Emerging Infectious Diseases - Global View

• Update on Avian Influenza A/H5N1
• Upsetting the balance
• Things that shouldn’t be there
• Things we weren’t aware of
• Unanticipated (but maybe not unexpected) changes

Avian Influenza H5N1

• Endemic in domestic poultry in certain areas
• Sporadic human infection from direct contact with infected poultry and/or wild birds
• Person-to-person spread of H5N1 virus from has been very rare, limited and unsustained
• No evidence of changes to H5N1 to increased transmissibility to or among humans, but infection seen in some mammals

Avian Influenza H5N1

• H5N1 resistant to amantadine and rimantidine, but sensitive to Oseltamivir and Zanamivir
• Some Oseltamivir resistant strains reported
• No available vaccine, work in progress
Epidemiologic Findings in Human H5N1 Cases

- **Thailand, 2004:** limited spread in a family from prolonged and very close contact. No transmission beyond one person.
- **Vietnam, 2004:** fatal case presented with fever, diarrhea, and seizures, and was initially diagnosed as encephalitis.
- **Vietnam, 2005:** Infection via ingestion of raw duck blood.
- **Azerbaijan, 2006:** teenagers infected by contact with wild dead birds (swans) removing feathers from the birds.
- **Indonesia, 2006:** 8 people in one family were affected, with 7 deaths. No further spread outside of the exposed family was documented or suspected.
- **Vietnam, 2006:** high viral concentration and elevated inflammatory cytokine levels in fatal cases. Inflammatory response appears to be implicated in the pathogenesis.

### Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

<table>
<thead>
<tr>
<th>Country</th>
<th>2003 cases</th>
<th>2004 deaths</th>
<th>2005 cases</th>
<th>2006 deaths</th>
<th>2007 cases</th>
<th>2008 deaths</th>
<th>Total cases</th>
<th>Total deaths</th>
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<tr>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Indonesia</td>
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<td>Peoples Democratic Republics</td>
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<tr>
<td>Thailand</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Turkey</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>3</td>
<td>3</td>
<td>29</td>
<td>20</td>
<td>19</td>
<td>8</td>
<td>83</td>
<td>59</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>4</strong></td>
<td><strong>46</strong></td>
<td><strong>43</strong></td>
<td><strong>115</strong></td>
<td><strong>79</strong></td>
<td><strong>282</strong></td>
<td><strong>241</strong></td>
</tr>
</tbody>
</table>

### Malaria Dominican Republic

- **1999-2000 outbreak, Hurricanes Mitch and George**
- **2004, Hurricane Jeanne, Punta Cana**
- **Heavy rains and flooding, increased mosquitoes**
- **Malaria-infected migrant workers**
- **3,000 malaria cases reported in 1999**
- **1,500-2,500 malaria cases now reported annually**
- **Europeans in Punta Cana All inclusive resorts, never left the grounds**
- **CDC recommend chloroquine prophylaxis for travelers to La Altagracia and Duarte provinces.**

Malaria risk area in Dominican Republic: Rural, with highest risk in provinces bordering Haiti. In addition, risk in all areas of La Altagracia Province, including resort areas.
Malaria in Kingston, Jamaica

- Fall 2006, confirmed malaria cases, Kingston, Jamaica where Malaria transmission does not normally occur
- Ant malarial drugs recommended.
- February 29, 2008 CDC removed temporary recommendation for malaria preventive medication (prophylaxis) for travel to Kingston Jamaica.
- Kingston continues to experience rare cases of malaria, but the risk to travelers appears to be minimal.

Recommendations for Travelers to Great Exuma

- Repeated instances of chloroquine-sensitive Plasmodium falciparum malaria occurring in travelers to the island of Great Exuma
- Ongoing, low-level risk of malaria for people traveling to the island.
- CDC recommends that travelers to Great Exuma, Bahamas take chloroquine malaria preventive medication (prophylaxis)
- There is currently no known risk of malaria on other islands of the Bahamas; therefore, prophylaxis is not necessary for those islands

Celebrities Who Own Islands in the Exumas

- Nicolas Cage
- Faith Hill and Tim McGraw
- David Copperfield
- Johnny Depp
Chikungunya Fever in Italy

- In Swahili Chikungunya: illness of the bended walker
- Fever, arthralgia, myalgia, headache and diffuse maculopapular rash.
- Symptoms 4–7 days after bite
- Arthralgia is often severe, persistent
- 12% of patients have chronic arthralgia 3 years after onset of illness
- Chikungunya is transmitted by *Aedes aegypti* or *A. albopictus*

Lancet. 2007 Dec 1;370(9602):1805-6

Chikungunya Fever in Italy

- CHIKV 1st Isolated in Tanzania in 1953
- Outbreaks: India, Comoros and La Réunion islands in the SW Indian Ocean in early 2005
- During these outbreaks, travelers from industrialized countries became infected with CHIKV and were still infected on returning home.
- *Aedes albopictus*—a vector of CHIKV—was introduced a number of years ago and is now widespread in Italy

85% of the cases were confirmed by either serology or PCR.

