Invasive pulmonary aspergillosis

June 14, 2020 by Josh Farkas

CONTENTS

- Basics [#basics]
- Epidemiology [#epidemiology]
- Presentation [#presentation]
- Investigations
  - Galactomannan [#galactomannan]
  - Beta-D-Glucan [#beta-D-glucan]
  - Sputum culture & fungal stain [#sputum_culture_&_fungal_stain]
  - PCR [#PCR]
  - Radiology [#radiology]
  - Bronchoscopy [#bronchoscopy]
  - Tissue diagnosis [#tissue_diagnosis]
- Overall approach to diagnosis [#approach_to_diagnosis]
- Treatment [#treatment]
- Special situations
  - Aspergillus complicating influenza [#invasiveaspergilluscomplcatinginfluenza]
  - Aspergillus complicating COVID-19 [#invasiveaspergilluscomplcatingCOVID19]
- Summary [#summary]
- Podcast [#podcast]
- Questions & discussion [#questions &_discussion]
- Pitfalls [#pitfalls]

basics
Aspergillus is a *ubiquitous* fungus. We are all exposed to it, but our immune systems generally resist it. However, as an opportunistic infection, it can cause disease in specific situations. Invasive pulmonary aspergillosis occurs in roughly two situations:

1. **Primary** pneumonia in a patient with profound immunocompromise (e.g., most commonly prolonged neutropenia). This is the classic form of invasive pulmonary aspergillus which has been recognized for decades.
2. **Secondary** nosocomial pneumonia which occurs among patients who are admitted to the ICU for another reason (e.g., ARDS due to influenza). This is fairly common, yet is an extremely challenging diagnosis. Critically ill patients super-infected with aspergillus usually aren't profoundly immunosuppressed. This superinfection can mimic bacterial pneumonia or simply ARDS, with a tendency to blend in among the numerous other issues which the patient has.

### epidemiology

**risk factors**

- **High-risk**
  - Neutropenia >10 days
  - Allogeneic stem-cell transplantation
  - Prolonged steroid use (at least 0.3 mg/kg/day prednisone equivalents for >3 weeks)
  - Treatment with recognized T-cell immunosuppressant
  - Inherited severe immunodeficiency (e.g., chronic granulomatous disease)
  - Severe influenza (and possibly COVID-19??)

- **Intermediate risk**
  - Neutropenia <10 days
  - Steroid use (less than 0.3 mg/kg/day prednisone equivalents for >3 weeks)
  - COPD
  - Cirrhosis
  - Malignancy treated with cytotoxic chemotherapy
  - Lung transplant, small bowel transplant, autologous stem cell transplantation
  - Advanced AIDS (e.g., CD4 count <50, or neutropenia due to antiviral therapy)

- **Low risk**
  - Non-lung solid organ transplantation (heart, kidney, liver, pancreas)
  - Short course steroid (e.g., <7 days)
  - Prolonged ICU stay
  - Diabetes
  - Renal failure, hemodialysis
  - Malnutrition, alcoholism

### presentation

*Invasive pulmonary aspergillosis tends to present differently in neutropenic and non-neutropenic patients. However, there may be overlap between these two presentation types. Overall, patients generally develop severe respiratory failure leading to intubation.*

**neutropenic patients: angioinvasion mimics pulmonary embolism • pneumonia**

- *Infection may initially center on the pulmonary arteries and behave a bit like a pulmonary embolism.*
- *Refractory fever* is a central finding (may persist even despite anti-fungal therapy).
- Signs of pulmonary infarction
  - Dry cough
  - Pleuritic chest pain
  - Hemoptysis (which can be massive).
- Metastatic infection may extend beyond the lungs

https://emcrit.org/ibcc/aspergillosis/
Abscesses in brain, liver, spleen, kidney
Skin lesions can be diagnostically helpful if present.

Dyspnea is a prominent symptom.
Copious sputum production is often seen.
Fever and chest pain are less frequent than in neutropenic patients.
This frequently occurs in the context of an intubated patient with ARDS. It may present as either a ventilator-associated pneumonia or simply "refractory ARDS."

