



Complete Summary

GUIDELINE TITLE

Practice guidelines for diseases caused by Aspergillus.

BIBLIOGRAPHIC SOURCE(S)

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]

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SCOPE

DISEASE/CONDITION(S)

Diseases caused by Aspergillus including:

- Invasive aspergillosis
- Pulmonary aspergilloma
- Allergic bronchopulmonary aspergillosis

GUIDELINE CATEGORY

Diagnosis
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review information on the diagnosis and treatment of three types of *Aspergillus* infections:

1. Invasive aspergillosis, involving several organ systems (particularly pulmonary disease)
2. Pulmonary aspergilloma
3. Allergic bronchopulmonary aspergillosis (ABPA)

TARGET POPULATION

Patients with or suspected of having diseases caused by *Aspergillus*

INTERVENTIONS AND PRACTICES CONSIDERED

Invasive aspergillosis

1. Antifungal therapy
 - Intravenous amphotericin B deoxycholate
 - Lipid-based amphotericin B
 - Oral itraconazole
 - Oral and intravenous triazole
2. Surgical excision
3. Combination chemotherapy
4. Immunotherapy

Aspergilloma

1. Surgical resection
2. Bronchial artery embolization
3. Radiation therapy
4. Endobronchial and intracavitary instillation of antifungals
5. Inhaled nebulized antifungals
6. Systemic antifungals

Allergic bronchopulmonary aspergillosis (ABPA)

1. Corticosteroids (e.g., prednisone)
2. Itraconazole

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

Not stated

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 at least one properly randomized, controlled trial
- II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of 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 applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Although the frequency of the diseases discussed in the guideline document is on the rise, there is a paucity of randomized comparative trials involving these entities; therefore, the recommendations represent a compromise and consensus among students of these diseases (i.e., the guideline authors). They have synthesized the recommendations from published and personal experience, including case series, open trials, and any comparative trials, as indicated.

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
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

The following provides a summary of the major recommendations presented in the guideline document. The reader is directed to the original guideline for a more extensive discussion of each of the topics presented below.

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-E) are repeated at the end of the Major Recommendations field.

Invasive aspergillosis

Because it is highly lethal in the immunocompromised host, even in the face of therapy, work-up must be prompt and aggressive, and therapy may need to be initiated upon suspicion of the diagnosis, without definitive proof (BIII).

Intravenous therapy should be used initially in rapidly progressing disease (BIII). The largest therapeutic experience is with amphotericin B deoxycholate, which should be given at maximum tolerated doses (e.g., 1–1.5 mg/kg/d) and should be continued, despite modest increases in serum creatinine levels (BIII). Lipid formulations of amphotericin are indicated for the patient who has impaired renal function or who develops nephrotoxicity while receiving deoxycholate amphotericin (AII). Oral itraconazole is an alternative for patients who can take oral medication, are likely to be adherent, can be demonstrated (by serum level monitoring) to absorb the drug, and lack the potential for interaction with other drugs (BII). Oral itraconazole is attractive for continuing therapy in the patient who responds to initial intravenous therapy (CIII). Therapy should be prolonged beyond resolution of disease and reversible underlying predispositions (BIII). Adjunctive therapy (particularly surgery and combination chemotherapy, also immunotherapy), may be useful in certain situations (CIII).

Aspergilloma

The optimal treatment strategy for aspergilloma is unknown. Therapy is predominantly directed at preventing life-threatening hemoptysis. Surgical removal of aspergilloma is definitive treatment, but because of significant morbidity and mortality it should be reserved for high-risk patients such as those with episodes of life-threatening hemoptysis, and considered for patients with underlying sarcoidosis, immunocompromised patients, and those with increasing *Aspergillus*-specific IgG titers (CIII). Surgical candidates would need to have adequate pulmonary function to undergo the operation. Bronchial artery embolization rarely produces a permanent success, but may be useful as a temporizing procedure in patients with life-threatening hemoptysis. Endobronchial and intracavitary instillation of antifungals or oral itraconazole may be useful for this condition. Since the majority of aspergillomas do not cause life-threatening hemoptysis, the morbidity and cost of treatment must be weighed against the clinical benefit.

Allergic bronchopulmonary aspergillosis

Although no well-designed studies have been carried out, the available data support the use of corticosteroids for acute exacerbations of allergic bronchopulmonary aspergillosis (AII). Neither the optimal corticosteroid dose nor the duration of therapy has been standardized, but limited data suggest the starting dose should be ~0.5 mg/kg/d of prednisone. The decision to taper corticosteroids should be made on an individual basis, depending on the clinical course (BIII). The available data suggest that clinical symptoms alone are inadequate to make such decisions, since significant lung damage may occur in asymptomatic patients. Increasing serum IgE levels, new or worsening infiltrate on chest radiograph, and worsening spirometry suggest that corticosteroids should be used (BII). Multiple asthmatic exacerbations in a patient with allergic bronchopulmonary aspergillosis suggest that chronic corticosteroid therapy should be used (BIII). Itraconazole appears useful as a corticosteroid sparing agent (BII).