Lancet. 2007 Dec 1;370(9602):1805-6
**Chikungunya Fever in Italy**

- Outbreak of a tropical disease in a non-tropical area
- Index case had recently traveled to an endemic area (India) to visit relatives
- Vector infestation traced to imported tires from a tire retreading company that had imported used tires infested with mosquito eggs from Georgia, USA.
- Other Diseases: Malaria, Yellow Fever, Dengue, ?

**Dengue in Texas**

- Dengue noted in 5 Texas border counties since 1980.
- Survey in Brownsville, Texas, and Matamoros, Tamaulipas, Mexico (n = 600), in 2004 to assess dengue seroprevalence.
- Recent dengue infection was detected in 2% and 7.3% of residents in Brownsville and Matamoros, respectively.
- Past infection was detected in 40% of Brownsville residents and 78% of Matamoros residents.

**Autochthonous Malaria**

- Inadvertent carriage of infective Anopheles mosquitoes by airplane, ship, baggage, or bilge water may be responsible for these occurrences.
- Also, large populations of migrants from areas highly endemic for malaria may act as human reservoirs for potential gametocyte carriers.
- Outbreaks of mosquito borne malaria in areas of New Jersey, New York, and Texas.
Outbreaks of Acute Gastroenteritis: Settings 2006

<table>
<thead>
<tr>
<th>Setting</th>
<th>Number of Outbreaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruise ships</td>
<td>37</td>
</tr>
<tr>
<td>Long-term care facilities</td>
<td>37</td>
</tr>
<tr>
<td>Restaurants</td>
<td>13</td>
</tr>
<tr>
<td>Hospitals</td>
<td>7</td>
</tr>
<tr>
<td>Colleges</td>
<td>3</td>
</tr>
<tr>
<td>Parties</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
</tr>
</tbody>
</table>

Norovirus

- Most common cause of infectious gastroenteritis among persons of all ages
- Responsible for 50% of all food-borne gastroenteritis outbreaks in the United States
- Major problem cruise ships, nursing homes and hospitals
- Detected in 35% of persons with sporadic gastroenteritis and in 14% of all children < 3 years old hospitalized for gastroenteritis.
- Cause of chronic diarrhea among transplant patients
- Diagnostic PCR available at CDC and State Health Dept.
- Emerging due to lifestyle changes vs. better tests

Norovirus

- Short, self-limited illness
- As few as 100 virus particles thought to infectious
- Stable in the environment and can survive freezing and heating to 60°C (140°F).
- Transmission to the oral mucosa via hand contact with materials, fomites, and environmental surfaces contaminated with feces or vomitus
- May be food borne or waterborne
- Susceptible to chlorination
Prevention of Norovirus Transmission

- Hand hygiene with alcohol-based hand gels;
- Disinfect surfaces: 1:10-50 dilution chlorine bleach
- Do not return to work or school for 24 to 72 hours after symptoms resolve

Chagas Disease

Trypanosoma cruzi in The USA

- American trypanosomiasis
- Endemic to Central and South America
  - Romaña’s Sign
  - Megacolon
  - Megaesophagus
  - Cardiomegaly
  - Reduvid Bug Vector
- Rare Transmission
  - IVDA
  - Transfusion

Prevention of Norovirus Transmission

- During outbreaks
  - Use contact precautions
  - Avoid sharing staff members between units or facilities with affected patients
  - Cluster symptomatic patients
  - Instruct visitors on hand hygiene
  - Close affected units to new admissions and transfers
Chagas Disease

- Cases of Chagas disease reported in the United States
  - 3 in infants in Texas
  - 1 in an infant in Tennessee
  - 1 in a 56-year-old woman in California
  - 1 in Louisiana 2006
- Vector in the USA is *Triatoma sanguisuga*,

- *T. cruzi* has been identified in >18 species of mammals
  - raccoons, opossums, armadillos, foxes, skunks, dogs, wood rats, squirrels, and nonhuman primates
- Lack of human cases in USA
  - Lack of habitat for the bugs in most US homes
  - a preference for animal hosts
  - delayed defecation of triatomines found in the US compared with those found in Latin America.