**non-neutropenic patients: mimics pneumonia**

Course is overall slower and with less prominent fever, making diagnosis more difficult. ([32140409](https://pubmed.ncbi.nlm.nih.gov/32140409/))

**serum galactomannan**

Most common cutoff is >0.5. In severely immunosuppressed patients, this cutoff yields a sensitivity of ~75% and a specificity of ~85%. ([ATS guideline 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))

Sensitivity is lower in non-neutropenic patients (perhaps ~50%), because circulating neutrophils will clear the galactomannan antigen. ([30299367](https://pubmed.ncbi.nlm.nih.gov/30299367/)) Anti-fungal prophylaxis or therapy may likewise decrease sensitivity.

Specificity is very good, but not perfect (~90%):

- Galactomannan cross-reacts with some other fungal antigens (e.g., penicillium species now renamed talaromycosis, histoplasmosis, fusarium species).
- False-positive results may also be caused by materials contaminated with galactomannan (e.g., some blood transfusion bags, some manufactures of plasmalyte, and in one case ingestion of ice-pops).
- Historically, piperacillin-tazobactam has caused false-positive results, but currently this doesn't seem to be an issue. ([ATS guideline 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))

**bronchoalveolar lavage (BAL) galactomannan**

The most commonly used cutoff is >0.5 optical density index. This yields a sensitivity of 79% with specificity of 84%. ([ATS guideline 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))

In non-neutropenic patients, BAL galactomannan may be superior to serum galactomannan, since the infection is centered on the airways. ([32140409](https://pubmed.ncbi.nlm.nih.gov/32140409/); [31361683](https://pubmed.ncbi.nlm.nih.gov/31361683/)) In one series of patients with post-influenza aspergillosis, sensitivity was 94%. ([30299367](https://pubmed.ncbi.nlm.nih.gov/30299367/))
basics

- Beta-D-glucan is a cell wall component of nearly all fungi (except cryptococcus and zygomycetes).
- This shouldn't be used as the sole serum test, but may be useful in combination with galactomannan. ([ESCMID18](https://pubmed.ncbi.nlm.nih.gov/29544767/))

sensitivity for invasive aspergillus

- Sensitivity ~75%. ([31970725](https://pubmed.ncbi.nlm.nih.gov/31970725/))
- Sensitivity is not reduced by the use of antifungal agents. Beta-D-glucan might have superior sensitivity compared to galactomannan in patients who aren't neutropenic.

specificity for invasive aspergillus

- Beta-D-glucan is less specific than galactomannan, perhaps ~80%. ([31970725](https://pubmed.ncbi.nlm.nih.gov/31970725/))
  - (1) False-positive results may occur due to hemodialysis with cellulose membranes, wound packing with gauze, albumin, or intravenous immunoglobulin.
  - (2) Positive results can also result from other fungal infections (e.g., Pneumocystis Jiroveci, histoplasmosis, blastomycosis, Candida colonization or invasive infection) or certain bacteria which contain beta-glucans (e.g., Pseudomonas aeruginosa).

sputum culture & fungal stain

sputum culture

- Sensitivity
  - Aspergillus overall is difficult to culture, with sputum culture sensitivity in the 30-50% range.
  - BAL culture sensitivity is 30-60%. ([ATS guideline 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))
- The specificity may be on the order of ~50% among intubated patients, where the rate of colonization is fairly high. Overall, the significance of a positive result varies greatly depending on the clinical context (e.g., degree of immunosuppression and background rate of colonization).
- Another limitation is that the culture usually takes 1-3 days to grow. Furthermore, speciation requires sporulation to occur, which can take even longer.

sputum evaluation with fungal stain

- Sputum should be evaluated for fungal organisms using a cytological stain to identify them (e.g., Gomori methenamine silver). Aspergillus species have septated hyphae with acute angle branching (with a similar appearance compared to Scedosporium species and Fusarium species).
- The combination of positive culture plus positive fungal staining may be more suggestive of true infection (rather than colonization).

