Complete Summary

GUIDELINE TITLE

Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, Kauffman CA, Infectious Diseases Society of America. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008 Jun 15;46(12):1801-12. [78 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Chapman SW, Bradsher RW, Campbell GD, Pappas PG, Kauffman CA. Practice guidelines for the management of patients with blastomycosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):679-83.

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SCOPE

DISEASE/CONDITION(S)

Blastomycosis (disease caused by the fungus *Blastomyces dermatitidis*)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide recommendations for the optimal treatment of the pulmonary and extrapulmonary forms of blastomycosis
- To update and replace previous management guidelines for blastomycosis published in April 2000

TARGET POPULATION

Patients with blastomycosis

INTERVENTIONS AND PRACTICES CONSIDERED

1. Antifungal therapy
    - Amphotericin B deoxycholate
    - Lipid preparations of amphotericin B
    - Itraconazole (including monitoring of drug serum levels)
    - Fluconazole
    - Voriconazole
2. Considerations for antifungal therapy in immunosuppressed patients, pregnant women, and children

MAJOR OUTCOMES CONSIDERED

- Abatement of symptoms and signs of blastomycosis
- Eradication of *Blastomyces dermatitidis* from involved tissue
- Drug toxicity
- Relapse rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Review and Analysis

For the 2007 update, the Expert Panel completed the review and analysis of literature on the treatment of blastomycosis that has been published since 2000 and reviewed the older literature as well. Computerized literature searches of PubMed (January 2000 through July 2007) were performed. Only English-language literature was reviewed. Searches focused on studies of humans but included a few experimental animal studies and in vitro studies.

The search yielded 62 articles: 30 case reports, 16 reviews, 1 clinical practice guideline, and 15 studies. Only 1 randomized, comparative treatment trial comparing amphotericin B (AmB) with 2-hydroxystilbamidine for the treatment of blastomycosis has been reported. There are no randomized, blinded trials comparing the currently available agents for the treatment of blastomycosis. However, several prospective, multicenter treatment trials of individual antifungal agents were reviewed and accorded the greatest importance. Prospective and retrospective studies that represented the treatment experience of single institutions and individual case reports were given an intermediate importance. Finally, selected reports dealing with the in vitro susceptibility of *Blastomyces dermatitidis* and experimental animal models were considered to be relevant but of lowest importance.

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 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

In evaluating the evidence with regard to the treatment of blastomycosis, the Panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation. Recommendations for the treatment of blastomycosis were derived primarily from case reports and nonrandomized treatment trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A panel of experts prepared these guidelines; the panel was composed of the authors of the guidelines, all infectious diseases specialists from North America with expertise in blastomycosis. The panelists have both clinical and laboratory experience in blastomycosis (see Appendix, Table A1 in the original guideline document).

In evaluating the evidence with regard to the treatment of blastomycosis, the Panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines.

The Panel met on 7 occasions via teleconference to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, to make writing assignments, and to discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline.

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

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

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the Standards and Practice Guidelines Committee (SPGC) and the Board of Directors before dissemination.

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

Pulmonary Blastomycosis

1. For moderately severe to severe disease, initial treatment with a lipid formulation of amphotericin B (AmB) at a dosage of 3 to 5 mg/kg per day or AmB deoxycholate at a dosage of 0.7 to 1 mg/kg per day for 1 to 2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of 6 to 12 months, is recommended **(A-III)**.
2. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6 to 12 months, is recommended **(A-II)**.
3. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure **(A-III**)

Disseminated Extrapulmonary Blastomycosis

4. For moderately severe to severe disease, lipid formulation AmB, 3 to 5 mg/kg per day, or AmB deoxycholate, 0.7 to 1 mg/kg per day, for 1 to 2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day for a total of at least 12 months, is recommended **(A-III)**.
5. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6 to 12 months, is recommended **(A-II)**.
6. Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy **(AIII)**.
7. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure **(A-III)**.

Central Nervous System (CNS) Blastomycosis

8. AmB, given as a lipid formulation at a dosage of 5 mg/kg per day over 4 to 6 weeks followed by an oral azole, is recommended. Possible options for azole therapy include fluconazole, 800 mg per day, itraconazole, 200 mg 2 or 3 times per day, or voriconazole, 200 to 400 mg twice per day, for at least 12 months and until resolution of CSF abnormalities **(B-III)**.