Wildlife, Exotic Pets, and Emerging Zoonoses

- May 22 – Child hospitalized because of festering lesions, fever, sweats, ocular discharge, and new skin lesions.

Photograph courtesy South Florida NRC

Photos courtesy of CDC
Monkeypox

- In 1958, monkeypox was noted as a viral disease that is found mostly in the rainforest countries of central and west Africa. Laboratory studies showed that the virus could also infect rats, mice, and rabbits.

- In 1970, monkeypox was identified as the cause of a rash illness in humans in remote African locations.

- In early June 2003, monkeypox was reported among several residents in the United States who became ill after having contact with sick pet prairie dogs. This is the first evidence of community-acquired monkeypox in the United States.

Wildlife, Exotic Pets and Emerging Zoonoses

- Petting zoos linked to *Escherichia coli* O157:H7, salmonellae, and *Coxiella burnetii*

- Salmonellosis from a Komodo dragon exhibit

- Twelve elephant handlers infected with *M. tuberculosis*, and 1 with active disease after 3 elephants died of tuberculosis.

- Human monkeypox related to pet prairie dogs
Wildlife, Exotic Pets and Emerging Zoonoses

- Lyssaviruses in pet bats
- Ringworm from African pygmy hedgehogs or chinchillas.
- Tularemia in commercially traded prairie dogs;
- ≈7% of human infections with salmonella in US are associated with having handled a reptile.

Meningococcemia

- Close contacts of persons with meningococcal disease have a higher risk for carriage and therefore invasive disease.
- Contacts should receive antibiotic chemoprophylaxis to eliminate nasopharyngeal carriage of *N. meningitidis* ASAP.
- Risk of secondary cases is highest immediately after onset of disease
- Secondary cases rarely occur after 14 days.
- Oral Ciprofloxacin is an effective single dose chemoprophylactic agent.

Attempt to Determine Reservoir of Marburg Virus (MARV)

- Democratic Republic of the Congo
- A mine associated with a protracted outbreak of Marburg hemorrhagic fever during 1998–2000
- MARV nucleic acid found in 12 bats, 3.0%–3.6% of 2 species of insectivorous bat and 1 species of fruit bat
- Antibody to the virus found in the serum of 9.7% of 1 of the insectivorous species and in 20.5% of the fruit bat species
- Attempts to isolate virus unsuccessful.

Quinolone-Resistant Neisseria meningitidis
Minnesota and North Dakota, 2007–2008

- In August 2006, a worker in a day care center in eastern North Dakota died of Group B Meningococcemia
- Children received rifampin, staff ciprofloxacin
- Secondary case, January 2007
  - Ciprofloxacin-resistant
- 2 unrelated cases, 2008
  - Ciprofloxacin-resistant
**Chemoprophylaxis for Meningococcal Disease with Possible Fluoroquinolone-resistance**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age group</th>
<th>Dosage</th>
<th>Duration/Route</th>
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</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>&lt;1 mo</td>
<td>5 mg/kg q 12 hrs</td>
<td>2 days PO</td>
</tr>
<tr>
<td></td>
<td>1 mo to &lt;15 yrs</td>
<td>10 mg/kg q 12 hrs</td>
<td>2 days PO</td>
</tr>
<tr>
<td></td>
<td>&gt;15 yrs</td>
<td>600 mg every 12 hrs</td>
<td>2 days PO</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&lt;15 yrs</td>
<td>125 mg</td>
<td>Single IM dose</td>
</tr>
<tr>
<td></td>
<td>&gt;15 yrs</td>
<td>250 mg</td>
<td>Single IM dose</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>&lt;15 yrs</td>
<td>10 mg/kg body weight</td>
<td>Single PO dose</td>
</tr>
<tr>
<td></td>
<td>&gt;15 yrs</td>
<td>500 mg</td>
<td>Single PO dose</td>
</tr>
</tbody>
</table>

**Plasmodium falciparum Malaria and Atovaquone-Proguanil Treatment Failure**

- **Atovaquone Resistance**
  - Single point mutation in plasmodial cytochrome b
- **Therapeutic Concerns**
  - Narrow margin for dosing errors with a large parasite load
  - Stress completion of course in a non-immune host
  - ? Lower drug levels if >100 kg at standard dose.
- **Recrudescent malaria 3-4 weeks after ATQ/PRO Rx**
  - Failure likely due to drug resistance
  - Quinine plus doxycycline, or artemether/lumefantrine (if available) should be used to treat relapse

**Plasmodium falciparum Malaria and Atovaquone-Proguanil Treatment Failure**

- **Atovaquone/proguanil (Malarone)**
  - Effective Rx: chloroquine-resistant *P. falciparum* malaria
  - Convenient route of administration (oral)
  - Short treatment course (three days-12 pills)
  - Attractive adverse-effect profile

**Emerging Infectious Diseases 2008 Challenges in Diagnosis and Management of Invasive Fungal Infections**

Julie E. Mangino, MD
Ohio State University Medical Center
**Trends in Mortality: Invasive Mycoses**

- Crude mortality rate (US) due to candidiasis and aspergillosis.