PCR

serum PCR

- Sensitivity is ~80%, with specificity of ~75%. ([ATS guidelines 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))
- This is probably less useful in non-neutropenic patients, among whom Aspergillus is less likely to spread hematogenously.

bronchoalveolar lavage PCR

- Sensitivity is 90%. ([ATS guidelines 2019](https://pubmed.ncbi.nlm.nih.gov/31469325/))
- A positive bronchoalveolar PCR doesn't distinguish between colonization versus invasive infection. Thus, the specificity will depend on the clinical context (as with a sputum culture).
  - A positive PCR doesn't prove invasive aspergillosis, but a negative PCR argues strongly against this diagnosis.
• PCR can also be performed using a tracheal aspirate in intubated patients unable to undergo bronchoscopy, although the precise yield is unclear. (32343223)

CT scan is the modality of choice

• CT scan is superior to chest X-ray in patients with immunosuppression and possible invasive aspergillosis. (ESCMID18)

neutropenic patients may present with a classic fungal pattern

• In neutropenia, infection often initially centers on the blood vessels. This leads to pulmonary infarction, with subsequent necrosis of infarcted tissue leading to cavitation.
• Initial finding is often nodular infiltrates.
  • Patchy, nodular opacities reflect infarction. These can be pleural-based and wedge-shaped.
  • Nodular infiltrates may be surrounded by ground-glass opacification due to hemorrhage, generating a “halo sign.”
• Later on, cavitation occurs. In neutropenic patients, this may coincide with recovery of the bone marrow and an increase in neutrophil count.
  • Necrosis of lung tissue creates cavities in the lung. The initial cavitation process yields an air-crescent sign (where there is a sliver of air within a forming cavity).
  • Clinically, cavitation often correlates with the development of hemoptysis.

non-neutropenic patients often have nonspecific imaging

• In non-neutropenic patients, infection often centers on bronchi and alveolar tissue (bronchoinvasion).
• This leads to a pattern of bronchopneumonia with airspace consolidation, which may look like other forms of pneumonia.
  • A “tree in bud” pattern may result from infection of bronchioles.
  • Thickening of trachea or bronchial walls may be seen.
• Classic features of aspergillosis can be seen in non-neutropenic patients (e.g., nodular infiltrates with halo sign, cavitation, and air-crescent signs). If present, these can be useful diagnostic clues, but they are infrequently seen.

Bronchoscopy

Bronchoscopy should be considered if the patient is stable enough to tolerate this (especially among patients who are already intubated).

Tests which may be obtained include:

• Culture and fungal stain (more on this above)
• Galactomannan (more on this above)
• PCR (more on this above)

Airway examination for Aspergillus plaques

• Invasive pulmonary aspergillosis may be accompanied by Aspergillus tracheobronchitis in up to 15% of patients. (30299367)
• Aspergillus tracheobronchitis is diagnosed on the basis of characteristic-appearing lesions seen in the trachea and large bronchi (findings may include ulceration, nodule, pseudomembrane, or plaque). Visualization of these lesions strongly supports invasive disease.
tissue diagnosis

- Definitive diagnosis requires tissue biopsy showing invasion of tissue. There are roughly three different ways to obtain lung tissue, each of which carries substantial risks:
  - (1) Surgical biopsy (i.e., wedge biopsy).
  - (2) Bronchoscopy with trans-bronchial biopsy.
  - (3) Interventional radiology trans-thoracic needle biopsy.
- Most critically ill patients are too unstable to undergo these procedures (due to risks of bleeding and pneumothorax).

[1] Suspicion for pulmonary aspergillosis

A trigger to evaluate for pulmonary aspergillosis is typically one of the following:

- Sputum culture or smear reveals Aspergillus.
- Imaging findings are highly suggestive of a fungal infection (e.g., nodular infiltrates with cavitation).
- Patient has a very high risk for aspergillosis (e.g., prolonged neutropenia) with persistent fevers or lung infiltrates.
- “Refractory pneumonia” marked by a combination of the following features:
  - i) Lung infiltrates with respiratory failure
  - ii) Refractory to antibiotics
iii) Underlying risk factors for aspergillosis

- Investigation of ventilator-associated pneumonia

**[2] Diagnostic workup for aspergillosis**

*This will vary depending on clinical context and the index of suspicion. Typical elements include the following:*

- CT scan of the chest
- Serum galactomannan antigen and beta-D-glucan
- Sampling of the lung if possible:
  - Endotracheal aspirate for culture, PCR, and fungal stain (if the patient is intubated and too unstable for bronchoscopy)
  - Bronchoalveolar lavage for culture & fungal stain, PCR, and galactomannan (if it can be accomplished safely)

