

Chapter 102

Approach to Aspergillosis in the ICU



102.1 Introduction

Invasive aspergillosis (IA) is a severe fungal infection predominantly affecting immunocompromised individuals or those with critical illnesses. The condition is associated with high morbidity and mortality rates, especially in intensive care unit (ICU) settings, due to delayed diagnosis and limited treatment windows. Effective management of IA requires a structured approach that involves identifying at-risk patients, recognizing clinical and diagnostic clues, and initiating timely antifungal therapy [1, 2] [Ref: Algorithm 102.1].

102.2 Assessing Risk Factors

The first step is to determine if the patient has risk factors for IA. Key risk factors include:

Severe Respiratory Illness:

- Acute Respiratory Distress Syndrome (ARDS)
- Ventilator dependence
- Chronic Obstructive Pulmonary Disease (COPD)
- Viral pneumonias such as influenza and COVID-19

Immunosuppressive Therapy:

- Corticosteroids
- Chemotherapy (e.g., induction/reinduction regimens for acute leukemia)
- Immunomodulatory agents

Underlying Conditions:

- Prolonged neutropenia
- Liver failure
- Subtle immune dysfunctions
- Hospitalized allogeneic HSCT recipients

ICU-Related Factors:

- Prolonged mechanical ventilation
- Use of broad-spectrum antibiotics

For patients without risk factors, monitor for new developments such as clinical deterioration or the emergence of new risk factors [3].

102.3 Assessing Clinical Signs

For at-risk patients, evaluate for clinical signs suggestive of IA:

- Fever unresponsive to broad-spectrum antibiotics
- Respiratory decline with worsening hypoxemia
- Hemoptysis or pleuritic chest pain

These signs, though nonspecific, raise suspicion for IA in critically ill patients, especially when unresponsive to standard therapies. If clinical signs are absent, reassess the patient only if new symptoms or risk factors develop.

102.4 Imaging Evaluation

CT scan: To be done when there is suspicion, regardless of chest radiograph findings. Obtain imaging studies, specifically a chest CT scan, to identify findings consistent with invasive pulmonary aspergillosis (IPA). Look for:

- Halo Sign: Ground-glass opacity surrounding a nodule.
- Wedge-Shaped Infarcts: Recently added as imaging criteria for probable IPA.
- Segmental or Lobar Consolidations: Inclusion enhances diagnostic sensitivity.
- Air Crescent Sign: May develop later in the disease

Bronchoscopy: Bronchoscopy and BAL should be done in patients with a suspicion of IPA (invasive pulmonary aspergillosis). BAL sample should be sent for routine culture and cytology as well as non-culture-based methods.

Imaging findings are often the first objective clues for IPA, as culture results may be delayed. The inclusion of wedge-shaped infarcts and segmental or lobar consolidations expands the radiological criteria, aiding in earlier diagnosis [4]. Consider alternative diagnoses but remain vigilant if clinical suspicion remains high.

102.5 Non-culture-Based Diagnostic Markers

Evaluate for fungal markers using advanced biomarker techniques:

- Galactomannan (GM) Assay:
- GM is not recommended for routine blood screening in patients receiving mold-active antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens.
- GM is an accurate marker for the diagnosis of IA in adults in certain patient subpopulations (hematologic malignancy, HSCT).
- β -D-Glucan Testing:
- Useful as a broad fungal biomarker (not specific for IA).
- *Aspergillus* PCR:
- Incorporated into the BM-AspICU algorithm for improved classification.
- Next-Generation Sequencing (NGS):
- Helpful in patients where biopsy is contraindicated.

Non-culture-based markers and molecular diagnostics like PCR and NGS enhance diagnostic sensitivity, especially in cases where imaging is inconclusive or invasive procedures are contraindicated. If markers are negative, move to step 5 (histopathological or sterile site identification).

102.6 Histopathology or Sterile Site Identification

If non-culture markers are inconclusive, attempt to identify *Aspergillus* in sterile body sites or tissue histopathology:

- Histopathological Examination:
- Look for hyphal structures or evidence of tissue invasion.
- Utilize rRNA sequencing when fungal invasion is observed.
- Sterile Site Sampling:
- Perform a biopsy or obtain fluid from a sterile site if clinically feasible.

Definitive diagnosis often requires direct visualization or isolation of the organism in sterile sites. Molecular diagnostics can provide additional confirmation. If no evidence is found, reconsider the diagnosis and evaluate for colonization or other conditions mimicking IA [1].

