

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.
Blood 2001; 97: 1604-1610.

Maertens J, Van Eldere J, Verhaegen J et al.
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.
European Journal of Pediatrics 2002; 161: 563-574.

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.
Reference method for broth dilution antifungal susceptibility testing of yeasts, approved standard M27-A. National Committee for Clinical Laboratory Standards, Wayne, PA, 1997.

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.
Southern Medical Journal 1999; 92: 289-295.

5 (vii) *Essential investigations for the laboratory diagnosis of systemic fungal infections*

San-Blas G, Niño-Vega G, Iturriaga T.
Paracoccidiodes brasiliensis and paracoccidioidomycosis: molecular approaches to morphogenesis, diagnosis, epidemiology, taxonomy and genetics.
Medical Mycology 2002; 40: 225-242.

Sato Y, Osabe S, Kuno H, Kaji M, Oizumi K.
Rapid diagnosis of cryptococcal meningitis by microscopic examination of cerebrospinal fluid sediment.
Journal of Neurological Sciences 1999; 164: 72-75.

Sendid B, Tabouret M, Poirot JL, Mathieu D, Fruit J, Poulain D.
New enzyme immunoassays for sensitive detection of circulating Candida albicans mannan and antimannan antibodies: useful combined test for diagnosis of systemic candidiasis.
Journal of Clinical Microbiology 1999; 37: 1510-1517.

Sendid B, Poirot JL, Tabouret M et al.
Combined detection of mannanaemia and antimannan antibodies as a strategy for the diagnosis of systemic infection caused by pathogenic Candida species.
Journal of Medical Microbiology 2002; 51: 433-442.

Stevens DA.
Diagnosis of fungal infections: current status.
Journal of Antimicrobial Chemotherapy 2002: 49 Suppl 1: 11-19.

Sulahian A, Boutboul F, Ribaud P et al.
Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study.
Cancer 2001; 15: 311-318.

Tabone MD, Vu-Thien H, Latge J-P et al.
Value of galactomannan detection by sandwich enzyme-linked immunosorbent assay in the diagnosis and follow-up of invasive aspergillosis.
Opportunistic Pathogens 1997; 9: 7-13.

Tadros TS, Workowski KA, Siegel RJ, Hunter S, Schwartz DA.
Pathophysiology of hyalohyphomycosis caused by Scedosporium apiospermum (Pseudallescheria boydii): an emerging mycosis.
Human Pathology 1998; 29: 1266-1272.

Tanner DC, Weinstein MP, Fedorciw B, Joho KL, Thorpe JJ, Reller L.
Comparison of commercial kits for detection of cryptococcal antigen.
Journal of Clinical Microbiology 1994; 32: 1680-1684.

Williamson EC, Leeming JP.
Molecular approaches for the diagnosis and epidemiological investigation of Aspergillus infection.
Mycoses 1999; 43 Suppl 2: 7-10.

Yeo SF, Wong B.
Current status of nonculture methods for diagnosis of invasive fungasl infections.
Clinical Microbiology Reviews 2002; 465-484.

Fungal species most commonly recovered from clinical specimens

6(i)

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*

6 (ii) *Fungal species most commonly recovered from clinical specimens*

Swabs

- *Aspergillus*
- *Candida*
- *Fusarium*
- *Rhizopus*

Miscellaneous body fluids

Urine

- *Candida*
- *Cryptococcus*

Chest, abdominal, and synovial

- *Aspergillus*
- *Candida*

Vitreous

- *Candida*

Bone marrow

- *Candida*
- *Cryptococcus*
- *Histoplasma*

Esophagitis

- endoscopically visualized plaques in the esophagus are clinically suggestive of fungal infection
- positive fungal culture
- pseudohyphae seen on Gram or other appropriate stain, or biopsy demonstrating invasive fungal elements

Pneumonia

PROOF OF CANDIDA PNEUMONIA REQUIRES:

- chest radiographs with acute infiltrate are clinically compatible with fungal pneumonia
- acceptable lower respiratory tract culture(s) with positive fungal growth;
- acceptable lower respiratory cultures include transthoracic needle aspiration, transbronchial biopsy, open lung biopsy, or thoroscopically directed biopsy
- pseudohyphae in appropriately stained biopsy sections

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)

7 (ii) *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 *Candida* antigenemia or high titers of anti-*Candida* antibody (Platelia Candida antigen ELISA; Platelia *Candida* antibody ELISA)

Acute disseminated candidosis

- fungemia plus culture or histologic evidence of deep tissue infection (including subcutaneous nodules)
- persistent *Candida* antigenemia or high titers of anti-*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

7 (iii)

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

8 *Assessment of the response to antifungal therapy – definitions*

Complete response

Resolution of all clinical signs and symptoms attributable to a systemic fungal infection

Partial response

Major improvement or resolution of the attributable clinical signs and symptoms and at least 50% improvement in radiologic findings

Good response

Denotes both complete and partial responses

Stable response

- intermediate responses (some improvement but <50% radiologic improvement)
- short courses of therapy with little assessment of response other than that the patient is alive, or death due to another documented cause
- some indication that the infection was improving, but not enough to reach a partial response

Failure

Progression and death due to systemic fungal infection

Antifungal Drugs

9 (i) *Amphotericin B*

Spectrum of activity

- *Aspergillus* species
- *Blastomyces dermatitidis*
- *Candida* species
- *Coccidioides 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

9 (iii) *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

De Pauw BE, Donnelly JP, Kulberg BJ.
Treatment of fungal infections in surgical patients using conventional antifungals.
Journal of Chemotherapy 1999; 11: 494-503.

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

Fichtenbaum CJ, Zackin R, Rajicic N, Powderly WG, Wheat LJ, Zingman BS.
Amphotericin B oral suspension for fluconazole-refractory oral candidiasis in persons with HIV infection. Adult AIDS Clinical Trials Group Study Team 295.
AIDS 2000; 14: 845-852.

Persat F, Schwartzbrod PE, Troncy J et al.
Abnormalities in liver enzymes during simultaneous therapy with itraconazole and amphotericin B in leukaemic patients.
Journal of Antimicrobial Chemotherapy 2000; 45: 928-929.

Popp AI, White MH, Quadri T, Walshe L, Armstrong D.
Amphotericin B with and without itraconazole for invasive aspergillosis: a three-year retrospective study.
International Journal of Infectious Diseases 1999; 3: 157-160.

Rex JH, Walsh TJ.
Editorial response: estimating the true cost of amphotericin B.
Clinical Infectious Diseases 1999; 29: 1408-1410.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.
Journal of Clinical Pharmacology and Therapeutics 1999; 24: 249-257.

Wingard JR, Kubilis P, Lee L et al.
Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis.
Clinical Infectious Diseases 1999; 29: 1402-1407.

10 *Regimen for rapid escalation of amphotericin B dosage*

Time infusion started (h)	Duration of infusion (h)	Dosage (mg)	Volume of solution 1 (ml)	Volume of solution 2 (ml)
0	2	1	10	40
4	4	24	240	760
16	4	25	250	750
40	4	50	500	500
(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)				
0	2	1	10	40
2	6	9	90	360
12	6	10	100	400
24	6	20	200	300
48	6	30	300	700
72	6	40	400	600
96	6	50	500	500
(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

Adapted with permission from: Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Management, 3rd Edition. Oxford: Blackwell Publishing, 2003.

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

Time infusion started (h)	Duration of infusion (h)	Dosage (mg)	Volume of solution 1 (ml)	Volume of solution 2 (ml)
0	2	1	10	40
2	6	9	90	360
24	6	10	100	400
48	6	20	200	300
72	6	30	300	700
96	6	40	400	600
120	6	50	500	500

(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

Adapted with permission from: Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Management, 3rd Edition. Oxford: Blackwell Publishing, 2003.

* Little need for this regimen except in rare circumstances

Liposomal amphotericin B (AmBisome®) 12 (i)

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

12 (ii) *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®) 12 (iii)

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

12 (iv) *Liposomal amphotericin B (AmBisome®)*

Key references

Adler-Moore J, Proffitt RT.
Effect of tissue penetration on AmBisome efficacy.
Current Opinion in Investigational Drugs 2003; 4: 179-185.

Adler-Moore J, Proffitt RT.
AmBisome: liposomal formulation, structure, mechanism of action and pre-clinical experience.
Journal of Antimicrobial Chemotherapy 2002; 49 (suppl 1): 21-30.

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.
Antimicrobial Agents and Chemotherapy 2002; 46: 828-833.