**[3] Integration of data**

*Having collected several data points, the next step is to integrate this information to reach a clinical decision. Key factors to consider are mycology, imaging, epidemiology, and clinical presentation:*

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mycology</th>
<th>Imaging</th>
<th>Epidemiology</th>
<th>Clinical features &amp; illness severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Serum Galactomannan (+)</td>
<td>CT scan suggests fungal infection, for example: +Dense nodules, +/- leuco sign</td>
<td>Neutropenia &gt;10 days</td>
<td>Severe respiratory failure requiring intubation (especially if failing to respond to conventional ti)</td>
</tr>
<tr>
<td></td>
<td>BAL fluid strongly Galactomannan positive (OD &gt;1.0)</td>
<td>Vascular tree, cavity formation</td>
<td>Allogeneic stem-cell transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroid use (&gt;0.3 mg/kg/day x 3 wks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment with T-cell immunosuppressants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhaled severe immunodeficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intubated patient with influenza or COVID-19</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>BAL fluid Galactomannan positive (OD 0.3-1)</td>
<td>CT scan non-specific, yet consistent with fungal infection.</td>
<td>Neutropenia &lt;10 days</td>
<td>Suggestive signs/symptoms</td>
</tr>
<tr>
<td></td>
<td>BAL or ET aspirate culture-positive</td>
<td></td>
<td>Steroid use (&gt;0.3 mg/kg/day x 3 wks)</td>
<td>Persistent fever despite antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Advanced AIDS (CD4&lt;50 or neutropenia)</td>
</tr>
<tr>
<td></td>
<td>X-ray non-specific, yet consistent with fungal infection.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>BAL or ET aspirate culture-positive, microspore-positive</td>
<td>X-ray non-specific, yet consistent with fungal infection.</td>
<td>Kidney, heart, liver, pancreas transplant</td>
<td>Suggestive signs/symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Short course steroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malnutrition, alcoholism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal failure, hemodialysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protegated ICU stay</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>PCR: Negative</td>
<td>Normal imaging</td>
<td>No underlying conditions, Cytologic fibrosis pit may be colonized with aspergillosis (without invasive infection)</td>
<td>No suggestive signs/symptoms</td>
</tr>
<tr>
<td></td>
<td>Multiple sputum samples negative by culture &amp; stain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Diagnosis of invasive aspergillosis is based on an integration of clinical, imaging, laboratory, and epidemiological data. Most ICU patients are too unstable to undergo biopsy, as diagnosis is based on clinical judgement rather than on any single gold-standard test.*

Adapted from Go et al. *N Engl J Med* 371:1863; Infection Control: Clinical Care

**when to treat?**

- This is unclear. Especially in the ICU, precise guidelines regarding how to diagnose invasive aspergillosis and when to initiate therapy are lacking.
- Treatment initiation depends on overall clinical judgement and risk assessment. Treatment initiation shouldn't wait for definitive diagnosis (which is often impossible in critically ill patients). Furthermore, many lab tests are send-outs which take days to return. When in doubt, it may be reasonable to initiate treatment with voriconazole or isavuconazonium while *simultaneously* obtaining additional diagnostic tests.

**voriconazole is traditionally the front-line agent**

- Typical dose is 6 mg/kg q12hr for one day followed by 2-4 mg/kg q12hr. It may be administered intravenously or orally (with excellent absorption).
- Voriconazole is metabolized in the liver by CYP2C19 and CYP3A4 systems, leading to numerous drug-drug interactions.
- Major side-effects include visual disturbance, hepatoxicity, skin rash, neurological symptoms, and QT prolongation.
- Intravenous voriconazole is contraindicated in renal dysfunction, due to its formulation in a cyclodextrin vehicle. However, *enteral* voriconazole is safe in this situation.
Therapeutic drug monitoring
- Check 3-5 days after treatment initiation and consider repeating the following week (or more frequently PRN). (ESCMID18 [https://pubmed.ncbi.nlm.nih.gov/29544767/])
- The target serum trough is 1-5.5 mg/L for most patients. Higher trough levels (2-6 mg/L) are recommended in multifocal disease, disseminated disease including CNS involvement, or resistant strains. (ESCMID18 [https://pubmed.ncbi.nlm.nih.gov/29544767/])