102.7 Initiating Antifungal Therapy

If IA is strongly suspected or confirmed, initiate antifungal treatment:

- First-Line Therapy:
- Voriconazole: Preferred due to its superior efficacy and tolerability.

- Dose: Loading dose of 6 mg/kg intravenous IV infusion or 400 mg BD orally for 24 hours, followed by a 4 mg/kg IV or 200 mg BID oral maintenance dose).
- Alternative Options:
- Isavuconazole: Effective against azole-resistant *Aspergillus fumigatus*.
- Loading dose: 372 mg PO/IV three times daily x six doses (48 hr).
- Maintenance: 372 mg PO/IV once daily.
- Liposomal Amphotericin B
- 3–5 mg/kg IV once daily
- Combination Therapy: Consider in refractory cases or when resistance is suspected.
- Susceptibility Testing:
- Essential for guiding therapy in the context of emerging azole resistance.
- Echinocandins:
- Echinocandins (micafungin or caspofungin) can be used in settings where azole and polyene antifungals are contraindicated.

Early initiation of appropriate antifungal therapy improves outcomes, reduces hospital costs, and shortens the length of stay. Awareness of azole resistance patterns is crucial for effective management. Reassess the diagnosis, consider susceptibility testing, and adjust therapy accordingly.

Adjunctive Measures:

- Reduce dose or avoid using immunosuppressive agents whenever possible.
- Colony-stimulating factors may be considered in neutropenic patients with diagnosed or suspected IA.
- Granulocyte Transfusion: in neutropenic patients with IA who are refractory or unlikely to respond to standard therapy, and for an anticipated duration of more than one week.
- Recombinant interferon- γ is recommended as prophylaxis in chronic granulomatous disease patients.
- Surgery for aspergillosis should be considered for localized disease that is easily accessible to debridement.

102.8 Monitoring Response to Therapy

Assess for clinical and radiological improvement following antifungal initiation:

- Clinical Improvement:
- Resolution of fever.
- Improved respiratory status.
- Radiological Improvement:
- Reduction in cavitary lesions or nodules.
- Serial monitoring of serum GM can be used; can also help to prognosticate.
- Therapeutic Drug Monitoring:

- Monitor antifungal drug levels to ensure therapeutic efficacy and minimize toxicity.

Continue antifungal therapy for 6–12 weeks, tailoring the duration to clinical response and patient-specific factors.

Reassess the diagnosis, consider combination antifungal therapy, explore emerging therapeutics, or evaluate for alternative conditions [2].

Refractory or Progressive Aspergillosis (Salvage Therapy)

- Individualized approach
- (i) Changing the class of antifungal, (ii) tapering or reversal of underlying immunosuppression when feasible, and (iii) surgical resection of necrotic lesions in selected cases.
- Antifungal from another class may be added to the ongoing regimen.
- Consider lipid formulations of AmB, micafungin, caspofungin, posaconazole, or itraconazole.

102.9 Host-Specific Tailoring

Customize diagnostic and therapeutic approaches based on the patient's immune status and comorbidities:

- Immune Status Assessment:
- Utilize the 2019 EORTC/MSGERC definitions for stratification.
- Comorbidity Considerations:
- Adjust treatment plans for patients with liver failure, renal impairment, or other significant comorbidities.

102.10 Extrapulmonary Aspergillosis

- CNS Aspergillosis: Primary Therapy: Voriconazole. Liposomal Amphotericin B in case of intolerance or refractory to Voriconazole.
- Endophthalmitis: Systemic oral or intravenous voriconazole plus intravitreal voriconazole or intravitreal AmB deoxycholate.
- Paranasal Sinus: Surgery and either systemic voriconazole or a Liposomal Amphotericin B.
- *Aspergillus* Endocarditis, Pericarditis, and Myocarditis: Early surgical intervention combined with Voriconazole or Liposomal Amphotericin B. Consider life-long antifungal therapy post surgery/valve replacement surgery.
- *Aspergillus* Osteomyelitis and Septic Arthritis: Surgery along with Voriconazole.
- *Aspergillus* Peritonitis: Removal of peritoneal dialysis catheter plus Voriconazole.

- Esophageal, Gastrointestinal, and Hepatic Aspergillosis: Voriconazole and surgery to treat/prevent complications like perforation, obstruction, infarction, or hemorrhage.
- Renal Aspergillosis: Voriconazole plus surgery (decompression with local instillation of Amphotericin B deoxycholate in the presence of ureteric obstruction).