Boswell GW, Buell D, Bekersky I.
AmBisome (liposomal amphotericin B): a comparative review.
Journal of Clinical Pharmacology 1998; 38: 583-592.

Coukell AJ, Brogan RN.
Liposomal amphotericin B. Therapeutic use in the management of fungal infections and visceral leishmaniasis.
Drugs 1998; 55: 585-612.

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.
British Journal of Haematology 1998; 103: 205-212.

Martin MT, Gavalda J, Lopez P et al.
Efficacy of high doses of liposomal amphotericin B in the treatment of experimental aspergillosis.
Journal of Antimicrobial Chemotherapy 2003; 52: 1032-1034.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.
Journal of Clinical Pharmacology and Therapeutics 1999; 24: 249-257.

Scarcella A, Pasquariello MB, Giugliano B, Vendemmia 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.
New England Journal of Medicine 1999; 341: 1153-1155.

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 colloidal dispersion (Amphocil®, Amphotec®) 13(i)

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

13 (ii) *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 (Amphocil®, Amphotec®) 13 (iii)

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 Amphocil®

Drug interactions

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

13 (iv) *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.
Antifungal agents. Part I. Amphotericin B preparation and flucytosine.
Mayo Clinic Proceedings 1998; 73: 1205-1225.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.
Journal of Clinical Pharmacology and Therapeutics 1999; 24: 249-257.

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.
International Journal of Infectious Diseases 1998; 3: 109-118.

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®) 14(i)

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

14 (ii) *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®) 14(iii)

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.
Journal of Clinical Pharmacology 1999; 39: 427-428.

Linden P, Lee L, Walsh TJ.
Retrospective analysis of the dosage of amphotericin B lipid complex for treatment of invasive fungal infections.
Pharmacotherapy 1999; 19: 1261-1268.

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.
Journal of Antimicrobial Chemotherapy 1999; 44: 569-572.

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 haematologic malignancies and prolonged neutropenia.
Chemotherapy 1999; 45: 205-212.

Patel R.
Antifungal agents. Part I. Amphotericin B preparations and flucytosine.
Mayo Clinic Proceedings 1998; 73: 1205-1225.

Robinson RF, Nahata MC.
A comparative review of conventional and lipid formulations of amphotericin B.
Journal of Clinical Pharmacology and Therapeutics 1999; 24: 249-257.

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.
International Journal of Infectious Diseases 1998; 3: 109-118.

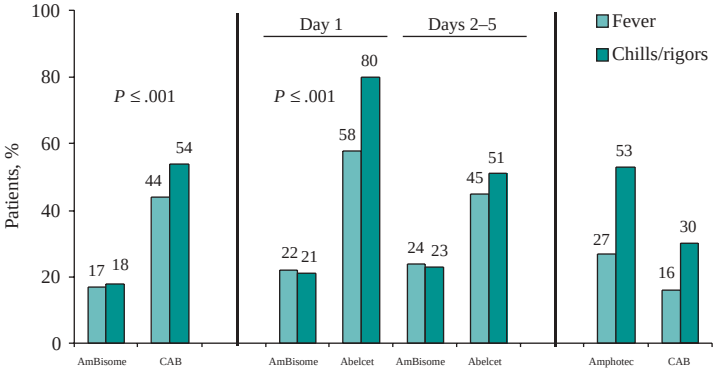
Walsh TJ, Seibel NL, Arndt C et al.
Amphotericin B lipid complex in pediatric patients with invasive fungal infections.
Pediatric Infectious Diseases Journal 1999; 18: 702-708.

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

15 *Pharmacokinetic comparisons of amphotericin B formulations*

		AmBisome®	ABCD	Amphotericin B	ABLC
Dose	mg/kg	3	1.5	1	5
Peak blood level	µg/ml	29	2.5	3.6	1.7
AUC	µg/ml/h	423	56.8	34.2	9.5
Clearance	ml/h/kg	22.2	28.4	40.2	211
Volume of distribution	l	25.9	553	111	2286
Half-life (elimination)	h	23 2nd phase	235 3rd phase	34 2nd phase	173.4

Polyene comparisons: infusion-related reactions 16(i)



Comments

- The figure above summarizes the incidence of infusion-related reactions associated with polyenes
- Infusion-related reactions (eg, 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®

16 (ii) *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

Bowden R, Chandrasekar P, White MH et al.
A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients.
Clinical Infectious Diseases 2002; 35: 359-366.

Walsh TJ, Finberg RW, Arndt C et al.
Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia.
New England Journal of Medicine 1999; 340: 764-771.

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.

Polyene comparisons: nephrotoxicity 17

• CAB	34%–60%	• CAB nephrotoxicity is dose dependent and cumulative
• AmBisome®	10%–20%	• Randomized trials demonstrate less nephrotoxicity than CAB
• Abelcet®	42%–63%	• No randomized trials showing Abelcet® to be less nephrotoxic than CAB
• Amphotec®	25%–40%	

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

Deray G.
Amphotericin B nephrotoxicity.
Journal of Antimicrobial Chemotherapy 2002; 49(suppl 1): 37-41.

Walsh TJ, Finberg RW, Arndt C et al.
Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia.
New England Journal of Medicine 1999; 340: 764-771.

Bowden R, Chandrasekar P, White MH et al.
A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients.
Clinical Infectious Diseases 2002; 35: 359-366.

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.

Oppenheim BA, Herbrecht R, Kusne S.
The safety and efficacy of amphotericin B colloidal dispersion in the treatment of invasive mycoses.
Clinical Infectious Diseases 1995; 21: 1145-1153.

18(i) *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 beigelii*
- *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 18 (ii)

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

18 (iii) *Caspofungin*

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

Key references

Arikan S, Lozano-Chiu M, Paetznick V, Rex JH.
In vitro synergy of caspofungin and amphotericin B against Aspergillus and Fusarium spp.
Antimicrobial Agents and Chemotherapy 2002; 46: 245-247.

Denning DW.
Echinocandin antifungal drugs.
Lancet 2003; 362: 1142-1151.

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.
Expert Opinion in Investigational Drugs 2001: 10: 269-280.

Groll AH, Walsh TJ.
Caspofungin: pharmacology, safety and therapeutic potential in superficial and invasive fungal infections.
Expert Opinion in Investigational Drugs 2001; 10: 1545-1548.

Kartsonis N, DiNubile MJ, Bartizal K, Hicks PS, Ryan D, Sable CA.
Efficacy of caspofungin in the treatment of esophageal candidiasis resistant to fluconazole.
Journal of Acquired Immune Deficiency Syndrome 2002; 31: 183-187.

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.
New England Journal of Medicine 2002; 347: 2020-2029.

Morrison VA.
The role of caspofungin and the echinocandins in the antifungal armamentarium.
Current Opinion in Investigational Drugs 2002; 10: 1432-1436.

Pacetti SA, Gelone SP.
Caspofungin acetate for treatment of invasive fungal infections.
Annals of Pharmacotherapy 2003; 37: 90-98.

Stone JA, Holland SD, Wickersham PJ et al.
Single- and multiple-dose pharmacokinetics of caspofungin in healthy men.
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.
Current Medical Research and Opinion 2003; 19: 263-271.

Villanueva A, Gotuzzo E, Arathon EG et al.
A randomised double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis.
American Journal of Medicine 2002; 113: 294-299.

Walsh TJ.
Echinocandins – an advance in the primary treatment of invasive candidiasis.
New England Journal of Medicine 2002; 347: 2070-2072.

Wiederhold NP, Lewis RE.
The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy.
Expert Opinion in Investigational Drugs 2003; 12: 1313-1333.

19 (i) *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

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

19 (iii) *Fluconazole*

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 1×10^9/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

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

19 (v) *Fluconazole*

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.

Brodell RT, Elewski B.
Antifungal drug interactions. Avoidance requires more than memorization.
Postgraduate Medicine 2000; 107: 41-43.

De Pauw BE, Donnelly JP, Kulberg BJ.
Treatment of fungal infections in surgical patients using conventional antifungals.
Journal of Chemotherapy 1999; 11: 494-503.

Graybill JR.
Fluconazole and itraconazole: a primer for the professional: Part I.
Infectious Diseases Clinical Practice 2000; 9: 43-50.

Graybill JR.
Fluconazole and itraconazole: a primer for the professional: Part II.
Infectious Diseases Clinical Practice 2000; 9: 51-58.

