Complete Summary

GUIDELINE TITLE

Treatment of Aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA, Wingard JR, Patterson TF, Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008 Feb 1;46(3):327-60. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, Bennett JE, Walsh TJ, Patterson TF, Pankey GA. Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):696-709. [202 references]

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

Drug Withdrawal

- January 24, 2008, Leukine (sargramostim): The current liquid formulation of Leukine (sargramostim) was withdrawn from the market in the U.S. and worldwide due to an upward trend in spontaneous reports of adverse reactions, including syncope (fainting).

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

different forms of *Aspergillosis* including:

- Invasive aspergillosis
- Chronic (and saprophytic) forms of aspergillosis
- Allergic forms of aspergillosis

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To summarize the current evidence for treatment of different forms of aspergillosis

TARGET POPULATION

Patients at risk for or suspected of having infections caused by *Aspergillosis*

INTERVENTIONS AND PRACTICES CONSIDERED

1. Antifungal therapy
    - Oral or IV triazoles (voriconazole, posaconazole, itraconazole) with or without therapeutic drug monitoring
    - IV lipid-based amphotericin B (amphotericin B lipid complex [ABLC], liposomal amphotericin B [L-AMB], amphotericin B colloidal dispersion [ABCD])

- IV amphotericin B deoxycholate (D-amphotericin B [D-AMB])
- IV echinocandins (caspofungin, micafungin, anidulafungin)

2. Combination chemotherapy
3. Surgical excision (primary or adjunctive)
4. Immunotherapy (colony-stimulating factor, interferon gamma, granulocyte transfusion)
5. Antifungal prophylaxis in high-risk patients
6. Corticosteroids

MAJOR OUTCOMES CONSIDERED

- Therapeutic efficacy
- Morbidity and mortality
- Adverse effects of therapy
- Disease progression
- Improvement in signs and symptoms

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline panel performed extensive review of all the randomized, controlled and observational trials published in the English-language literature.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grades reflecting the quality of evidence on which recommendations are based:

I. Evidence from $\geq$1 properly randomized, controlled trial
II. Evidence from $\geq$1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III. Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Treatment recommendations were rated according to the standard scoring system of the Infectious Diseases Society of America (IDSA) and United States Public Health Service (USPHS) for rating recommendation in clinical guidelines. Final recommendations were discussed by the Infectious Diseases Society of America (IDSA) Aspergillus Guidelines Committee panel and determined by consensus.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation

COST ANALYSIS

Pharmoeconomics and Costs

The complex issues of pharmacoeconomics and fiscal costs of antifungal therapy are beyond the scope of these guidelines; however, these issues often occur in the setting of lipid formulation amphotericin Bs (LFABs) versus amphotericin B deoxycholate (D-AMB). The poor outcomes and fiscal costs of D-AMB-induced renal impairment in compromised hosts are well documented. Whether there is a population for whom D-AMB can be used as first line therapy is an important question. Some pediatric patients, particularly neonates, may tolerate D-AMB with minimal or reversible renal impairment. The use of D-AMB in adult patients needs to be assessed on an individual basis for the relative risks and consequences of renal impairment. In many resource-limited settings, D-AMB may be the only agent for primary treatment of invasive aspergillosis and as such may be considered the standard of care.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After extensive review and discussion by the Infectious Diseases Society of America (IDSA) Guidelines committee, the guideline was subjected to extensive peer review and was approved by the IDSA Standards and Practice Guidelines Committee and the IDSA Board of Directors.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-C) are repeated at the end of the Major Recommendations field.

Invasive Aspergillosis

Invasive Pulmonary Aspergillosis

Key Recommendations

Early initiation of antifungal therapy in patients with strongly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted (A-I) (Greene et al., 2007; Cornely et al., 2007). The decision of medical therapy for treatment of invasive pulmonary aspergillosis has been greatly facilitated by a randomized, controlled trial of voriconazole versus deoxycholate amphotericin B (D-AMB).

