Invasive Fungal Infections (IFI)

A Clinician’s Perspective – Joseph Brewer, MD
Fungal Infections

- Almost always in immune-compromised host
- Can involve almost any organ (lung, sinuses, heart, kidney, etc.)

**EORTC / NIAID-MSG definition for IFI**

- **Proven:** histopathological documentation of infection and a positive culture from a normally sterile body site
- **Probable:** host factors + clinical features + microbiological evidence
- **Possible:** host factors + clinical features BUT no microbiological support

*Picture Source: aspergillus.org.uk*
Clinically Significant Fungal Infections

Invasive Candidiasis
• Most common IFI and 4th most common cause of hospital acquired blood stream infection in USA.

Invasive Aspergillosis
• Second most common cause of invasive fungal infections.
• Mortality rate 90% in mostly severe immunocompromised patients (Cancer, HIV and Transplantation-SOT, HSCT).

Mucormycosis
• No routine serologic tests for mucormycosis are currently available.
• Regrettably, the diagnosis is too often first made at autopsy.

The clinical management is hampered by difficulties in diagnosis
### IFI in Patients with Solid Organ Transplantation

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>8-15%</td>
<td>50-60%</td>
</tr>
<tr>
<td>Lung</td>
<td>15-35%</td>
<td>30-75%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.5-6%</td>
<td>NR</td>
</tr>
<tr>
<td>Pancreas</td>
<td>9%</td>
<td>NR</td>
</tr>
<tr>
<td>Heart</td>
<td>2.2%</td>
<td>30%</td>
</tr>
<tr>
<td>HSCT</td>
<td>3.9% (Al)</td>
<td>50%</td>
</tr>
</tbody>
</table>

NR: not reported.

Fungal prophylaxis and transplant Abdala E et al. CLINICS 2012;67(6):681-684
Timing of IFI after Organ Transplantation

Emerging fungal infections in immunocompromised patients
Chian-Yong . Medicine Reports 2011
Whom To Treat?

- Treat all patients at risk.
- Prophylaxis vs. Empirical vs. Diagnostic approaches
Prophylaxis Approach

- Administer broad-spectrum antifungals to all high risk patients.
- Approach has proven to reduce IFIs but not fungal-free survival.

Limitations

- Drug toxicity
- Drug-drug interactions
- Interference with current diagnostic test (galactomannan assay)
- Induction of resistant fungi
- Breakthrough infections
- Cost
Early and Rapid Detection of Invasive Fungal Infections

- Patients with neutropenia
- Persistent or relapsing fever despite 4-7 days of broad-spectrum antibiotics
- Conventional radiology and laboratory findings
- Specific investigations for IFI such as CT scan, Galactomannan Assay

Limitations

- Low positive predictive value of persistent fever.
- May miss IFI in patients on steroids or immunosuppressive drugs.
- Does not identify breakthrough infections.
- Long work up results in delayed therapy or interventions.
Diagnostic Approach

- Specificity and sensitivity of current test are limiting.

- Negative predictive values in some test may delay therapy in patients with an IFI.

- Multiple test require adequate logistic support from multiple disciplines to have a successful outcome.
# Early and Rapid Detection of Invasive Fungal Infections

## Accuracy of Diagnostic Testing for Invasive Fungal Infection

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture Methods</td>
<td>50%</td>
<td>100%</td>
<td>Gold standard; allows susceptibilities</td>
<td>Delay in diagnosis; low sensitivity</td>
</tr>
<tr>
<td>PCR Methods</td>
<td>90%</td>
<td>100%</td>
<td>Highest accuracy</td>
<td>Low commercial availability</td>
</tr>
<tr>
<td>β-D-glucan</td>
<td>70% - 100%</td>
<td>87% - 96%</td>
<td>Panfungal marker; high sensitivity and specificity</td>
<td>Many false-positive results;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>methodological concerns</td>
</tr>
<tr>
<td>Galactomannan</td>
<td>80% - 90%</td>
<td>80% - 90%</td>
<td>Increased accuracy for detection of Aspergillus in</td>
<td>Only for Aspergillus; many false-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hematologic illnesses</td>
<td>positive results; not useful in non-</td>
</tr>
<tr>
<td>Mannan or Antimannan</td>
<td>60% - 89%</td>
<td>80% - 84%</td>
<td>Good specificity and sensitivity with combined use</td>
<td>Results vary; limited experience</td>
</tr>
<tr>
<td>Combination</td>
<td>87%</td>
<td>84%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONFIDENTIALITY and SECRECY NOTICE:** This transmission (including attachments) are covered by the Communications Privacy Act, 18 U.S.C. Sections 2510-2521 and contain information that is proprietary, confidential and/or privileged. Any form of reproduction, dissemination, copying, disclosure, modification, distribution and or publication of this material is strictly prohibited.
Diagnostic Approach Improved with PCR

- This represents opportunity for early diagnosis.
- Offers specificity in identification of IFI agent
- Offers the ability to evaluate therapy effectiveness
- Provides the ability to identify breakthrough infections
- Provide the ability to identify resistant fungal species

**DNA-based techniques for detection are not yet fully standardized or commercially available**
How To Treat?

• How do we know what infective agent we should be treating?
  • This question could be answered with a diagnostic test that identifies specific species

• How do we know a selected therapy is effective?
  • This question could be answered with a diagnostic test that can identify fungal load
What to DO?

- The clinician should “trust but verify”
- Trust their clinical judgment
- Verify their diagnosis using the best diagnostic tools available
- That diagnosis will be made using the AdvaTect Diagnostic MycoDART – PCR probes.