**Excess Mortality, Length of Stay (LOS), and Associated Costs**

**Invasive Candidemia in the United States**
- Excess mortality rates: 10%-49%
- Excess LOS in hospital: 3.4-30 days
- Excess costs: $6200-$92,000
- Average total cost of candidemia: $44,536*

**Candida - A High Priority in the ICU: Bloodstream Infection Pathogens**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>% BSI (n=10,515)</th>
<th>Crude Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative Staph</td>
<td>35.9 (1)*</td>
<td>25.7</td>
</tr>
<tr>
<td>*Staphylococcus aureus</td>
<td>16.8 (2)*</td>
<td>34.4</td>
</tr>
<tr>
<td>*Candida species</td>
<td>10.1 (3)</td>
<td>47.1</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>9.8 (4)</td>
<td>43.0</td>
</tr>
<tr>
<td>*Pseudomonas aeruginosa</td>
<td>4.7 (5)</td>
<td>47.9</td>
</tr>
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</table>

*P<.05 for patients in ICU vs non-ICU settings.

**Increased Hospital Costs for Candidemia**

- Hospital Stay $37,681 (84.6%)
- Adverse Drug Reactions $615 (1.4%)
- Diagnostic Procedures $1053 (3.4%)
- Antifungal Therapy $4770 (10.3%)

Total Cost of Candidemia: $44,536*
Risk Factors for Candidemia

- Central venous catheters
- Systemic antibiotic exposure
- Length of stay in ICU >72 hours
- Major surgery, especially abdominal
- Pancreatitis
- Dialysis
- Neutropenia
- Immunosuppressive agents (steroids, etc)
- Colonization with Candida species
- Total parenteral nutrition, hyperalimentation

Factors Associated With C glabrata Infection

- Emergence of C glabrata as an important bloodstream pathogen may not be just a matter of selection with drug pressure
  - Nosocomial transmission pattern
  - Patient age (increases with age)
    - Changes in mucosal defenses with age
    - Colonization by C glabrata (40%, >70 years)

Distribution of Common Candida Species

<table>
<thead>
<tr>
<th>Candida Species</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>C albicans</td>
<td>36%</td>
</tr>
<tr>
<td>C glabrata</td>
<td>22%</td>
</tr>
<tr>
<td>C parapsilosis</td>
<td>20%</td>
</tr>
<tr>
<td>C tropicalis</td>
<td>15%</td>
</tr>
<tr>
<td>C krusei</td>
<td>3%</td>
</tr>
<tr>
<td>C lusitaniae</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
</tbody>
</table>

Factors Associated With C glabrata Infection

- Underlying diseases
- Geographic location (United States > worldwide)
- Previous exposure to specific antimicrobials
  - Azoles
  - Piperacillin-tazobactam, Vancomycin,
  - Anti-anaerobic agents

Traditional Diagnosis

- **Blood cultures**
  - Negative: 50% sensitivity by autopsy data
  - Intense research to improve techniques

- **Biopsies and other cultures**
  - Not always feasible
  - Contaminant vs real?

LIMITED BY BIOLOGY OF THE DISEASE

Candidemia Cases - MICU - 2001-2007

Candidemia Management: Who and When to Treat?

- Asymptomatic, positive superficial cultures or beta-D-glucan
- Signs and symptoms
- Full-blown disease
- Sequelae
- Prophylaxis
- Preemptive
- Empirical
- Therapy
- Asymptomatic, high-risk febrile patient (chemo, ICU?)