Because of better survival and improved responses of initial therapy with voriconazole, primary therapy with D-AMB is not recommended (A-I). **For primary treatment of invasive pulmonary aspergillosis, intravenous or oral voriconazole is recommended for most patients (A-I). Oral therapy can be maximized by using a dose of 4 mg/kg rounded up to convenient pill sizes (B-III). For seriously ill patients, the parenteral formulation is recommended (A-III)**. A randomized trial compared 2 initial dosages of L-AMB (3 mg/kg/day and 10 mg/kg/day) and showed similar efficacy in both arms but greater toxicity in the higher-dose arm. **These results suggest that liposomal AMB (L-AMB) may be considered as alternative primary therapy in some patients (A-I). For salvage therapy, agents include lipid formulations of amphotericin (LFABs) (A-II), posaconazole (B-II), itraconazole (B-II), caspofungin (B-II), or micafungin (B-II)**. In that context, the diagnosis should be confirmed. **Therapeutic options include a change of class using an AMB formulation or an echinocandin (B-II)**; additional use of an azole should take into account prior therapy, host factors, and pharmacokinetic considerations.

In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended (B-II). The committee recognizes, however, that in the context of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used (B-II). In addition, management of breakthrough invasive aspergillosis in the

context of mould-active azole prophylaxis or suppressive therapy is not defined by clinical trial data but would suggest a switch to another drug class (B-III). Paramount to the successful treatment of invasive pulmonary aspergillosis is the reversal of immunosuppression (e.g., reduction in the dosage of corticosteroids) or recovery from neutropenia. **Surgical resection of *Aspergillus*-infected tissue may be useful in patients with lesions that are contiguous with the great vessels or pericardium, lesions causing hemoptysis from a single focus, and lesions causing erosion into the pleural space or ribs (B-III)**.

Duration of antifungal therapy for invasive pulmonary aspergillosis is not well defined. The guideline panel generally recommends that treatment of invasive pulmonary aspergillosis be continued for a minimum of 6 to 12 weeks; in immunosuppressed patients, therapy should be continued throughout the period of immunosuppression and until lesions have resolved. Long-term therapy of invasive aspergillosis is facilitated by the availability of oral voriconazole in stable patients. **For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection (A-III)** (Karp, Burch & Merz, 1988; Sipsas & Kontoyiannis, 2006).

Therapeutic monitoring of invasive pulmonary aspergillosis includes serial clinical evaluation of all symptoms and signs, as well as performance of radiographic imaging, usually with computerized tomography (CT), at regular intervals. The frequency with which CT should be performed cannot be universally defined and should be individualized on the basis of the rapidity of evolution of pulmonary infiltrates and the acuity of the individual patient. The volume of pulmonary infiltrates may increase for the first 7 to 10 days of therapy—especially in the context of granulocyte recovery. The use of serial serum galactomannan assays for therapeutic monitoring is promising but remains investigational. Progressive increase in *Aspergillus* antigen levels over time signifies a poor prognosis. **However, resolution of galactomannan antigenemia to a normal level is not sufficient as a sole criterion for discontinuation of antifungal therapy (B-III)**. Further data elucidating the prognostic and therapeutic value of serial galactomannan levels in patients with invasive pulmonary aspergillosis are needed.

Antifungal Therapy

- Measurement of itraconazole serum levels are generally recommended to document absorption of drug (**B-II**).
- Salvage therapy of itraconazole for treatment of invasive pulmonary aspergillosis refractory to primary therapy with voriconazole is not recommended because of the same mechanism of action or possible resistance and because of the erratic bioavailability and toxicity (**B-II**).
- The aggregate body of data thus far warrants that an antifungal triazole should be used instead of amphotericin B (AMB) in the primary treatment of infections due to *A. terreus* (**A-II**) (Steinbach et al., 2004).

Use of Colony-Stimulating Factors

- Although high-risk neutropenic patients with invasive aspergillosis may already be receiving granulocyte colony-stimulating factor (GCSF) or granulocyte-macrophage colony stimulating factor (GMCSF) as a component of their cancer chemotherapy, those neutropenic patients who are not receiving a CSF may benefit from the addition of GCSF or GMCSF (**B-III**).
- Individual case reports suggest a role for interferon (IFN)-gamma as an adjunctive antifungal therapy for invasive aspergillosis in immunocompromised non-neutropenic patients, particularly those with chronic granulomatous disease (CGD) (**-BIII**).

Management of Immunosuppressive Therapies

- Withdrawal of corticosteroids or reduction of dosage is often critical for successful outcome in invasive aspergillosis (**A-III**).
- For patients with chronic immunosuppression, continuation of antifungal therapy throughout the duration of immunosuppression seems to be associated with a more favorable outcome (**A-III**).