Gupta AK, Katz I, Shear NH.
Drug interactions with itraconazole, fluconazole, and terbinafine and their management.
Journal of the American Academy of Dermatology 1999; 41: 237-249.

Gupta AK, Shear NH.
Safety review of the oral antifungal agents used to treat superficial mycoses.
International Journal of Dermatology 1999; 38: 40-52.

Montane BS, Mazza I, Abitbol C et al.
Fungal peritonitis in pediatric patients.
Advances in Peritoneal Dialysis 1998; 14: 251-254.

Penk A, Pittrow L.
Therapeutic experience with fluconazole in the treatment of fungal infection in diabetic patients.
Mycoses 1999; 43 [Suppl 2]: 97-100.

Pittrow L, Penk A.
Special pharmacokinetics of fluconazole in septic, obese and burn patients.
Mycoses 1999; 43 [Suppl 2]: 87-90.

Rayatt S, Wienbren M, Clarke J.
Fluconazole use in burns patients.
Burns 2000; 26: 109-110.

Rocco TR, Reinert SE, Simms HH.
Effects of fluconazole administration in critically ill patients: analysis of bacterial and fungal resistance.
Archives of Surgery 2000; 135: 160-165.

Sheehan DJ, Hitchcock CA, Sibley CM.
Current and emerging azole antifungal agents.
Clinical Microbiology Reviews 1999; 12: 40-79.

Terrell CL.
Antifungal agents. Part II. The azoles.
Mayo Clinic Proceedings 1999; 74: 78-100.

Flucytosine (5-fluorocytosine) 20 (i)

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

20 (ii) *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) 20 (iii)

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

Key references

Patel R.
Antifungal agents. Part I. Amphotericin B preparations and flucytosine.
Mayo Clinic Proceedings 1998; 73: 1205-1225.

Vermes A, van Der Sijs H, Guchelaar HJ.
Flucytosine: correlation between toxicity and pharmacokinetic parameters.
Chemotherapy 2000; 46: 86-94.

Vermes A, Guchelaar HJ, Dankert J.
Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions.
Journal of Antimicrobial Chemotherapy 2000; 46: 171-179

21 *Regimens for administration of flucytosine in renal impairment*

Creatinine clearance (ml/min)	Individual dosage (mg/kg)	Dosage interval (h)
>40	25.0–37.5	6
40–20	25.0–37.5	12
10–20	25.0–37.5	>24*

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.

Adapted with permission from: Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Management, 3rd Edition. Oxford: Blackwell Publishing, 2003.

Itraconazole 22 (i)

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

22 (ii) *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
- most metabolites inactive – excreted with bile and urine
- 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.

22 (iv) *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

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

22 (vi) Itraconazole

Key references

Bradbury BD, Jick SS.
Itraconazole and fluconazole, and certain rare, serious adverse events.
Pharmacotherapy 2002; 22: 697-700.

De Rosso JQ, Gupta AK.
Oral itraconazole therapy for superficial, subcutaneous, and systemic infections.
Postgraduate Medicine 1999; Special number: 46-52.

Groll AH, Wood L, Roden M et al.
Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis.
Antimicrobial Agents and Chemotherapy 2002; 46: 2554-2563

Glasmacher A, Hahn C, Molitor E et al.
Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-beta-cyclodextrin oral solution or coated-pellet capsules.
Mycoses 1999; 42: 591-600.

Glasmacher A, Djulbegovic B, Prentice A et al.
Meta-analysis of itraconazole antifungal prophylaxis trials reveals a dose-response effect for the prevention of invasive fungal infections, including aspergillus, in neutropenic patients.
Abstract: American Society for Hematology 2002.

Gupta AK, Katz I, Shear NH.
Drug interactions with itraconazole, fluconazole, and terbinafine and their management.
Journal of the American Academy of Dermatology 1999; 41: 237-249.

Gupta AK, Shear NH.
Safety review of the oral antifungal agents used to treat superficial mycoses.
International Journal of Dermatology 1999; 38: 40-52.

Gupta AK, Chwetzoff E, Del Rosso J, Baran R.
Hepatic safety of itraconazole.
Journal of Cutaneous Medical Surgery 2002; 6: 210-213.

Kageyama S, Masuya M, Tanaka I et al.
Plasma concentration of itraconazole and its antifungal prophylactic efficacy in patients with neutropenia after chemotherapy for acute leukemia.
Journal of Infection and Chemotherapy 1999; 5: 213-216.

Koks CH, Meenhorst PL, Bult A, Beijnen JH.
Itraconazole solution: summary of pharmacokinetic features and review of activity in the treatment of fluconazole-resistant oral candidosis in HIV-infected persons.
Pharmacology Research 2002; 46: 195-201.

Pea F, Furlanut M.
Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions.
Clinical Pharmacokinetics 2001; 40: 833-868.

Persat F, Schwartzbrod PE, Troncy J et al.
Abnormalities in liver enzymes during simultaneous therapy with itraconazole and amphotericin B in leukaemic patients.
Journal of Antimicrobial Chemotherapy 2000; 45: 928-929.

Potter M.
European experience with oral solution and intravenous itraconazole.
Oncology (Huntington) 2001; 15 (suppl 9): 27-32.

Rambali B, Fernandez JA, Van Nuffel L. et al.
Susceptibility testing of pathogenic fungi with itraconazole: a process analysis of test variables.
Journal of Antimicrobial Chemotherapy 2001; 48: 163-177.

Slain D, Rogers PD, Cleary JD, Chapman SW.
Intravenous itraconazole.
Annals of Pharmacotherapy 2001; 35: 720-729.

Szente L, Szejtli J.
Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development.
Advances in Drug Delivery Reviews 1999; 36: 17-28.

Terrell CL.
Antifungal agents. Part II. The azoles.
Mayo Clinic Proceedings 1999; 74: 78-100.

Tortorano AM, Dannaoui E, Meletiadis J et al.
Effect of medium composition on static and cidal activity of amphotericin B, itraconazole, voriconazole, posaconazole and terbinafine against Aspergillus fumigatus: a multicenter study.
Journal of Chemotherapy 2002; 14: 246-252.

Verweij PE, Te Dorsthorst DT, Rijs AJ et al.
Nationwide survey of in vitro activities of itraconazole and voriconazole against clinical Aspergillus fumigatus isolates cultured between 1945 and 1998.
Journal of Clinical Microbiology 2002; 40: 2648-2650.

Willems L, van der Geest R, de Beule K.
Itraconazole oral solution and intravenous formulations: a review of the pharmacokinetics and pharmacodynamics.
Journal of Clinical Pharmacological Therapy 2001; 26: 159-169.

Zhao O, Zhou H, Pesco-Koplowitz L.
Pharmacokinetics of intravenous itraconazole followed by itraconazole oral solution in patients with human immunodeficiency virus infection.
Journal of Clinical Pharmacology 2001; 41: 1319-1328.

23 (i) *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

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

23 (iii) *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 <40kg
  - 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

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

23(v) *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.
Journal of Clinical Microbiology 2003; 41: 97-99.

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.
Antimicrobial Agents and Chemotherapy 2002; 46: 2546-2553.

Ullmann AJ.
Review of the safety, tolerability, and drug interactions of the new antifungal agents caspofungin and voriconazole.
Current Medical Research and Opinion 2003; 19: 263-271.

Therapy of Specific Infections

24 (i) *Aspergillosis*

Disease type	Therapies
Allergic (ABPA)	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
Aspergilloma	Surgical resection with perioperative amphotericin B Intracavitary instillation of amphotericin B 10–20 mg in 10–20 ml distilled water
Chronic necrotizing	Surgical resection Itraconazole 200–400 mg per day Parenteral and local amphotericin B
Sinonasal	
• Allergic sinusitis	Surgical debridement to remove polyps and allergic mucion Conservative surgical drainage plus antibiotics Amphotericin B solution Itraconazole oral solution (single cases) Frequent recurrence
• 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

Disease type	Therapies
• 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

24 (iii) *Aspergillosis*

Disease type	Therapies
Cerebral	Poor prognosis AmBisome® 3–5 mg/kg and higher Itraconazole 600 mg/day and higher
Endocarditis	Amphotericin B 1.0 mg/kg/day, 2–3 months' duration Replace infected valves 1–2 weeks after treatment started
Bone infection	Surgical debridement Amphotericin B 1.0 mg/kg/day Itraconazole i.v.
Prophylaxis	Usefulness controversial Itraconazole oral solution 400 mg per day or Amphotericin B 0.5 mg/kg per day
Empirical	Amphotericin B 1 mg/kg per day AmBisome® 3 mg/kg per day

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.
Journal of Clinical Oncology 1997; 15: 139-147.