**isavuconazole**

- This is an alternative front-line treatment. Isavuconazole could be preferred in patients when the specific diagnosis of aspergillosis is unclear, because it covers a broader range of fungal species.
- Isavuconazole was non-inferior to voriconazole in the SECURE trial, yet with better tolerance. (26684607 [https://pubmed.ncbi.nlm.nih.gov/26684607/])
  - The regimen used was 372 mg IV q8hr for two days, followed by 372 mg IV/PO once daily (note: 372 mg isavuconazonium sulfate is equivalent to 200 mg isavuconazonium base; different countries use different units).
- Advantages of isavuconazole over voriconazole:
  1. Broader spectrum of activity (including mucorales and endemic fungi).
  2. More favorable safety profile (especially regarding renal dysfunction and QT prolongation).
- Close attention is still needed for co-administration with medications that affect the CYP3A4 system. (31970725 [https://pubmed.ncbi.nlm.nih.gov/31970725/])

**liposomal amphotericin-B**

- Not generally a front-line therapy, due to nephrotoxicity.
- May be indicated in selected situations:
  1. Hepatic failure
  2. Azole-resistant Aspergillus

**echinocandins (e.g., micafungin, caspofungin)**

- These are not usually recommended for monotherapy.
- Echinocandins exert synergistic activity when combined with triazoles (e.g., voriconazole). Combination antifungal therapy isn't usually recommended as primary treatment, but can be used in the following situations:
  1. Salvage therapy due to clinical failure of an azole
  3. High regional rates of azole-resistance
  4. Treating a species with higher rates of resistance (e.g., Aspergillus calidoustus).

**reduction of immunosuppression**

- Depending on the context, immunosuppression should be limited as much as possible.

**sensitivity testing & infectious disease consultation**

- Determination of species and their drug sensitivities should be performed if possible.
- Some PCR-based tests offer the ability to detect azole resistance very rapidly.
- Infectious disease specialists will generally be involved at this point. Patients will require long-term therapy with antifungal agents and infectious disease follow-up.

**invasive aspergillosis complicating influenza**

- Determination of species and their drug sensitivities should be performed if possible.
- Some PCR-based tests offer the ability to detect azole resistance very rapidly.
- Infectious disease specialists will generally be involved at this point. Patients will require long-term therapy with antifungal agents and infectious disease follow-up.

**epidemiology**

- Retrospective series have found that invasive aspergillosis complicates ~7-19% of ICU patients with influenza. Given challenges in making the diagnosis, it's possible that some studies have under-estimated this. Overall, it might be reasonable to guess that roughly ~5-10% of...
Invasive pulmonary aspergillosis complications in ICU patients with influenza-related ICU deaths may be precipitated by Aspergillus superinfection.

- The risk of Aspergillus seems to be highest following H1N1 influenza.
- Aspergillus infection may be diagnosed relatively soon in the ICU course (a median of 3-5 days after admission).
- Aspergillus infection is common in severe influenza, even in the absence of typical risk factors (e.g., immunosuppression).

Clinical implications

- There should be a high index of suspicion for aspergillosis among ICU patients with influenza who aren't responding to conventional therapies.

Epidemiology

- Data regarding COVID-19 is rapidly emerging and still incomplete. As in other contexts, it is challenging to distinguish between colonization versus invasion. Nonetheless, several reports suggest that COVID-19 patients are susceptible to invasive pulmonary aspergillosis in a similar fashion to severe influenza patients (section above).

  - Aspergillus was detected an average of one week following intubation. (32488446)

  - Nodular infiltrates on CT scan were often reported. (3239350)
There should be a high index of suspicion for invasive aspergillosis among intubated COVID-19 patients who aren't responding to conventional therapies.

When evaluating for superinfection among intubated COVID-19 patients, respiratory specimens should be tested for Aspergillus in addition to bacterial pathogens (e.g., using PCR, fungal stains, and galactomannan). Serum galactomannan may also be helpful.