Hemoptysis and Surgical Management

- Surgical therapy may be useful in patients with lesions contiguous with the great vessels or the pericardium, hemoptysis from a single cavitary lesion, or invasion of the chest wall (**B-II**). Another relative indication for surgery is the resection of a single pulmonary lesion prior to intensive chemotherapy or hematopoietic stem cell transplantation (HSCT) (**B-II**).

Tracheobronchial Aspergillosis

Key Recommendations

Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis (B-II). Little experience is available with caspofungin or other echinocandins in treating this infection. **Because the use of D-AMB may result in increased nephrotoxicity in association with calcineurin inhibitors, an LFAB is recommended if a polyene is considered in the patient (e.g., lung transplant recipient) (B-III)**. Bronchoscopic evaluation is the most important aspect of initial diagnosis; CT will assess the lack of progression to the remainder of the pulmonary tree. Reduction of immunosuppression, where possible, is an important element in improving therapeutic outcome. **Aerosolized D-AMB or LFAB may have some benefit for delivering high concentrations of polyene therapy to the infected (often anastomotic) site; however, this approach has not been standardized and remains investigational (C-III)**. Cases of tracheobronchial aspergillosis in immunocompromised patients who have not received a transplant may be managed with a similar approach.

Chronic Necrotizing Pulmonary Aspergillosis (CNPA) (Subacute Invasive Pulmonary Aspergillosis)

Key Recommendations

The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole (B-III). Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available for its use in (CNPA) (B-III). Because long-term treatment is required, oral antifungal therapy is preferred over parenteral therapy.

Single Organ, Extrapulmonary Forms of Invasive Aspergillosis

Focal extrapulmonary invasive aspergillosis can develop as a single-organ infection or can occur in the context of disseminated infection. Because these are uncommon infections and occur in a wide spectrum of clinical conditions, no randomized clinical trials have been completed to assess therapeutic approaches in patients with these infections. Thus, there are very limited data on the treatment of these infections, and most involve D-AMB as primary therapy simply because of its longstanding availability. **However, based on the strength of the randomized study comparing voriconazole to D-AMB (Herbrecht, et al., 2002), the panel recommends voriconazole for primary treatment of these uncommon manifestations of invasive aspergillosis (B-III)**. The use of voriconazole in these contexts is further supported by case series and anecdotal cases documenting the efficacy of voriconazole in extrapulmonary infections, some of which have historically been associated with abysmal responses, including CNS infection, osteomyelitis, and endocarditis. The use of alternative agents and salvage therapy can be approached in a manner similar to that described for invasive pulmonary aspergillosis.

Aspergillosis of the CNS

Key Recommendations

Aggressive diagnostic and therapeutic intervention is important in patients with otherwise documented invasive pulmonary aspergillosis and signs of neurological deficits or unexplained abnormalities by CT or magnetic resonance imaging (MRI). **The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of CNS aspergillosis (A-II). Itraconazole, posaconazole, or LFAB are recommended for patients who are intolerant or refractory to voriconazole (B-III)**. There are few data supporting the use of echinocandins as a single agent in salvage treatment of CNS aspergillosis. Combination therapy with voriconazole and caspofungin is used for CNS aspergillosis but with minimal data to date. Surgical resection of lesions may be the definitive treatment and may prevent serious neurological sequelae. Surgical resection of lesions that would not result in worsening of neurological deficits also may improve outcome. Treatment of contiguous infections of the paranasal sinuses or vertebral bodies is a necessary part of management of this infection. Reversal of any underlying immune deficits is paramount for successful outcome of CNS aspergillosis. Because there may be progression of neurological deficits, there may be a tendency to use corticosteroids. The role of corticosteroids in this context, however, is deleterious and should be avoided where possible (C-III). The practice of intrathecal or intralesional antifungal chemotherapy is not recommended for treatment of CNS aspergillosis (B-III). Intrathecal administration of AMB does not allow penetration beyond the pia mater and may induce chemical arachnoiditis, seizures, severe headache, and

altered mental status. Instead, high-dose systemic antifungal therapy is recommended to achieve higher parenchymal concentrations.