Centers for Disease Control and Prevention.
Guidelines for prevention of nosocomial pneumonia.
Morbidity and Mortality Weekly Report 1997; 46 (RR-01): 1-79.

Centers for Disease Control and Prevention.
Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients.
Morbidity and Mortality Weekly Report 2000; 49 (RR-10): 1-125.

Denning DW.
Chronic forms of pulmonary aspergillosis.
Clinical Microbiology and Infection 2001; 7(suppl 2): 25-31.

Herbrecht R, Denning DW, Patterson TF et al.
Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis.
New England Journal of Medicine 2002; 347: 408-415.

Ellis M.
Amphotericin B and invasive aspergillosis – how do the data guide us?
Journal of Medical Microbiology 2002; 51: 95-97.

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.
Journal of Thoracic and Cardiovascular Surgery 2000; 119: 1286-1287.

Ikemoto H.
Medical treatment of pulmonary aspergilloma.
Internal Medicine 2000; 39: 191-192.

Kaestel M, Meyer W, Mittelmeier HO, Gebhardt C.
Pulmonary aspergilloma – clinical findings and surgical treatment.
Thoracic and Cardiovascular Surgery 1999; 47: 340-345.

Kawamura S, Maesaki S, Tomono K et al.
Clinical evaluation of 61 patients with pulmonary aspergilloma.
Internal Medicine 2000; 39: 209-212.

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

Kuhn FA, Javer AR.
Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents.
Otolaryngologic Clinics of North America 2000; 33: 419-32.

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.
Clinical Infectious Diseases 2001; 32: 358-366.

Maertens J, Van Eldere J, Verhaegen J et al.
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, Boeckh 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.
Infectious Disease Clinics of North America 2002; 16: 875-894.

Perea S, Patterson TF.
Invasive Aspergillus infections in hematologic malignancy patients.
Seminars in Respiratory Infections 2002; 17: 99-105.

24 (v) *Aspergillosis*

Regnard JF, Icard P, Nicolosi M et al.
Aspergilloma: a series of 89 surgical cases.
Annals of Thoracic Surgery 2000; 69: 893-903.

Rodriguez DL, Lopez CA, Cobos EB, Blanco AJ, Fernandez AF, Araujo LF.
Invasive cerebral aspergillosis in a patient with aplastic anemia. Response to liposomal amphotericin B and surgery.
Haematologia 1999; 84: 758-759.

Salez F, Brichet A, Desurmont S, Grosbois JM, Wallaert B, Tonnel AB.
Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis.
Chest 1999; 116: 1665-1668.

Stevens DA, Kan VL, Judson MA et al.
Practice guidelines for diseases caused by Aspergillus.
Clinical Infectious Diseases 2000; 30: 696-709.

Stevens DA, Schwartz HJ, Lee JY et al.
A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis.
New England Journal of Medicine 2000; 342: 756-762.

Van Burik JH, Colven R, Spach DH.
Cutaneous aspergillosis.
J Clin Microbiol 1998; 36: 3115-3121.

Various authors.
Advances against aspergillosis.
Clinical Infectious Diseases 2003; 37(suppl 3): S155-S292.

Yeghen T, Kibbler CC, Prentice HG et al.
Management of invasive pulmonary aspergillosis in hematology patients: a review of 87 consecutive cases at a single institution.
Clinical Infectious Diseases 2000; 31: 859-868.

Preventative strategy	Comments
Avoidance of exposure to *Aspergillus* conidia	Heavily contaminated areas including compost heaps, grain silos, moldy hay, and marijuana. Consider water as a source of bioaerosols in hospitals
Implement surveillance program	Air sampling, dust sampling, water analysis, and patient surveillance
Remove all environmental sources in hospital environments	Potted plants, flowers, food items such as spices and tea, thorough cleaning
High-efficacy particulate air (HEPA) filters or laminar air-flow (LAF)	Expensive, but HEPA or LAF should be considered for patients at very high risk for invasive aspergillosis
Prophylaxis: itraconazole, low-dose amphotericin B, amphotericin B inhalation	Efficacy data conflicting, should be considered in high-risk group
Administration of colony-stimulating factors to neutropenic patients	Expensive, considered as part of overall strategy
Empirical cAMB	Strongly recommended – shown to reduce mortality – 0.6 mg/kg per day
Empirical AmBisome®	Reduces emerging infections
Secondary prophylaxis (antifungal treatment to prevent recrudescence of proven invasive aspergillosis treated during a prior episode of immunosuppression)	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

25 (ii) *Prevention of invasive aspergillosis*

Key references

Alberti C, Bouakline A, Ribaud P et al.
Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients.
Journal of Hospital Infection 2001; 48: 198-206.

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

Bouakline A, Lacroix C, Roux N et al.
Fungal contaminatio Microbiology 2000; 38: 4272-4273.

Centers for Diease Control and Prevention.Guidelines for prevention of nosocomial pneumonia.
Morbidity and Mortality Weekly Report 1997; 46 (RR-01): 1-79.

Centers for Diease Control and Prevention.
Guidelines for preventing opportunistic infections among hematopoietic stem cell trransplant recipients.
Morbidity and Mortality Weekly Report 2000; 49 (RR-10): 1-125.

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.

Fridkin SK, Jarvis WR.
Epidemiology of nosocomial fungal infections.
Clinical Microbiology Reviews 1996; 9: 499-511.

Glasmacher A, Hahn C, Molitor E, Sauerbruch T, Schmidt-Wolf IG, Marklein G.
Fungal surveillance cultures during antifungal prophylaxis with itraconazole in neutropenic patients with acute leukaemia.
Mycoses 1999; 42: 395-402.

Glasmacher A, Hahn C, Leutner C et al.
Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole.
Mycoses 1999; 42: 443-451.

Hajjeh RA, Warnock DW.
Counterpoint: invasive aspergillosis and the environment – rethinking our approach to prevention.
Clinical Infectious Diseases 2001; 33: 1549-1552.

Harrousseau JL, Dekker AW, Stamatoullas-Bastard A et al.
Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo, multicentre trial comparing itraconazole and amphotericin B.
Antimicrobial Agents and Chemotherapy 2000; 44: 1887-1893.

Kelsey SM, Goldman JM, McCann S et al.
Liposomal amphotericin (AmBisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study.
Bone Marrow Transplantation 1999; 23: 163-168.

Manuel RJ, Kibbler CC.
The epidemiology and prevention of invasive aspergillosis.
Journal of Hospital Infection 1998; 39: 95-109.

Menichetti F, Del Favero A, Martino P et al.
Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomised, placebo-controlled, double-blind, multicenter trial.
Clinical Infectious Diseases 1999; 28: 250-255.

Morris G, Kokki MH, Anderson K, Richardson MD.
Sampling of Aspergillus spores in air.
Journal of Hospital Infection 2000; 44: 81-92.

Overberger PA, Wadowsky RM, Schaper MM.
Evaluation of airborne particulates and fungi during hospital renovation.
American Industrial Hygiene Association Journal 1995; 56: 706-712.

Patterson JE, Peters J, Calhoon JH et al.
Investigation and control of aspergillosis and other filamentous fungal infections in solid organ transplant recipients.
Transplantation Infectious Diseases 2000; 2: 22-28.

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.
Key Advances in Systemic Fungal Infection, Royal Society of Medicine Press, 2003.

Richardson MD, Rennie S, Marshall I et al.
Fungal surveillance of an open haematology ward.
Journal of Hospital Infection 2000; 45: 288-292.

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.
Journal of Hospital Infection 2001; 47: 143-148.

26(i) *Blastomycosis*

Type of disease	Treatment
Pulmonary: mild/moderate disease	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 Oral ketoconazole 400 mg per day, increasing to 600–800 mg/kg as required Fluconazole 400–800 mg/kg if itraconazole not absorbed
Pulmonary: life threatening	Amphotericin B 0.7–1.0 mg/kg/d. If good response itraconazole 200–400 mg/d. Little experience with lipid formulations of amphotericin B
Disseminated: mild/moderate disease	If no CNS involvement: – itraconazole 200–400 mg/d for at least 6 months – fluconazole 400–800 mg/d if itraconazole not tolerated CNS involvement: amphotericin B 0.7–1.0 mg/kg/d to a total dose of 2 g
Disseminated: life-threatening	Amphotericin B 0.7–1.0 mg/kg per day to a total dose of 1.5–2.5 g
Disseminated: osteomyelitis	Amphotericin B 0.5–0.7 mg/kg per day Itraconazole 12 months

Key references

Chapman SW, Bradsher RW, Campbell GD.
Practice guidelines for the management of patients with blastomycosis.
Clinical Infectious Diseases 2000; 30: 679-683.