102.11 Management of Breakthrough Infections

- Aggressive and prompt attempt to establish a specific diagnosis with bronchoscopy and/or CT-guided biopsy.
- Therapeutic drug monitoring of Azole levels (if available).
- Change to an alternative class of antifungal with anti-*Aspergillus* activity.
- Reduction/Stop immunosuppression.

Empirical Treatment:

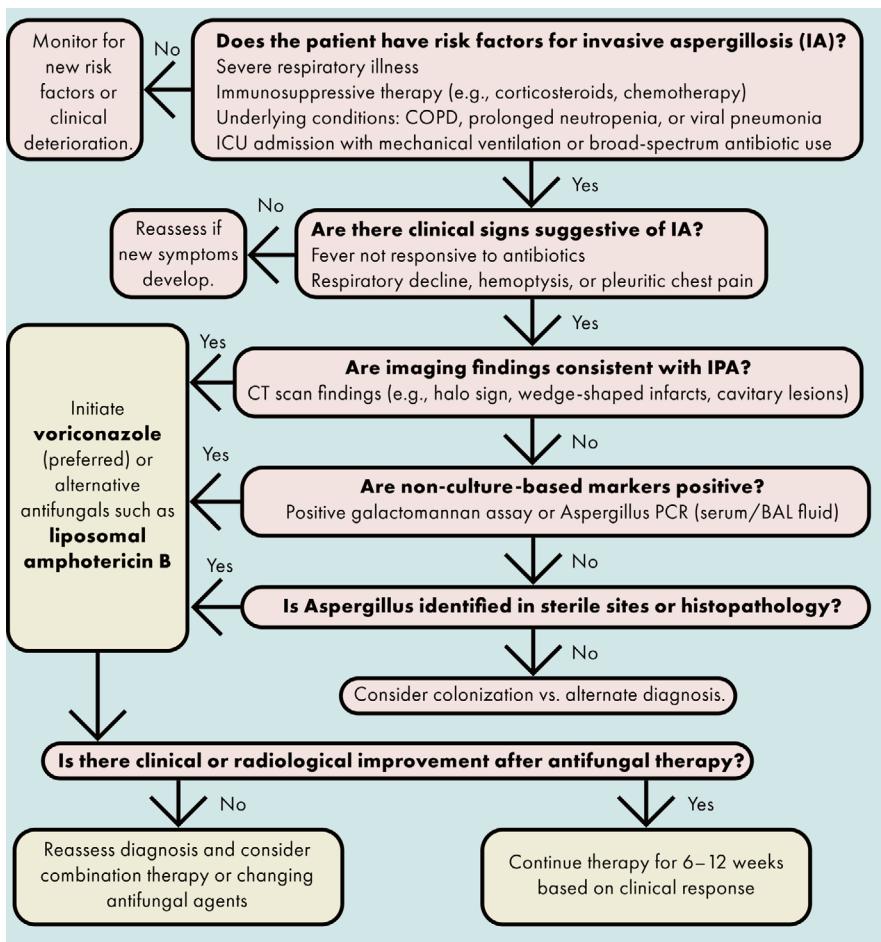
- High-risk patients with prolonged neutropenia with persisting febrile episodes not responding to broad-spectrum antibiotics.
- Avoid empirical therapy in neutropenia with <10 days duration.
- Use preemptive approach over empirical therapy: BAL fungal biomarkers such as GM or (1 → 3)- β -D-glucan in.

102.12 Conclusion

Managing IA in the ICU requires a vigilant, stepwise approach focused on early identification, accurate diagnosis, and prompt treatment. Key principles include:

1. Recognizing High-Risk Patients Early:
 - Including emerging risk groups with subtle immune dysfunctions
2. Utilizing Advanced Diagnostic Tools:
 - Incorporating updated biomarkers, molecular diagnostics, and expanded imaging criteria
3. Initiating Appropriate Antifungal Therapy Promptly:
 - Considering azole resistance and tailoring therapy accordingly
4. Monitoring and Tailoring Treatment:
 - Based on patient-specific factors and treatment responses

Adherence to this comprehensive algorithm can improve outcomes by minimizing delays in diagnosis and treatment, reducing economic burdens, and enhancing patient prognoses through personalized care strategies.

Algorithm 102.1: Approach to aspergillosis in the ICU**Bibliography**

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