Invasive Sinonasal Aspergillosis

Key Recommendations

Early recognition and therapeutic intervention with systemic antifungal therapy and surgical resection and/or debridement (where indicated) is important. The patient's immune status, extent of surgery necessary, concomitant coagulopathy, and morbidity associated with the surgical procedure(s) should be carefully weighed. Although randomized trials are lacking for this indication, AMB, itraconazole, voriconazole, or presumably, posaconazole are reasonable choices for initial therapy. **If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated (B-III)**. If one selects voriconazole or itraconazole as primary therapy, recognition of sinonasal zygomycosis is critical, because these triazoles lack clinical activity against this group of fungal organisms. **Thus, if the etiological organism is not known or histopathologic examination is still pending, an AMB formulation should be initiated in anticipation of possible sinus zygomycosis (A-III). Posaconazole demonstrates salvage activity in extrapulmonary aspergillosis and offers the theoretical advantage of activity against Zygomyetes in this context, although published clinical experience is limited (B-III)**. There are limited data supporting echinocandin use in *Aspergillus* sinusitis.

Aspergillus Endocarditis, Pericarditis, and Myocarditis

Key Recommendations

Early recognition, followed by rapid, aggressive medical and surgical intervention is critical to preventing embolic complications and valvular decompensation. **Voriconazole has been successfully used in case reports and may be the preferred agent (B-III)** (Vassiloyanakopoulos et al., 2006; Walsh, Heir & Caplan, 1985), based on data from a randomized trial data conducted mostly in pulmonary infection. D-AMB historically has been recommended as the preferred initial treatment, and D-AMB therapy should be continued for a minimum of 6 weeks after surgical intervention (B-III). **Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole (C-III)**.

Aspergillus Osteomyelitis and Septic Arthritis

Key Recommendations

Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis (B-III). Diagnostic imaging with CT and/or MRI is essential for staging disease and for providing a guide for orthopedic and/or neurosurgical intervention. **Although**

there is currently limited experience with voriconazole for treatment of Aspergillus osteomyelitis, voriconazole appears to be effective for this indication (B-II). Historically, AMB has been used and would be appropriate therapy in this context (B-II). Treatment for a minimum of 6 to 8 weeks is warranted in nonimmunocompromised patients. For immunocompromised patients, consideration for long-term suppressive therapy or treatment throughout the duration of immunosuppression is appropriate.

Aspergillus Endophthalmitis and Aspergillus Keratitis

Key Recommendations

Following a diagnostic vitreal tap, IV AMB and, where appropriate, intravitreal AMB plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis (B-III). Voriconazole administered intravitreally or systemically is an alterative regimen (B-III). Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with AMB, voriconazole, or itraconazole (B-III). Ophthalmologic surgical intervention has been warranted in cases with potential corneal perforation or progression despite medical therapy.

Cutaneous Aspergillosis

Key Recommendation

Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole (A-I) recommended as primary therapy. Alternative agents include L-AMB (A-I), posaconazole, itraconazole, or an echinocandin (B-II). Surgical intervention, particularly for primary cutaneous infection, may be useful; biopsy for confirmation of mycological diagnosis is very important to distinguish other potential pathogens (e.g., *Fusarium* species and Zygomycetes).

Aspergillus Peritonitis

Key Recommendation

Removal of peritoneal dialysis catheter and intraperitoneal dialysis with AMB in addition to IV administration of AMB are recommended (B-III). Itraconazole or an extended spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy (C-III).

Esophageal and Gastrointestinal Aspergillosis

Key Recommendation

Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. Systemic antifungal therapy as used for disseminated invasive aspergillosis is appropriate.

Hepatic Aspergillosis

Key Recommendation

Medical therapy of hepatic aspergillosis should be considered as initial therapy (C-III). For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted (C-III). For localized lesions that are refractory to medical therapy, surgical consultation is recommended.

Renal Aspergillosis

Key Recommendations

A combined approach of medical and urological management of renal aspergillosis allows flexibility for the various patterns of renal aspergillosis. Nephrostomy may reduce the complications of ureteral obstruction and allow for AMB lavage of the pelvicalyceal system. All of the available antifungal agents with activity against aspergillosis penetrate renal parenchyma. **However, because none of these agents is excreted primarily into the pelvis of the kidney or urine, the management of pelvicalyceal and ureteral infection may require nephrostomy with instillation of AMB (C-III)**.

Empirical Antifungal Therapy of Neutropenic Patients with Prolonged Fever Despite Antibacterial Therapy and Presumptive Therapy for Invasive Aspergillosis

Key Recommendations

Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk neutropenic patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy (A-I). Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection (B-III).