Goldman M, Johnson PC, Sarosi GA.
Fungal pneumonias. The endemic mycoses.
Clinics in Chest Medicine 1999; 20: 507-519.

Lemos LB, Baliga M, Guo M.
Blastomycosis: The great pretender can also be an opportunist. Initial clinical diagnosis and underlying diseases in 123 patients.
Annals of Diagnostic Pathology 2002; 6: 194-203.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.
Journal of Antimicrobial Chemotherapy 1999; 43: 321-331.

Martynowicz MA, Prakash UB.
Pulmonary blastomycosis: an appraisal of diagnostic techniques.
Chest 2002; 121: 768-773.

Pappas PG, Dismukes WE.
Blastomycosis: Gilchrist's disease revisited.
Current Clinics in Tropical Infectious Diseases 2002; 22: 61-77.

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.
Southern Medical Journal 1999; 92: 289-295.

Whaet LJ, Goldman M, Sarosi G.
State-of-the-art review of pulmonary fungal infections.
Seminars in Respiratory Infections 2002; 17: 158-181.

27 (i) *Candidosis*

Type of disease	Treatment
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

Type of disease	Treatment
Genitourinary	
• Urinary tract infections	Therapy not generally required in asymptomatic candiduria Catheter removal Fluconazole 200 mg per day, 7–14 days; if *C. glabrata* or *C. krusei* is causal agent use i.v. amphotericin B (0.3–1.0 mg/kg 1–7 d
Candidemia	
• Non-neutropenic	Removal of all existing central venous catheters Fluconazole 800 mg loading dose, followed by 400 mg per day for 2 weeks Amphotericin B 0.5 mg/kg per day, 2 weeks Amphotericin B 0.75–1 mg/kg per day – less sensitive yeasts Abelcet® 5 mg/kg per day AmBisome® 1–3 mg/kg per day or higher Amphotec® 2–6 mg/kg per day Caspofungin 70 mg loading dose, followed by 50 mg/day. Infuse over 1 h
• Persistent neutropenia	Catheter removal Amphotericin B 1 mg/kg per day plus flucytosine AmBisome® 1–3 mg/kg per day or higher Neonates Amphotericin B
• *Candida glabrata* infection	Amphotericin B ≥ 0.7 mg/kg per day
• *Candida krusei* infection	Amphotericin B 1.0 mg/kg per day
• *Candida lusitaniae* infection	Fluconazole 400 mg per day

27 (iii) *Candidosis*

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

Type of disease	Treatment
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

27 (v) Candidosis

Key references

Blot SI, Vandewoude KH, Hoste EA, Colardyn FA.
Effects of nosocomila candidemia on outcomes of critiically ill patients.
American Journal of Medicine 2002; 113: 480-485.

Blumberg HM, Jarvis WR, Soucie JM, et al.
Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study.
Clinical Infectious Diseases 2001; 33: 177-186.

Calderone RA (ed).
Candida and candidiasis.
Washington, DC: ASM Press, 2002.

Dinubile MJ, Lupinacci RJ, Berman RS, Sable CA.
Response and relapse rates of candidal esophagitis in HIV-infected patients treated with caspofungin.
AIDS Res Hum Retroviruses 2002; 18: 903-908.

Edwards JE, Bodey GP, Bowden RA et al.
International conference for the development of a consensus on the management and prevention of severe candidal infections.
Clinical Infectious Diseases 1997; 25: 43-59.

Ellis ME, Al-Abdely H, Sandridge A et al.
Fungal endocarditis: evidence in the world literature, 1965-1995.
Clinical Infectious Diseases 2001; 32: 50-62.

Fernandez M, Moylett EH, Noyola DE et al.
Candidal meningitis in neonates: a 10-year review.
Clinical Infectious Diseases 2000; 31: 458-463.

Gubbins PO, McConnell SA, Penzak SR.
Current management of funguria.
American Journal of Health System Pharmacy 1999; 56: 1929-1935.

Kauffman CA, Vazquez JA, Sobel JD et al.
Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group.
Clinical Infectious Diseases 2000: 30: 14-18.

Koks CH, Meenhorst PL, Bult A, Beijnen JH.
Itraconazole solution: summary of pharmacokinetic features and review of activity in the treatment of fluconazole-resistant oral candidosis in HIV-infected persons.
Pharmacological Research 2002; 46: 195-201.

Kontoyiannis DP, Luna MA, Samuels BI et al.
Hepatosplenic candidiasis. A manifestation of chronic disseminated candidiasis.
Infectious Disease Clinics of North America 2000; 14: 721-739.

Leleu G, Aegerter P. Guidet B.
Systemic candidiasis in intensive care units: a multicenter, matched-cohort study.
Journal of Critical Care 2002; 17: 168-175

Martinez-Vazquez C, Fernandez-Ulloa J, Bordon J, et al.
Candida albicans endophthalmitis in brown heroin addicts: response to early vitrectomy preceded and followed by antifungal therapy.
Clinical Infectious Diseases 1998; 27: 1130-1133.

Montane BS, Mazza I, Abitbol C et al.
Fungal peritonitis in pediatric patients.
Advances in Peritoneal Dialysis 1998; 14: 251-254.

Nucci M, Anaissie E.
Should vascular catheters be removed from all patients with candidemia? An evidence-based review.
Clinical Infectious Diseases 2002; 34: 591-599.

Pelz RK, Hendrix CW, Swoboda SM et al.
Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients.
Annals of Surgery 2001; 233: 542-548.

Pfaller MA, Diekema DJ.
Role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility.
Journal of Clinical Microbiology 2002; 40: 3551-3557.

Powderly WG, Mayer KH, Perfect JR.
Diagnosis and treatment of oropharyngeal candidiasis in patients infected with HIV: a critical assessment.
AIDS Research and Human Retroviruses 1999; 15: 1405-1412.

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.
Pediatric Infectious Disease Journal 2000; 19: 319-324.

Saag MS, Fessel WJ, Kaufman CA et al.
Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients.
AIDS Research and Human Retroviruses 1999; 15: 1413-1417.

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

Schwarze R, Penk A, Pittrow L.
Treatment of candidal infections with fluconazole in neonates and infants.
European Journal of Medical Research 2000; 23: 203-208.

Sobel JD, Kauffman 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.
Clinical Infectious Diseases 2000; 30: 19-24.

Taillandier J, Esnault Y, Alemanni M.
A comparison of fluconazole oral suspension and amphotericin B oral suspension in older patients with oropharyngeal candidosis. Multicentre Study Group.
Age and Ageing 2000; 29: 117-123.

Trick WE, Fridkin SF, Edwards JR et al.
Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999.
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 eosophageal candidiasis.
American Journal of Medicine 2002; 113: 294-299.

Wise GJ, Talluri GS, Marella VK.
Fungal infections of the genitourinary system: manifestations, diagnosis, and treatment.
Urology Clinics of North America 1999; 26: 701-718.

Worthington HV, Clarkson JE.
Prevention of oral mucositis and oral candidiasis for patients with cancer treated with chemotherapy: Cochrane systematic review.
Journal of Dental Education 2002; 66: 903-911.

28 (i) *Coccidioidomycosis*

Type of disease	Treatment
Primary pulmonary	
• no dissemination risk	Observe, or fluconazole 400 mg per day for 3–6 months
• dissemination risk	Amphotericin B 0.5–0.7 mg/kg per day, followed by fluconazole 400 mg for 6 months
Pulmonary cavity (uncomplicated) or fibronodular disease	Surgical resection or closure 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
Progressive pulmonary or disseminated (non-meningeal)	
• immediately life-threatening	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
• slowly progressive or stable	Fluconazole 400–800 mg/kg per day, or itraconazole 200 mg b.d.
Meningitis	Fluconazole 600–1200 mg per day Itraconazole 400–600 mg per day Amphotericin B directly into CSF together with systemic therapy followed by oral fluconazole 600–1200 mg/kg/day
HIV-infected	Control infection, followed by lifelong therapy with fluconazole 400 mg per day, or itraconazole 200 mg b.d. In meningitis fluconazole 800 mg/d

Key references

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

Deresinski SC.
Coccidioidomycosis: efficacy of new agents and future prospects.
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.
Clinics in Chest Medicine 1999; 20: 507-519.