Treatment for Immunosuppressed Patients with Blastomycosis

9. AmB, given as a lipid formulation, 3 to 5 mg/kg per day, or AmB deoxycholate, 0.7 to 1 mg/kg per day, for 1 to 2 weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with acquired immunodeficiency syndrome (AIDS) **(A-III)**.
10. Itraconazole, 200 mg 3 times per day for 3 days and then twice per day, is recommended as step-down therapy after the patient has responded to initial treatment with AmB and should be given to complete a total of at least 12 months of therapy **(B-III)**.
11. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure **(A-III)**.
12. Lifelong suppressive therapy with oral itraconazole, 200 mg per day, may be required for immunosuppressed patients if immunosuppression cannot be reversed **(A-III)** and in patients who experience relapse despite appropriate therapy **(CIII)**.

Treatment for Blastomycosis in Pregnant Women and in Children

13. During pregnancy, lipid formulation AmB, 3 to 5 mg/kg per day, is recommended **(A-III)**. Azoles should be avoided because of possible teratogenicity **(A-III)**.
14. If the newborn shows evidence of infection, treatment is recommended with AmB deoxycholate, 1.0 mg/kg per day **(A-III)**.
15. For children with severe blastomycosis, AmB deoxycholate, 0.7 to 1.0 mg/kg per day, or lipid formulation AmB, at a dosage of 3 to 5 mg/kg per day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg per day (up to 400 mg per day) as step-down therapy, for a total of 12 months **(B-III)**.
16. For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg per day (to a maximum of 400 mg orally per day) for 6 to 12 months, is recommended **(B-III)**.
17. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure **(A-III)**.

Definitions of Strength of Recommendation and Quality of Evidence Ratings

Quality of Evidence

I. Evidence from $\geq$1 properly randomized, controlled trial
II. Evidence from $\geq$1 well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from >1 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

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

Reduced morbidity and mortality

Subgroups Most Likely to Benefit

Immunocompromised patients and patients with progressive pulmonary disease or extrapulmonary disease.

POTENTIAL HARMS

- Drug-drug interactions are a major clinical issue in the use of azole antifungal agents.
- All azoles have been reported to cause hepatitis. Hepatic enzymes should be measured before starting therapy, at least at 2 to 4 weeks after therapy has begun, and every 3 months during therapy.

CONTRAINDICATIONS

CONTRAINDICATIONS

The azoles are teratogenic and embryotoxic in animals and should be avoided during pregnancy, especially during the first trimester. Long-term fluconazole administration during pregnancy has been associated with congenital anomalies.

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 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

Audit Criteria/Indicators
Personal Digital Assistant (PDA) Downloads

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

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, Kauffman CA, Infectious Diseases Society of America. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008 Jun 15;46(12):1801-12. [78 references] PubMed

ADAPTATION

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

DATE RELEASED

2000 Apr (revised 2008 Jun 15)

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

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Expert Panel complied with the Infectious Diseases Society of America (IDSA) policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested about employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Potential Conflicts of Interest: L.A.P. has served as a speaker and consultant to Schering-Plough and Pfizer. P.G.P. has received grant support from Schering-Plough, Pfizer, Merck, and Astellas; has been an adhoc consultant for Pfizer; and has been a speaker for Pfizer and Astellas. C.A.K. has received research grants from Merck, Astellas, and Schering-Plough and serves on the speaker's bureau for Merck, Astellas, Pfizer, and Schering–Plough. All other authors: no conflicts.

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GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Diseases Society of America (IDSA) Web site.

Print copies: Available from Dr. Carol A. Kauffman, Veterans Affairs Ann Arbor Healthcare System, 2215 Fuller Rd., Ann Arbor, MI 48105, Email: ckauff@umich.edu.

AVAILABILITY OF COMPANION DOCUMENTS

A PDA version of the original guideline document is available from Infectious Diseases Society of America (IDSA) Web site.

Performance measures are available in the original guideline document.

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 summary was updated by ECRI Institute on July 31, 2008. The updated information was verified by the guideline developer on August 19, 2008.

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