Prophylaxis against Invasive Aspergillosis

Key Recommendation

Antifungal prophylaxis with posaconazole can be recommended in HSCT recipients with graft versus host disease (GVHD) who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who are at high risk for invasive aspergillosis (A-I). Itraconazole may be effective but tolerability limits its use (B-I). Further investigation of antifungal prophylaxis is recommended in this population and other high-risk groups.

Chronic and Saprophytic Forms of Aspergillosis

Aspergilloma and Chronic Pulmonary Aspergillosis

Key Recommendation

Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk (B-III). Surgical resection or intracavitary antifungal therapy may be appropriate in selected patients with a single aspergilloma who are carefully evaluated for the risks mentioned in the original guideline document (see "Guideline Availability" field). **Long-term, perhaps lifelong, antifungal treatment is required for chronic cavitary pulmonary aspergillosis (CCPA) (B-III)**.

Aspergillus Otomycosis (Otic Aspergillosis)

Key Recommendation

Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis (C-III). For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate (C-III).

Allergic Forms of Aspergillosis

Allergic Bronchopulmonary Aspergillosis (ABPA)

Key Recommendation

Treatment of ABPA should consist of a combination of corticosteroids and itraconazole (A-I).

Allergic *Aspergillus* Sinusitis (AAS)

Key Recommendations

Endoscopic drainage may be useful in patients with obstructive symptoms (C-III). Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis (AAS) (C-III). Nasal or systemic corticosteroids may be useful in some patients (C-III). The benefits of endoscopic surgical sinus drainage outweigh the risks of surgery in cases of AAS that present with complications of sinus obstruction. Systemic corticosteroids are beneficial but may be fraught with serious systemic complications with long-term use. Nasal corticosteroids are partially effective and well absorbed but, when used continuously in high doses, can damage or atrophy the nasal mucosa. **The benefits of itraconazole in AAS outweigh the potential for toxicity (C-III)**. Because patients with either AAS or ABPA may be receiving nonsedating antihistamines, caution is required to assess the potential for adverse drug interactions with some of those agents associated with prolonged QT interval and torsades de pointe.

Summary

Table: Summary of Recommendations for the Treatment of Aspergillosis

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 hours for 1 day, followed by 4 mg/kg IV every 12 hours; oral dosage is 200 mg every 12 hours	L-AMB, 3-5 mg/kg/day IV; ABLC, 5 mg/kg/day IV; Caspofungin, 70 mg day 1 IV, and 50 mg/day IV thereafter; Micafungin IV 100-150 mg/day (dose not established);[c] Posaconazole 200 mg 4 times daily (QID) initially, then 400 mg twice daily (BID) PO after stabilization of disease[d] Itraconazole (dosage depends upon formulation)[e]	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients. Dosage in pediatric patients for voriconazole is 5–7 mg/kg IV every 12 hours and for caspofungin is 50 mg/m^2/day. Limited clinical experience is reported with anidulafungin. Dosage of posaconazole in pediatric patients has not been defined. Indications for surgical intervention are outlined in the table below.
Invasive sinus aspergillosis	Similar to invasive	Similar to invasive	Similar to invasive pulmonary

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
	pulmonary aspergillosis	pulmonary aspergillosis	aspergillosis
Tracheobronchial aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis
Chronic necrotizing pulmonary aspergillosis (subacute invasive pulmonary aspergillosis)	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Because chronic necrotizing pulmonary aspergillosis requires a protracted course of therapy measured in months, an orally administered triazole, such as voriconazole or itraconazole would be preferred over a parenterally administered agent.
Aspergillosis of the central nervous system	Similar to invasive pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	This infection is associated with the highest mortality among all of the different patterns of invasive aspergillosis; drug interactions with anticonvulsant therapy.
Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)	f	Similar to invasive pulmonary aspergillosis	Endocardial lesions caused by *Aspergillus* species require surgical resection; aspergillus pericarditis usually requires pericardiectomy.