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.
Journal of Antimicrobial Chemotherapy 1999; 43: 321-331.

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.

TorresHA, Rivero GA, Kontoyiannis DP.
Endemic mycoses in a cancer hospital.
Medicine (Baltimore) 2002; 81: 201-212.

29 (i) *Cryptococcosis*

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

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

29 (iii) *Cryptococcosis*

Key references

Aberg JA, Price RW, Heeren DM.
A pilot study of the discontinuation of antifungal therapy for disseminated disease in patients with acquired immunodeficiency syndrome, following immunologic response to antiretroviral therapy.
Journal of Infectious Diseases 2002; 185: 1179-1182.

Aller AI, Maretin-Mazuelos E, Lozano F et al.
Correlation of fluconazole MICs with clinical outcome in cryptococcal infection.
Antimicrobial Agents and Chemotherapy 2000; 44: 1544-1548.

Apisarnthanarak A, Powderly WG.
Treatment of acute cryptococcal disease.
Expert Opinion in Pharmacotherapy 2001; 2: 1259-1268.

Arayawichanont A, Prayooniwat N, Churojana A, Sangruchi T, Poungvarin N.
Successful medical treatment of multiple cryptococcomas: report of a case and review.
Journal of the Medical Association of Thailand 1999; 82: 991-999.

Brant ME, Pfaller MA, Haijeh RA et al.
Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates in the United States: 1992 to 1994 and 1996 to 1998.
Antimicrobial Agents and Chemotherapy 2001; 45: 3065-3069.

Centers for Disease Control and Prevention.
Guidelines for preventing opportunistic infections among HIV-infected persons, 2002.
Morbidity and Mortality Weekly Report 2002; 51 (RR-8): 1-52.

Graybill JR, Sobel J, Saag M et al.
Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups.
Clinical Infectious Diseases 2000; 30: 47-54.

Imwidthaya P, Poungvarin N.
Cryptococcosis in AIDS.
Postgraduate Medical Journal 2000; 76: 85-88.

Larsen RA.
Editorial response: A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis.
Clinical Infectious Diseases 1999; 28: 297-298.

McKinsey DS, Wheat LJ, Cloud GA et al.
Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group.
Clinical Infectious Diseases 1999; 28: 1049-1056.

Neuville S, Dromer F, Morin O, Dupont B, Ronin O, Lortholary O.
Primary cutaneous cryptococcosis: a distinct clinical entity.
Clinical Infectious Diseases 2003; 36: 337-347.

Pappas PG, Perfect JR, Cloud GA et al.
Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy.
Clinical Infectious Diseases 2001; 33: 690-699.

Perfect JR, Casadevall A.
Cryptococcosis.
Infectious Diseases Clinics of North America 2002; 16: 837-874.

Robinson PA, Bauer M, Leal MAE et al.
Early mycological treatment failure in AIDS-associated cryptococcal meningitis.
Clinical Infectious Diseases 1999; 28: 291-296.

Saag MS, Cloud GA, Graybill JR et al.
A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group.
Clinical Infectious Diseases 1999; 28: 291-296.

Saag MS, Graybill RJ, Larsen R et al.
Practice guidelines for the management of cryptococcal disease.
Clinical Infectious Diseases 2000; 30: 710-718.

Vilchez RA, Fung J, Kusne S.
Cryptococcosis in organ transplant recipients: an overview.
American Journal of Transplantation 2002; 2: 575-580.

Type of disease	Treatment
Acute pulmonary	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
Chronic pulmonary	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
Disseminated	
• non-immunosuppressed	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
• AIDS	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

30 (ii) *Histoplasmosis*

Type of disease	Treatment
Focal infections	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%

Key references

Bamberger DM.
Successful treatment of multiple cerebral histoplasmomas 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.
Clinics in Chest Medicine 1999; 20: 507-519.

Kauffman CA.
Management of histoplasmosis.
Expert Opinion in Pharmacotherapy 2002; 3: 1067-1072.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.
Journal of Antimicrobial Chemotherapy 1999; 43: 321-331.

Odio CM, Navarrete M, Carrillo JM et al.
Disseminated histoplasmosis in infants.
Pediatric Infectious Diseases Journal 1999; 18: 1065-1068.

Wheat J, Sarosi G, McKinsey D et al.
Practice guidelines for the management of patients with histoplasmosis.
Clinical Infectious Diseases 2000; 30: 688-695.

31 (i) *Mucormycosis*

Type of disease	Treatment
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.
Mycoses 2001; 44: 253-260.

Ferguson BJ.
Mucormycosis of the nose and paranasal sinuses.
Otolaryngologic Clinics of North America 2000; 33: 349-365.

Gonzalez CE, Rinaldi MG, Sugar AM.
Zygomycosis.
Infectious Disease Clinics of North America 2002; 16: 895-914.

Hendrickson RG, Olshaker J, Duckett O.
Rhinocerebral mucormycosis: a case of a rare, but deadly disease.
Journal of Emergency Medicine 1999; 17: 641-645.

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.
Annals of Plastic Surgery 2000; 49: 385-390.

Mondy KE, Haughey B, Custer PL et al.
Rhinocerebral mucormycosis in the era of lipid-based amphotericin B: case report and literature review.
Pharmacotherapy 2002; 22: 519-526.

Oh D, Notrica D.
Primary cutaneous mucormycosis in infants and neonates: case report and review of the literature.
Journal of Pediatric Surgery 2002; 37: 1607-1611.

Ribes JA, Vanover-Sams CL, Baker DJ.
Zygomycosis in human disease.
Clinical Microbiology Reviews 2000; 13: 236-301.

Talmi YP, Goldschmied-Reouven A, Bakon M et al.
Rhino-orbital and rhino-orbito-cerebral mucormycosis.
Otolaryngology Head and Neck Surgery 2002: 127: 22-31

Van Steenwegen S, Maertens J, Boogaerts M, Deneffe G, Verbeken E, Nackaerts K.
Mucormycosis, a threatening opportunistic mycotic infection.
Acta Clinica Belgica 1999; 54: 99-102.

Warwar RE, Bullock JD.
Rhino-orbital-cerebral mucormycosis: a review.
Orbit 1998; 17: 237-245.

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

Bethlem EP, Capone D, Maranhao B et al.
Paracoccidioidomycosis.
Current Opinion in Pulmonary Medicine 1999; 5: 319-325.

Del Negro GM, Pereira CN, Andrade HF et al.
Evaluation of tests for antibody response in the follow-up of patients with acute and chronic forms of paracoccidioidomycosis.
Journal of Medical Microbiology 2000; 49: 37-46.

Goldman M, Johnson PC, Sarosi GA.
Fungal pneumonias. The endemic mycoses.
Clinics in Chest Medicine 1999; 20: 507-519.

Han RC, Fontes CJ, Batista RD, Hamdan JS.
In vitro comparison of activities of terbinafine and itraconazole against Paracoccidioides brasiliensis.
Journal of Clinical Microbiology 2002; 40: 2828-2831.

Lortholary O, Denning DW, Dupont B.
Endemic mycoses: a treatment update.
Journal of Antimicrobial Chemotherapy 1999; 43: 321-331.

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

Shikanai-Yasuda MA, Benard G, Higaki Y et al.
Randomised trial with itraconazole, ketoconazole and sulfadiazine in paracoccidioidomycosis.
Medical Mycology 2002; 40: 411-417.

33 *Penicillium marneffei infection*

Type of disease	Preferred treatment
Mild	Itraconazole 200–400 mg per day or ketoconazole 400 mg per day
Severe	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

Key references

Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE.
A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand.
Clinical Infectious Diseases 2002; 15: 277-284.

Drouhet E.
Penicilliosis due to Penicillium marneffei: a new emerging systemic mycosis in AIDS patients travelling or living in Southeast Asia.
Journal of Medical Mycology 1993; 3: 195-224.

Nittayananta W.
Penicilliosis marneffei: another AIDS defining illness in Southeast Asia.
Oral Disease 1999; 5: 286-293.

Ungpakorn R.
Cutaneous manifestations of Penicllium marneffei infection.
Current Opinion in Infectious Diseases 2000; 13: 129-134.

34 *Sporotrichosis*

Type of disease	Preferred therapy
Pulmonary	Difficult to treat, relapse common Clinical 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.