Definitions of Strength of Recommendation and Quality of Evidence Ratings:

Quality of evidence:

- I. Evidence from at least one properly randomized, controlled trial
- II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of 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
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

Invasive aspergillosis

An aggressive diagnostic approach in patients at-risk and prompt institution of antifungal therapy may be essential for patient survival.

Pulmonary aspergilloma

- Prevent life-threatening hemoptysis
- Prevent the progression of pulmonary aspergilloma to invasive pulmonary aspergillosis, which is often fatal

Allergic bronchopulmonary aspergillosis (ABPA)

Corticosteroids are useful in the management of acute allergic bronchopulmonary aspergillosis (ABPA). Therapy aims to treat acute asthmatic exacerbations and avoiding end-stage fibrotic disease.

POTENTIAL HARMS

Antifungal Therapy

- Conventional amphotericin B is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity.
- Lipid formulations of amphotericin B, although offering several therapeutic advantages over conventional amphotericin B, are considerably more expensive, ranging from 10- to 20-fold higher in cost.
- One potential limitation of the azole antifungal drugs is the frequency of their interactions with coadministered drugs, which results in adverse clinical consequences. One type of azole-drug interaction may lead to decreased plasma concentration of the azole, related to either decreased absorption or increased metabolism of the azole. A second type of azole-drug interaction may lead to an unexpected toxicity of the coadministered drug, relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system.
- A second potential limitation of the azoles is the emergence of resistance of fungal organisms, especially *Candida* species, to fluconazole.

Combination Therapy

Flucytosine may exacerbate myelosuppression in patients with neutropenia, and maintaining nontoxic blood levels may be difficult when concurrent amphotericin is given, owing to the latter's tendency to impair function of the excretory route (renal) of flucytosine. Rifampin may have significant drug interactions, owing to potent hepatic enzyme-induction, particularly in transplant recipients who are already receiving glucocorticoids, cyclosporine, or tacrolimus, and this property also precludes the possibility of itraconazole use for weeks.

Surgery

Surgery has been associated with a high morbidity and mortality. Pulmonary resection is hazardous, owing to the presence of dense vascular adhesions and the possibility of aspergillus infection of the postsurgical space. Operative mortality is >7%, and serious postoperative complications, such as hemorrhage and bronchopleural fistulae, are common.

Subgroups Most Likely to Be Harmed:

- Patients with marginal renal function or patients receiving other nephrotoxic drugs.
- Immunocompromised patients and/or patients with HIV infection.
- Surgical risk factors are more common in clinically ill individuals with poor pulmonary function.
- Symptomatic abatement has been noted in patients with evidence of allergy (e.g., eosinophilia, total IgE elevation, and aspergillus scratch test positivity, etc.) given systemic corticosteroid therapy; however, such therapy raises the risk of conversion to invasive or disseminated disease and/or exacerbation of an undiagnosed concurrent infection.

QUALIFYING STATEMENTS

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Although the frequency of the diseases discussed in the guideline document is on the rise, there is a paucity of randomized comparative trials involving these entities; therefore, the recommendations represent a compromise and consensus among students of these diseases (i.e., the authors). They have synthesized the recommendations from published and personal experience, including case series, open trials, and any comparative trials, as indicated.

In addition, guidelines for prophylaxis and empirical therapy for invasive aspergillosis in neutropenic hosts have recently been published and are not addressed in this guideline.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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]

ADAPTATION

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

DATE RELEASED

2000 Apr

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: David A. Stevens, Virginia L. Kan, Marc A. Judson, Vicki A. Morrison, Stephen Dummer, David W. Denning, John E. Bennett, Thomas J. Walsh, Thomas F. Patterson, and George A. Pankey

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Infectious Diseases Society of America \(IDSA\) Web site](#). Also available in [HTML format](#).

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

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. *Clinical Infectious Diseases* 2001; 32:851-4.
- Gross PA. Practice guidelines for infectious diseases: Rationale for a work in progress. *Clin Infect Dis*. 1998 May; 26(5): 1037-41.
- Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of quality standards for infectious diseases. *Infectious Diseases Society of America. Clin Infect Dis* 1994 Mar; 18(3): 421.

Electronic copies: Available from the [Infectious Diseases Society of American \(IDSA\) Web site](#).

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

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.

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