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Aspergillus osteomyelitis and septic arthritis	f	Similar to invasive pulmonary aspergillosis	Surgical resection of devitalized bone and cartilage is important for curative intent.
Aspergillus infections of the eye (endophthalmitis and keratitis)	Intra-ocular AMB indicated with partial vitrectomy[f]	Similar to invasive pulmonary aspergillosis; limited data with echinocandins	Systemic therapy may be beneficial in management of aspergillus endophthalmitis; ophthalmologic intervention and management is recommended for all forms of ocular infection; topical therapy for keratitis is indicated.
Cutaneous aspergillosis	f	Similar to invasive pulmonary aspergillosis	Surgical resection is indicated where feasible.
Aspergillus peritonitis	f	Similar to invasive pulmonary aspergillosis	
Empirical and pre-emptive antifungal therapy	For empirical antifungal therapy, L-AMB (3 mg/kg/day IV) caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), itraconazole (200 mg every day IV or 200 mg twice daily), voriconazole, (6 mg/kg IV every		Pre-emptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result).

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
	12 hours for 1 day, followed by 3 mg/kg IV every 12 hours; oral dosage is 200 mg every 12 hours)		
Prophylaxis against invasive aspergillosis	Posaconazole 200 mg every 8 hours	Itraconazole (200 mg every 12 hours IV for 2 days, then 200 mg every 24 hours IV) or itraconazole (200 mg PO every 12 hours); micafungin (50 mg/day)	Efficacy of posaconazole prophylaxis demonstrated in high risk patients (patients with Graft vs. Host disease and neutropenic patients with AML and MDS).
Aspergilloma[g]	No therapy or surgical resection	Itraconazole or voriconazole; similar to invasive pulmonary aspergillosis	The role of medical therapy in treatment of aspergilloma is uncertain. Penetration into pre-existing cavities may be minimal for AMB but is excellent for itraconazole.
Chronic cavitary pulmonary aspergillosis[g]	Itraconazole or voriconazole	Similar to invasive pulmonary aspergillosis	Innate immune defects demonstrated in most of these patients; long-term therapy may be needed. Surgical resection may lead to significant complications. Anecdotal responses to IFN-gamma.

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Allergic bronchopulmonary aspergillosis	Itraconazole	Oral voriconazole (200 mg PO every 12 hours) or posaconazole (400 mg PO twice daily)	Corticosteroids are a cornerstone of therapy. Itraconazole has a demonstrable corticosteroid sparing effect.
Allergic aspergillus sinusitis	None or itraconazole	Few data on other agents	

[a] Duration of therapy for most conditions for aspergillosis has not been optimally defined. Most experts attempt to treat pulmonary infection until resolution or stabilization of all clinical and radiographic manifestations. Other factors include site of infection (e.g., osteomyelitis), level of immunosuppression, and extent of disease. Reversal of immunosuppression, if feasible, is important for a favorable outcome for invasive aspergillosis.
[b] Alternative (salvage) therapy for patients refractory to or intolerant of primary antifungal therapy.
[c] Micafungin has been evaluated as salvage therapy for invasive aspergillosis but remains investigational for this indication and the dosage has not been established.
[d] Posaconazole has been approved for the salvage treatment of invasive aspergillosis in the European Union but has not been evaluated as primary therapy for invasive aspergillosis.
[e] Dosage of itraconazole in treatment of invasive pulmonary aspergillosis depends on formulation. The dosage for tablets is 600 mg/day for 3 days, followed by 400 mg/day. Although used in some case reports, oral solution is not licensed for treatment of invasive aspergillosis. Parenteral formulation has been studied in a limited series using a dosage of 200 mg every 12 hours IV for two days, followed by 200 mg daily thereafter (whether this is an optimal dosage has not been defined).
[f] Most of these cases have been treated primarily with deoxycholate AMB in individual case reports. Although the preponderance of cases treated with voriconazole in the randomized trial consisted of pulmonary invasive aspergillosis, successful treatment of other cases of extrapulmonary and disseminated infection allows one to infer that voriconazole would also be effective in these cases so that voriconazole is recommended as primary therapy for most these patients.
[g] A more recent classification divides aspergilloma into 2 categories – chronic cavitary and single aspergilloma. The latter does not require antifungal therapy but does require surgery under some circumstances, and the former requires long-term antifungal therapy.