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

Morris-Jones R.
Sporotrichosis.
Clinical and Experimental Dermatology 2002; 27: 427-431.

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

Disease	Therapy
Fusariosis (*Fusarium* species)	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)
Pseudallescheriosis (*Pseudallescheria boydii, Scedosporium apiospermum)*	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
Phaeohyphomycosis	Skin and subcutaneous tissue disease Occasional dissemination: surgical excision Itraconazole (oral solution) 400 mg per day
Trichosporonosis *(Trichosporon species*)	Correct neutropenia Amphotericin B 1.0–1.5 mg/kg per day
Paecilomyces lilacinus	Itraconazole 200 mg per day 3 months
Malassezia (Pityrosporum) septicemia	Remove intravascular catheter Fluconazole 1 g i.v. per day if fungemia exists

Key references

Anaissie EJ, Kuchar RT, Rex JH et al.
Fusariosis associated with pathogenic Fusarium species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections.
Clinical Infectious Diseases 2001; 33: 1871-1878.

Bodey GP, Boktour M, Mays S et al.
Skin lesions associated with Fusarium infection.
Journal of the American Academy of Dermatology 2002; 47: 659-666.

Boutati EI, Anaissie EJ.
Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management.
Blood 1997; 90: 999-1008.

Castiglioni B, Sutton DA, Rinaldi MG et al.
Pseudallescheria boydii (anamorph Scedosporium apiospermum) infection in solid organ transplant recipients in a tertiary medical center and review of the literature.
Medicine (Baltimore) 2002; 81: 333-348.

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.

Erer B, 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.
Infectious Disease Clinics of North America 2002; 16: 915-933.

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.
Clinical Microbiology and Infection 2001; 7 (suppl 2): 8-24.

Guarro J, Gene J.
Opportunistic fusarial infections in humans.
European Journal of Clinical Microbiology and Infectious Diseases 1995; 14: 741-754.

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.
European Journal of Clinical Microbiology and Infectious Disease 1999; 18: 814-818.

LaRocco MT, Burgert SJ.
Infection in the bone marrow transplantation recipient and role of the microbiology laboratory in clinical transplantation.
Clinical Microbiology Reviews 1997; 10: 277-297.

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.
British Journal of Haematology 2000; 108: 544-548.

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.
Clinical Infectious Diseases 1996; 22: 73-80.

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.
Transplant Infectious Diseases 1999; 1: 247-261.

Prophylaxis

36(i) *Prophylaxis alternatives*

Drug	Dose	Comment
Fluconazole	100–400 mg per day High-risk patients, 400 mg/kg per day	Effective for prevention of candidosis in immunocompromised patients Does not prevent emergence of *Candida glabrata* and *C. krusei* infections Offers no protection against aspergillosis or mucormycosis
Itraconazole (capsule)	400 mg per day	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
Itraconazole (oral solution)	2.5 mg/kg twice daily	Benefit in reducing emergent IPA and non-*albicans* species of *Candida*; reliable absorption Start immediately prior to cytostatic treatment and generally 1 week before transplant procedure
Amphotericin B (i.v.)	0.15–0.25 mg/kg per day	Higher dose (0.25 mg/kg per day) has shown benefit
Amphotericin B (aerosol)	10 mg 3 times daily	Problems with tolerance: nausea and vomiting Caution in asthmatics — monitor peak flow and use bronchodilators prior to inhalation, benefits uncertain

Key references

Ascioglu S, de Pauw BE, Meis JF.
Prophylaxis and treatment of fungal infections associated with haematological malignancies.
International Journal of Antimicrobial Agents 2000; 15: 159-168.

Cornely OA, Ullmann AJ, Karthaus M.
Evidence based assessment of primary antifungal prophylaxis in patients with hematological malignancies.
Blood 2003; 101: 3365-3372.

De Rosso JQ, Gupta AK.
Oral itraconazole therapy for superficial, subcutaneous and systemic infections. A panoramic view.
Postgraduate Medicine 1999; Special number: 46-52.

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.

Glasmacher A, Hahn C, Molitor E, Sauerbruch T, Schmidt-Wolf IG, Marklein G.
Fungal surveillance cultures during antifungal prophylaxis with itraconazole in neutropenic patients with acute leukaemia.
Mycoses 1999; 42: 395-402.

Glasmacher A, Hahn C, Leutner C et al.
Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole.
Mycoses 1999; 42: 443-451.

Glasmacher A, Hahn C, Molitor E et al.
Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-beta-cyclodextrin oral solution or coated-pellet capsules.
Mycoses 1999; 42: 591-600.

Glasmacher A, Djulbegovic B, Prentice A et al.
Meta-analysis of itraconazole antifungal prophylaxis trials reveals a dose-response effect for the prevention of invasive fungal infections, including aspergillus, in neutropenic patients.
Abstract: American Society for Hematology 2002.

Hamacher J, Spiliopoulos A, Kurt AM et al.
Pre-emptive therapy with azoles in lung transplant patients. Geneva Lung Transplantation Group.
European Respiratory Journal 1999; 13: 180-186.

Harrousseau JL, Dekker AW, Stamatoullas-Bastard A et al.
Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo, multicentre trial comparing itraconazole and amphotericin B.
Antimicrobial Agents and Chemotherapy 2000; 44: 1887-1893.

Kelsey SM, Goldman JM, McCann S et al.
Liposomal amphotericin (AmBisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study.
Bone Marrow Transplantation 1999; 23: 163-168.

Lorf T, Braun F, Ruchel R, Muller A, Sattler B, Ringe B.
Systemic mycoses during prophylactic use of liposomal amphotericin B (AmBisome) after liver transplantation.
Mycoses 1999; 42: 47-53.

McKinsey DS, Wheat LJ, Cloud GA et al.
Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group.
Clinical Infectious Diseases 1999; 28: 1049-1056.

Menichetti F, Del Favero A, Martino P et al and the GIEMA Infection Program.
Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomised, placebo-controlled, double-blind, multicenter trial.
Clinical Infectious Diseases 1999; 28: 250-255.

Morgenstern GR, Prentice AG, Prentice HG, Ropner JE, Schey SA, Warnock DW.
A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies.
British Journal of Haematology 1999; 105: 901-911.

36(iii) *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.
Liver Transplantation 2000; 6: 376-379.

Singh N, Yu VL.
Prophylactic fluconazole in liver transplant recipients.
Annals of Internal Medicine 2000; 132: 843-844.

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.
Transplantation 2002; 74: 688-695.

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

37

Risk factor	Suggested prophylaxis
Gram-negative bacteremia	Fluconazole + p.o. amphotericin B
Heavy colonization with *C. albicans* at 2 or more sites	Fluconazole + p.o. amphotericin B
Heavy colonization with non-*albicans* species at 2 or more sites	Itraconazole + p.o. amphotericin B
Colonization with *C. tropicalis*	i.v. amphotericin B
Unexpected neutropenia >21 days	Itraconazole + p.o. amphotericin B
GVHD	Itraconazole + p.o. amphotericin B
Relapsed/refractory leukemia	Itraconazole + p.o. amphotericin B

Adapted with permission from: Prentice HG, Kibbler CC, Prentice AG. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. British Journal of Haematology 2000; 110: 273-284.

Empirical Treatment of the Persistently Febrile Neutropenic Patient

Recommended empirical treatment 38

- 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.
Pre-emptive therapy with azoles in lung transplant patients. Geneva Lung Transplantation Group.
European Respiratory Journal 1999; 13: 180-186.

Jones BL, McLintock LA.
Impact of diagnostic markers on early antifungal therapy
Current Opinion in Infectious Diseases 2003; 16: 521-526.

Marr KA.
Empirical antifungal therapy: new options, new tradeoffs.
New England Journal of Medicine 2002; 346: 278-280.

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/flucytosine.
Mycoses 1999; 43 (suppl 2): 101-104.

Walsh TJ, Finberg RW, Arndt C et al.
Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia.
New England Journal of Medicine 1999; 340: 764-771.

Wingard JR.
Liposomal amphotericin B for fever and neutropenia.
New England Journal of Medicine 1999; 341: 1153, 1154-1155.

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.

39 *Current recommended initial strategy*

Risk group	Prophylaxis	Pre-emptive treatment	Empirical treatment	Targeted treatment
Low	No	Yes	?	Yes
Intermediate				
• Low (not colonized, HEPA filtration)	No	Yes	?	Yes
• High (Colonized)	Yes	NR**	Yes	Yes
High	Yes	NR**	Yes	Yes

**NR: Not relevant

Adapted with permission from: Prentice HG, Kibbler CC, Prentice AG. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. British Journal of Haematology 2000; 110: 273-284.

