Mayo Clinic

Antifungal Algorithms

See Mayo Clinic Formulary Web site for additional algorithms and information (type "formulary" in your browser’s address line)
The Antifungal Task Force has composed a set of algorithms outlining the appropriate use of currently available antifungal agents. These algorithms include:

- Treatment for specific clinical syndromes and fungal pathogens.
- Detailed information on each antifungal agent available in the Mayo Clinic Formulary.

This booklet contains frequently used algorithms. For the complete list of antifungal algorithms, please see the Formulary Intranet site.

**What will the algorithms accomplish?**

The algorithms are intended to:

- Optimize and standardize patient care through selection of the most effective antifungal agent for a specific clinical situation or targeted fungal pathogen.
- Educate concerning appropriate, evidence-based treatment of fungal infections, empiric and pre-emptive therapy, appropriate use of each antifungal agent, and the formulation of the various agents.
- Provide cost-effective treatment strategies and reduce unnecessary drug expense. (In 2002, Mayo sites spent over $5 million on antifungal agents.)

**Compliance with algorithms**

Compliance with and adherence to the algorithm is expected. When ordering antifungal therapy, the infectious indication should be included on the order form. The Mayo Pharmaceutical Formulary Committee (MPFC) recognizes that the algorithms may not fit all cases of suspected or documented fungal infections. Alternative antifungal therapy ordered by a prescriber will be administered promptly to the patient. The Infectious Disease Task Force will review situations where alternative agents are prescribed. Antifungal utilization information will also be reviewed to determine where the algorithms can be improved/modified based on new literature, cost, adverse effect, or other considerations. The Pharmacy and Therapeutics Committee supports the Antifungal Algorithms. Calls or interventions by pharmacists related to the algorithms are under the direction of the Pharmacy and Therapeutics Committee.
*Empiric Antifungal Treatment of Neutropenic Fever*

**Preferred Therapy**

**Voriconazole**
Consider IV induction therapy (risk/benefit for continued IV use if CI\textsubscript{Cr} < 50 ml/min)
Consider oral for maintenance therapy and in presence of renal insufficiency

**Alternatives**

**Ambisome**
3-5 mg/kg/day
(recommend starting at 3 mg/kg/day for stable patient)

**Itraconazole**
(risk benefit for IV if CI\textsubscript{Cr} < 30 ml/min)

**Under investigation**

**Caspofungin**

*Reassess Therapy When Culture/Susceptibility Results are Available*
*Empiric Therapy In Immunocompromised Patients for Infiltrative/Nodular Pulmonary Disease

considerations include Aspergillus, Cryptococcus, Histoplasma, Blastomyces, Coccidioides, Zygomycetes and others

**Preferred Therapy**

**Voriconazole**
(if Zygomycetes not suspected)
Consider IV induction therapy (risk/benefit for continued IV use if CI\textsubscript{Cr} < 50 ml/min)
Consider oral for maintenance therapy and in presence of renal insufficiency

**Alternatives**

- **Ambisome**
  5 mg/kg/day

- **Itraconazole**
  (if Zygomycetes not suspected)
  (risk benefit for IV if CI\textsubscript{Cr} < 30 ml/min)

- **Caspofungin**
  (if Zygomycetes, Cryptococcus and endemic mycoses not suspected)

*Reassess Therapy When Culture/Susceptibility Results are Available*
Definitive invasive aspergillosis as defined by a clinically compatible illness plus ≥1 of the following:

a. Isolation of aspergillus from a normally sterile site.

b. Hyphae consistent with aspergillus in a biopsy specimen or aspirate plus culture of aspergillus from the same organ (i.e., lung tissue, transbronchial biopsy, liver, CNS, etc.).

c. Radiographic pulmonary lesions, not attributable to other factors, and a culture of bronchoalveolar lavage fluid that is positive for aspergillus.*

d. Tracheobronchial lesions confirmed by bronchoscopy, with a positive culture for aspergillus.

Probable invasive aspergillosis as defined by a clinically compatible illness plus ≥1 of the following:

a. Hyphae consistent with aspergillus in a tissue biopsy or aspirate without culture.

b. Presence of a “halo” or “air-crescent” sign on CT scan of the chest.*

c. Radiographic pulmonary lesions, not attributable to other factors, with either hyphae consistent with aspergillus from BAL fluid or a sputum culture that was positive for aspergillus.*

d. Clinical evidence of sinusitis, opacification of a sinus on CT/MRI and the presence of hyphae or positive culture for aspergillus from a lesion in the nose or paranasal sinus.*

*in a neutropenic or transplant patient
Candidemia/Invasive Candidiasis in Hem/Onc/Transplant/Immunocompromised Patient

Neutropenic/Immuno-compromised, *Unstable*
- **Preferred Therapy**
  - **Caspofungin** 70 mg load, 50 mg daily
  - Fluconazole load then 400-800 mg daily
  - Caspofungin 70 mg load, 50 mg daily
- **Alternative**
  - **Ambisome**

Without Speciation
- **Preferred Therapy**
  - **Caspofungin** 70 mg load, 50 mg daily
  - Fluconazole load then 400-800 mg daily
  - Caspofungin 70 mg load, 50 mg daily
- **Alternatives**
  - Voriconazole
  - Ambisome