Table: Relative Indications for Surgery in Treatment of Invasive Aspergillosis[a]

Condition	Surgical Procedure	Comment
Pulmonary lesion in proximity to great vessels or pericardium	Resection of pulmonary lesion	May prevent erosion of pulmonary lesions into great vessels and into pericardial space

Condition	Surgical Procedure	Comment
Pericardial infection	Pericardiectomy	Pericardiectomy reduces organism burden around heart and prevents tamponade
Invasion of chest wall from contiguous pulmonary lesion	Resection of pulmonary lesion	Resection of lesion may relieve pain and prevent pleurocutaneous fistula
Aspergillus empyema	Placement of chest tube	Reduces burden of organism in closed space
Persistent hemoptysis from a single cavitary lesion	Resection of cavity	May prevent exsanguinating hemoptysis. Other measures to reduce hemoptysis include embolization of involved blood vessel and cauterization; however, recurrence of bleeding is possible.
Infection of skin and soft tissues	Debridement wide margin surgical resection	Surgical judgment used in extent of debridement and resection, if indicated
Infected vascular catheters and prosthetic devices	Removal of catheters and devices	Removal of infected catheters and devices provides definitive eradication
Endocarditis	Resection of vegetation and infected valve	Vegetations may be valvular or mural; single mural lesions are resectable, particularly if pedunculated
Osteomyelitis	Debridement of infected bone	Debridement of necrotic and infected bone reduces organism burden and allows better drug penetration. Surgical judgment determines extent of debridement
Sinusitis	Resection of infected tissues	Extent of debridement may vary from no intervention to wide resection, depending upon surgical judgment.
Cerebral lesions	Resection of	Extent of debridement may vary from

Condition	Surgical Procedure	Comment
	infected tissue	no intervention to complete resection depending upon location, neurological sequelae, accessibility, and surgical judgment

[a] Indications depend upon multiple variables, severity of lesion, surgical judgment and the ability of patient to tolerate the operative procedure, as well as potential role of alternative medical therapy.

Definitions:

Quality of Evidence

I. Evidence from at least one properly randomized, controlled trial
II. Evidence from one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Strength of Recommendation

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Reduction in morbidity and mortality from *Aspergillus* infection

POTENTIAL HARMS

Antifungal Therapy

- Deoxycholate amphotericin B (D-AMB) causes acute infusion-related reactions and dose-limiting nephrotoxicity. Infusion-related reactions include fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headaches, and bronchospasm.
- Infusion-related side effects of fever, chills, and rigor are less frequent with liposomal AMB (L-AMB) in comparison to those of D-AMB. However, individual cases of substernal chest discomfort, respiratory distress and sharp flank pain have been noted during infusion of L-AMB, and in a comparative study, hypoxic episodes associated with fever and chills were more frequent in amphotericin B colloidal dispersion (ABCD)-recipients than in D-AMB recipients. Mild increases in serum bilirubin and alkaline phosphatase have been observed with all three formulations.
- Voriconazole's profile of adverse reactions includes transient visual disturbances (characterized principally by photopsia), hepatotoxicity which may be dose-limiting (manifested by elevated serum bilirubin, alkaline phosphatase, and hepatic aminotransferase enzymes), skin rash (usually in sunlight-exposed areas), visual hallucinations, and others.
- Most observed reactions to itraconazole are transient, and include nausea and vomiting, hypertriglyceridemia, hypokalemia, and elevated hepatic aminotransferase enzymes. As itraconazole use may infrequently cause negative inotropic effects, it should be administered with caution to patients with ventricular dysfunction.
- The most frequently reported adverse effects of echinocandins include increased liver aminotransferase enzymes, gastrointestinal upset, and headaches.

Immunotherapy

- Granulocyte transfusions can be accompanied by transfusion reactions, including pulmonary dysfunction evidenced by hypoxia and the acute onset of adult respiratory distress syndrome-like pulmonary infiltrates. Granulocyte transfusions are also associated with transmission of cytomegalovirus (CMV) infection. In CMV-seronegative HSCT recipients, only CMV-seronegative donors should be used for granulocyte transfusions. As there has been an association with some of these reactions with simultaneous infusion of amphotericin, patients undergoing granulocyte transfusion with concurrent use of amphotericin B products usually have the amphotericin staggered by several hours from the granulocytes with careful monitoring for this complication.
- The long-term adverse effects of corticosteroids may result in profound immunosuppression and debilitating metabolic abnormalities, including diabetes mellitus, hyperlipidemia, and osteoporosis. Corticosteroid-induced immunosuppression may very rarely result in progression of allergic bronchopulmonary aspergillosis (ABPA) to invasive pulmonary aspergillosis. Itraconazole spares the effect of corticosteroids, but may interact with inhaled corticosteroids leading to iatrogenic Cushing's syndrome in rare cases. The

benefits of addition of itraconazole outweigh the risks of chronic administration of high dose prednisone.