Key reference

Jones BL, McLintock LA.
Impact of diagnostic markers on early antifungal therapy.
Current Opinion in Infectious Diseases 2003; 16: 521-526.

Combination Treatment and Antifungals Under Development

40 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

Antoniadou A, Kontoyiannis DP.
Status of combination therapy for refractory mycoses.
Current Opinion in Infectious Diseases 2003; 16: 539-545.

Kontoyiannis DP, Lewis RE.
Combination chemotherapy for invasive fungal infections: what laboratory and clinical studies tell us so far.
Drug Resistance Update 2003; 6: 257-269.

Lewis RE, Kontoyiannis DP.
Rationale for combination antifungal therapy.
Pharmacotherapy 2001; 21: 149S-164S.

Rubin MA, Carroll KC, Cahill BC.
Caspofungin in combination with itraconazole for the treatment of invasive aspergillosis in humans.
Clinical Infectious Diseases 2002; 34: 1160-1161.

Popp AI, White MH, Quadri T et al.
Amphotericin B with and without itraconazole for invasive aspergillosis: a three-year retrospective study.
International Journal of Infectious Diseases 1999; 3: 157-160.

Steinbach WJ, Stevens DA, Denning DW.
Combination and sequential antifungal therapy for invasive aspergillosis: review of published in vitro and in vivo interactions and 6281 clinical cases from 1966 to 2001.
Clinical Infectious Diseases 2003; 37(suppl 3): S188-S224.

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

41(ii) *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*
  - *Cryptoccocus 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, Coccidioides 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

41(iv) *Antifungals under development*

Micafungin (continued)

- Phase II – HIV-infected patients with *Candida* esophagitis
  - Doses up to 50 mg/day evaluated
  - Resolution/improvement in 100% patients after 8 days at 50 mg/day
- Phase III: no data currently available
- may be useful as empirical treatment in patients with PUO based on broad antifungal activity in experimental infection
- 'fungistatic' activity against *Aspergillus* species indicates further evaluation
- may be useful in combination with amphotericin B and antifungal triazoles

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.
Lancet 2003; 362: 1142-1151.

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

Fromtling 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.
Dermatology Clinics 2003; 2: 565-576.

Wiederhold NP, Lewis RE.
The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy.
Expert Opinion in Investigational Drugs 2003; 12: 1313-1333.

General references

Ablordeppey SY, Fan P, Ablordeppey JH, Mardenborough L.
Systemic antifungal agents against AIDS-related opportunistic infections: current status and emerging drugs in development.
Current Medical Chemistry 1999; 6: 1151-1195.

Ajello L, Hay RJ (eds).
Medical mycology.
Volume 4 of Topley & Wilson's Microbiology and Microbial Infections (eds Collier L, Balows A, Sussman M). London: Arnold, 1998. [See also: www.topleyonline.com for updates]

Anaissie EJ, McGinnis M, Pfaller M (eds.).
Clinical Mycology
London: Churchill Livingstone, 2003.

Bohme A, Ruhnke M, Buchheidt D et al.
Treatment of fungal infections in hematology and oncology – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO).
Annals of Hematology 2003; 82(suppl 2): S133-S140.

Canto MM, Rodero FG.
Antifungal drug resistance to azoles and polyenes.
Lancet Infectious Diseases 2002; 2: 550-563.

Casadevall A, Perfect JR.
Cryptococcus neoformans.
Washington, DC: ASM Press, 1998.

Chapman RL.
Candida infections in the neonate.
Current Opinion in Pediatrics 2003; 15: 97-102

Conces DJ.
Endemic fungal pneumonia in immunocompromised patients.
Journal of Thoracic Imaging 1999; 14: 1-8.

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

De Pauw BE, Donnelly JP, Kullberg BJ.
Treatment of fungal infections in surgical patients using conventional antifungals.
Journal of Chemotherapy 1999; 11: 494-503.

Denning DW, Evans EGV, Kibbler CC et al.
Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation.
European Journal of Clinical Microbiology and Infectious Diseases 1997; 16: 424-436.

Denning DW, Kibbler CC, Barnes RA, British Society for Medical Mycology.
British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections.
Lancet Infectious Diseases 2003; 3: 230-240.

Dodds ES, Drew RH, Perfect JR.
Antifungal pharmacodynamics: review of the literature and clinical applications.
Pharmacotherapy 2000; 20: 1335-1355.

Edwards JE, Bodey GP, Bowden RA et al.
International conference for the development of a consensus on the management and prevention of severe candidal infections.
Clinical Infectious Diseases 1997; 25: 43-59.

Flanagan PG, Barnes RA.
Fungal infection in the intensive care unit.
Journal of Hospital Infection 1998; 38: 163-177.

Fromtling RA.
Human mycoses and advances in antifungal therapy.
Drug News Perspectives 2001; 14: 181-192.

Gallagher JC, Dodds Ashley ES, Drew RH, Perfect JR.
Antifungal pharmacotherapy for invasive mould infections.
Expert Opinion Pharmacotherapy 2003; 4: 147-164.

Goldman M, Johnson PC, Sarosi GA.
Fungal pneumonias. The endemic mycoses.
Clinics in Chest Medicine 1999; 20: 507-519.

Groll AH, Gea-Banacloche JC, Glasmacher A, Just-Nuebling G, Maschmeyer G, Walsh TJ.
Clinical pharmacology of antifungal compounds.
Infectious Disease Clinics of North America 2003; 17: 159-191.

Groll AH, Piscitelli SC, Walsh TJ.
Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development.
Advances in Pharmacology 1999; 44: 343-500.

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

Jones BL, McLintock LA.
Impact of diagnostic markers on early antifungal therapy.
Current Opinion in Infectious Diseases 2003; 16: 521-526.

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.
Journal of Antimicrobial Chemotherapy 1999; 43: 321-331.

Luna B, Drew RH, Perfect JR.
Agents for treatment of invasive fungal infections.
Otolaryngologic Clinics of North America 2000; 33: 277-299.

Marty F, Mylonakis E.
Antifungal use in HIV infection.
Expert Opinion in Pharmacotherapy 2002; 3: 91-102.

Muller FM, Groll AH, Walsh TJ.
Current approaches to diagnosis and treatment of fungal infections in children infected with human immunodeficiency virus.
European Journal of Pediatrics 1999; 158: 187-199.

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.
British Journal of Haematology 2000; 110: 273-284.

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

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

Richardson MD, Johnson EM.
Pocket Guide to Fungal Infection.
Oxford: Blackwell Publishing, 2000.

Richardson MD, Warnock DW.
Fungal Infection: Diagnosis and Management, Third Edition.
Oxford: Blackwell Publishing, 2003.

Sanglard D, Odds FC.
Resistance of Candida species to antifungal agents: molecular mechanisms and clinical consequences
Lancet Infectious Diseases 2002; 2: 73-85.

Sheehan DJ, Hitchcock CA, Sibley CM.
Current and emerging azole antifungal agents.
Clinical Microbiology Reviews 1999; 12: 40-79.

Sugar A, Lyman CA.
A practical guide to medically important fungi and the diseases they cause.
Hagerstown: Lippincott-Raven Publishers, 1997.

Summers KK, Hardin TC, Gore SJ et al.
Therapeutic drug monitoring of systemic antifungal therapy.
Journal of Antimicrobial Chemotherapy 1997; 40: 753-764.

Sutton DA, Fothergill AW, Rinaldi MG.
Guide to clinically significant fungi.
Baltimore: Williams & Wilkins, 1998.

Valgus JM.
What's new in antifungals?
Current Infectious Diseases Report 2003; 5: 16-21.

Virgili A, Zampino MR, Mantovani L.
Fungal skin infections in organ transplant recipients.
American Journal of Clinical Dermatology 2002; 3: 19-35.

Warnock DW, Richardson MD (eds).
Fungal infection in the compromised patient, second edition.
Chichester: John Wiley & Sons, 1991.

Wheat LJ, Goldman M, Sarosi G.
State-of-the-art review of pulmonary fungal infections.
Seminars in Respiratory Infections 2002; 17: 158-181.

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

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.reviberoammicol.com/
(ejournal: *Revista Iberoamericana de Micologia*)

MYCOLOGY DISCUSSION FORUMS

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

Abbreviations

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