One center instituted prophylactic nebulized amphotericin B among intubated COVID-19 patients. This concept may bear further investigation. ([32488446](https://pubmed.ncbi.nlm.nih.gov/32488446/))

**summary**

([back to contents](#top))
Invasive pulmonary aspergillosis

Key red flags for possible aspergillosis

- You get lucky and trip over it:
  - Sputum culture shows Aspergillus.
  - CT shows nodules, cavitation, or halo signs.
  - Pneumonia in patient with neutropenia for >10 days, chronic steroid use, or stem cell transplantation.
  - Nosocomial complication of critical illness:
    - When you’re evaluating for ventilator-associated PNA (especially if not responding to antibiotics).
    - Intubated patient with viral pneumonia who isn’t recovering (especially influenza or COVID-19).

Consider risk factors for aspergillosis, how well it fits the clinical picture, and competing diagnoses. If there is persistent concern, then investigate further.

Evaluation for possible aspergillosis

- Chest CT scan
  - Nodules & cavitation support aspergillosis.
  - Non-specific infiltrates can be seen as well (especially in non-neutropenic patients).
- Bloodwork
  - Galactomannan & beta-D-glucan antigens
  - PCR for Aspergillus if immunosuppressed
  - Endotracheal aspirate if unable to tolerate bronch
  - Culture & fungal stain
  - PCR for Aspergillus
- Bronchoscopy with lavage if safe to do so:
  - Culture & fungal stain
  - PCR for Aspergillus
  - Galactomannan antigen

Integrative diagnosis of invasive aspergillosis among ICU patients (without biopsy evidence)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mycology</th>
<th>Imaging</th>
<th>Epidemiology</th>
<th>Clinical features &amp; illness severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Serum Galactomannan (*)</td>
<td>CT scan suggests fungal infection, for example: Nodules Right-lung sign Carina formation</td>
<td>Neutropenia &gt;10 days Allogeneic stem-cell transplantation Steroid use (≥0.3 mg/kg/day x 3 wks) Treatment with T-cell Immunosuppressant Inhhibited severe Immune deficiency Intubated patient with influenza or COVID-19</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>BAL fluid Galactomannan positive (OD 0.5-1)</td>
<td>CT scan non-specific, yet consistent with fungal infection.</td>
<td>Neutropenia ≤10 days Steroid use (≥0.3 mg/kg/day x 3 wks) COPD Cirrhosis Multifocal x/p cysts/foci Chronic Lung or mal debranching transplant, allogeneic stem cell transplantation Advanced AIDS (CD4&lt;5 or neutropenia)</td>
<td>Suggestive signs/symptoms Persistent fever despite antibiotics Pneumonia refractory to antibiotics Hemoptysis Pleuritic chest pain</td>
</tr>
<tr>
<td>Low</td>
<td>BAL or ET aspirate culture-positive x-ray microscopy-positive</td>
<td>X-ray non-specific, yet consistent with fungal infection.</td>
<td>Kidney, heart, liver, pancreas transplant Short course steroid Malnutrition, alcoholism Diabetes Renal failure, hemodialysis Prolonged ICU stay</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>PCR: Negative</td>
<td>Normal imaging</td>
<td>No underlying condition. Cystic fibrosis pts may be colonized with aspergillus (without invasive infection).</td>
<td>No suggestive sign/symptoms</td>
</tr>
</tbody>
</table>

Diagnosis of invasive aspergillosis is based on an integration of clinical, imaging, laboratory, and epidemiological data. Most ICU patients are too unstable to undergo biopsy, so diagnosis is based on clinical judgement rather than on any single gold-standard test.

• Failure to recognize that invasive aspergillosis can manifest in different ways among different patient populations (e.g., angioinvasion with lung necrosis and high-grade fevers is common in neutropenia, but less common in non-neutropenic invasive aspergillosis).

• When testing for ventilator-associated pneumonia in the ICU, consider adding sputum analysis for Aspergillus in at-risk patients (especially patients with influenza or COVID-19).

Going further:

• Angioinvasive aspergillus (https://radiopaedia.org/articles/angioinvasive-aspergillosis?lang=us) (Radiopaedia, Mostafa El-Feky and Frank Gaillard et al.)

• Airway invasive aspergillus (https://radiopaedia.org/articles/airway-invasive-aspergillosis?lang=us) (Radiopaedia, Naim Qaqish and Yuranga Weerakkody et al.)

References


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.