Surgery

Surgery has been associated with a high morbidity and mortality. Pulmonary resection for aspergilloma is difficult surgery.

Refer to the original guideline document for additional information on adverse effects of antifungal therapy, immunotherapy, and surgery.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, the Infectious Diseases Society of America (IDSA) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA, Wingard JR, Patterson TF, Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008 Feb 1;46(3):327-60. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

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Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

T.J.W. has Cooperative Research & Development Agreements with Vicuron (subsequently acquired by Pfizer) and with Fujisawa (Astellas); T.F.P. has had grant support from Astellas Pharma US Inc., Enzon, Nektar Therapeutics, Merck & Co., Pfizer Inc., and Schering-Plough Corporation and has been a consultant for Merck & Co., Pfizer Inc., Schering-Plough Corporation, Basilea, Nektar Therapeutics, and Stiefel Laboratories, Inc. and has been on the speaker's bureau for Merck & Co., Pfizer Inc., and the Schering-Plough Corporation; E.J.A. has received grant support from Astellas, Curagen, Enzon, Nuvelo, OrthoBiotech, and Pfizer and has been a consultant for Astellas, Gilead Sciences, Merck, Pfizer, and Schering Plough and has been on the speaker's bureau for Astellas, Gilead

Sciences, Merck and Pfizer; D.W.D. has received grant support from Astellas, Merck, Pfizer, F2G, OrthoBiotech, Sigma-Tau, Indevus, Basilea, the Fungal Research Trust, the Wellcome Trust, t 1528 he Moulton Trust, and has been an advisor/consultant to Merck, Basilea, Vicuron (now Pfizer), Schering-Plough, Indevus, F2G, Nektar, Daiichi, Sigma Tau, Astellas and York Pharma. and has been paid for talks on behalf of Astellas, Merck, GSK, Chiron, AstraZenca and Pfizer and holds founder shares in F2G Ltd and Myconostica Ltd; R.H. has been a member of the advisory board for Astellas, Gilead, Merck, Pfizer, and Schering-Plough, and has been a member of the speaker's bureau of Gilead, Pfizer, Schering-Plough, and Zeneus; D.P.K. has received research support and honoraria from Schering-Plough, Pfizer, Astellas Pharma Inc., Enzon Pharmaceuticals, and Merck & Co., Inc.; K.A.M. has served as a consultant for Astellas, Enzon, Basilea, Merck, Nektar Therapeutics, Pfizer, Schering-Plough, Basilea, Merck and Nektar; V.A.M. is a consultant for Schering-Plough, Berlex and BiogenIDEC and is on the speaker's bureau for Amgen, Berlex, Celgene, Merck, Pfizer, and Schering-Plough; B.H.S. has received speaker honoraria from Merck and Pfizer and has served as on consultation/advisory boards for Pfizer, Schering-Plough, Berlex, and Enzon and has been a compensated member of a data review committee for Schering-Plough, and has been provided laboratory support from Enzon and Pfizer; W.J.S. has served on the speaker's bureaus for Pfizer and Astellas, and has served as a consultant for Astellas, Merck, and Enzon; D.A.S. has served on the advisory boards for Merck, Schering-Plough, and Gilead and has served as a speaker for Janssen, Enzon and Astellas and has received grant support from Merck, Pfizer, Gilead, Schering-Plough, Enzon and Astellas; J.A.V. has served on the speaker's bureaus for Schering-Plough and Astellas and has served as a clinical trial investigator for Schering-Plough, Merck, and Astellas and has served as a consultant for Merck; J.R.W. has received speaker's honoraria from Pfizer and Merck and has received grants from Merck and Pfizer and has served as an advisor for Pfizer, Merck, and Schering-Plough

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, Bennett JE, Walsh TJ, Patterson TF, Pankey GA. Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):696-709. [202 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Infectious Diseases Society of America (IDSA) Web site.

Print copies: Available from the University of Chicago Press; fax: (773) 702-6096.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Treatment of Aspergillosis. Pocketcard. Available from the International Guidelines Center Web site.
- Treatment of Aspergillosis. PDA version. Available from the Infectious Diseases Society of America (IDSA) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001. This NGC summary was updated by ECRI Institute on December 11, 2007. The updated information was verified by the guideline developer on January 7, 2008.

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