Non-neutropenic, Stable
- With Speciation
  - C. albicans, C. tropicalis, C. paropsilosis (consider susceptibilities but usually fluconazole susceptible)
  - Assume
    - fluc ≤ 8 S
    - fluc 16-32 SDD
    - fluc >64R
  - Preferred Therapy
    - Fluconazole load then 400 mg daily
    - Caspofungin 70 mg load, 50 mg daily
    - Fluconazole load then 800 mg daily
    - Caspofungin 70 mg load, 50 mg daily
  - Check susceptibilities
  - Other species

Fluconazole maintenance therapy may be considered for susceptible organisms in a stable patient after clearance of organism from blood.*

*Consider addition of flucytosine for unstable patients*

*1. C. lusitaniae and C. guilliermondi can be ampho tolerant/resistant; azoles recommended*

*2. C. krusei and C. glabrata response to ampho may be dose dependent*
Documentation of at least one criterion is required for pharmacists to dispense a lipid amphotericin product drug without Infectious Disease Approval/Consultation or Department chair approval.

**Ambisome Ordered:**

1. **Renal Dysfunction (A, B, or C below)**
   A. Baseline renal dysfunction:
      Adult patient with serum creatinine $> 1.5$ (not on chronic hemodialysis) or creatinine clearance of $< 50$ ml/min.
      Pediatric patient with demonstrated renal dysfunction and not on chronic hemodialysis.
   B. Nephrotoxicity:
      Nephrotoxicity to amphotericin B deoxycholate as marked by drop in creatinine clearance to $< 50$ ml/min or 2-fold increase in serum creatinine.
   C. Concurrent Nephrotoxins:
      Patient on concomitant cyclosporine, tacrolimus, or aminoglycoside therapy.

2. **Hematology/Oncology or Transplant Patient** (adult or pediatric) if there is concern regarding possible renal dysfunction by amphotericin B deoxycholate and subsequent compromise in chemotherapy/immunosuppressant therapy.

3. **Serious infusion-related toxicity or other serious toxicity** (e.g., pulmonary toxicity, severe hyper/hypotension) to amphotericin B deoxycholate despite maximal supportive management; or previous documented severe adverse infusion-related reaction.

**Abelcet ordered:**
Patient meets at least one lipid amphotericin criterion above and has had a serious infusion-related or other toxicity related to Ambisome (e.g., pulmonary, hyper/hypotension).

If criteria above are not met, approval and/or consultation by Infectious Diseases or Department Chair approval is required.
(One dose may be dispensed pending approval if during evening/nighttime hours.)
### Alternatives

<table>
<thead>
<tr>
<th>Usual Dose</th>
<th>Amphotericin B Deoxycholate</th>
<th>Ambisome</th>
<th>Caspofungin</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-1.25 mg/kg/day</td>
<td>3-5 mg/kg/day</td>
<td>70 mg load then 50 mg once daily</td>
<td>Load then 200-800 mg daily IV or PO; dose depends on illness and susceptibility of organism</td>
<td>IV induction: 6 mg/kg q12h x 2 doses, then 4 mg/kg q12h; PO maint if &gt;40 kg: 200 mg bid (can incr to 300 mg bid)</td>
<td>IV: 200 mg q12h x 4 then 200 mg q24h (PO absorption is variable, Usual PO dose: 200 mg qd or 200 mg bid)</td>
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</table>

### Important Cautions
- Nephrotoxicity, hypokalemia, hypomagnesemia, infusion-related toxicities
- Nephrotoxicity and infusion-related toxicity (significantly lower incidence than amphi b deoxycholate), hypokalemia/hypomagnesemia
- Infrequent increased LFTs, use with cyclosporine may increase risk (risk/benefit)
- Hepatotoxicity, P450 drug interactions (lower degree than vori/itra)
- Visual disturbances (acuity, field, color)
- Hepatotoxicity, P450 drug interactions, IV: risk/benefit for CICr <50 ml/min due to accumulation of vehicle, (clinical significance unknown)
- Hepatitis, numerous drug interactions, negative inotropic effect/CHF reported rarely, variable absorption with tablet; IV: risk/benefit for CICr <30 ml/min due to accumulation of vehicle

### Excretion/ Metabolism
- Elimination: Primarily non-renal, not well-defined.
- Elimination: Primarily non-renal, not well-defined.
- Metabolism: Liver; for mod hepatic impairment, consider loading dose of 70 mg, and decreased maint. dose of 35 mg/day
- Elimination: Primarily renal; give loading dose and decreased maint. dose if CICr <50; numerous drug interactions
- Metabolism: Extensive in GI tract and liver - numerous drug interactions
- Metabolism: Extensive in GI tract and liver - numerous drug interactions

### Mayo Treatment Indications
(see Formulary Web site also for current FDA Indications)

<table>
<thead>
<tr>
<th>Preferred Option</th>
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<tbody>
<tr>
<td></td>
<td>5. Neutrop fever (investig)</td>
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<td>5. Fusarium</td>
<td>Alternative Option</td>
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<td>6. Cryptococcus</td>
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</tbody>
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2. Infiltrative/nodular lung disease (Zygomyces unlikely)
3. Suspected fungal sinusitis (Zygomyces unlikely)
4. Suspected disseminated fungal disease/skin lesions (Fusarium unlikely)