No disease

Markers

Symptomatic, high-risk febrile patient receiving antibiotics
Use of Beta-D-Glucan Assay to Diagnose Candidemia

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Sampling</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obayashi et al.</td>
<td>Febrile patients</td>
<td>Single</td>
<td>90</td>
<td>100</td>
<td>59</td>
<td>97</td>
</tr>
<tr>
<td>Odabasi et al.</td>
<td>AML / MDS</td>
<td>Multiple, 2+</td>
<td>65</td>
<td>96</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>Ostrosky-Zeichner</td>
<td>Hospitalized patients</td>
<td>Single</td>
<td>64</td>
<td>92</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>Mohr et al.</td>
<td>ICU patients, surveillance</td>
<td>Multiple, 2+</td>
<td>100</td>
<td>63</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>


Clinical Manifestations of Candidiasis

- Superficial disease: mucous membranes
  - Thrush, esophagitis, vaginitis, cutaneous syndromes in neutropenic patients, or IV drug users
- Deep organ involvement
  - Candidemia (most common)
  - CNS (neonates)
  - Respiratory tract (rare)
  - Cardiac (surgery)
  - Urinary (management issue)
  - Arthritis, osteomyelitis, myositis (long-term treatment)
  - Peritoneum, liver, spleen, gallbladder (hepatosplenic candidiasis to postsurgical collections)
  - Ocular
  - Disseminated candidiasis (liver/spleen in neutropenics with candidemia)

An Eye for an Eye...

- Dilated eye exam
  - All with candidemia
  - Particularly in prolonged fungemia
  - Endophthalmitis
  - Consider intravitreal treatment / vitrectomy

Lifelines

- Lines and foreign bodies
  - Remove if possible—better outcomes
  - Tunneled catheters are lower risk
- Neutropenic patients
  - Gut vs line?
- Biofilms are important
  - Polymers and echinocandins

### Antifungal Drugs By Mechanism of Action

<table>
<thead>
<tr>
<th>Membrane disrupting agents:</th>
<th>Amphotericin B, Ampho B lipid formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergosterol synthesis inhibitors:</td>
<td>Azoles: fluconazole, itraconazole, voriconazole</td>
</tr>
<tr>
<td>Nucleic acid inhibitor:</td>
<td>Flucytosine</td>
</tr>
<tr>
<td>Glucan synthesis inhibitors:</td>
<td>Echinocandins: caspofungin, anidulafungin and micafungin</td>
</tr>
</tbody>
</table>

### Principles of Managing Invasive Candidiasis

<table>
<thead>
<tr>
<th>Evaluate the bug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider species-specific features</td>
</tr>
<tr>
<td>Consider susceptibility testing</td>
</tr>
<tr>
<td>Remove prosthetic devices, if possible</td>
</tr>
<tr>
<td>Consider options for antifungal therapy</td>
</tr>
</tbody>
</table>

### Principles of Managing Invasive Candidiasis

<table>
<thead>
<tr>
<th>Consider the source of infection:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Local epidemiology</td>
</tr>
<tr>
<td>Establish the diagnosis</td>
</tr>
<tr>
<td>✓ Repeat cultures, pursue imaging</td>
</tr>
<tr>
<td>Consider the type of patient</td>
</tr>
<tr>
<td>✓ Colonized? Trauma? Neutropenic? Future chemo?</td>
</tr>
</tbody>
</table>

### Revised IDSA Guidelines for Candidemia

<table>
<thead>
<tr>
<th>Choice of therapy depends on clinical status of the patient and knowledge of species</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Remove all lines, if feasible</td>
</tr>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>✓ Fluconazole ≥6 mg/kg/d (400 mg), or</td>
</tr>
<tr>
<td>✓ Caspofungin 50 mg/d, anidulafungin 100 mg/d, or micafungin 100 mg/d, * or</td>
</tr>
<tr>
<td>✓ AMB (0.6-1.0 mg/kg/d for AMB or 3 mg/kg/d for liposomal formulations of AMB) in selected circumstances*</td>
</tr>
<tr>
<td>✓ Treat 2 weeks after last positive blood culture and resolution of signs and symptoms of infection</td>
</tr>
</tbody>
</table>

*Transition to fluconazole, when appropriate, is encouraged once the Candida sp is known and the patient is stable. Pappas et al, guideline revisions in progress.*
Proposed Approach: Immunocompromised Patients

Yeast in blood culture

Immunocompromised (transplant, BMT, AIDS)
Start (lipid) polyene and wait for identification (ID)
Endemic mycosis
Candida

Continue (lipid) polyene until stable; consider fluconazole or itraconazole as appropriate

Proposed Approach: Non-immunocompromised Patients

Yeast in blood culture

Non-immunocompromised

Immunocompromised (transplant, BMT, AIDS)
Start (lipid) polyene and wait for identification (ID)
Endemic mycosis
Candida

Hemodynamically stable, no previous azoles
Hemodynamically unstable, previous azoles

Start fluconazole, wait for ID and monitor response
Start echinocandin or lipid polyene, wait for ID and monitor response

Non-immunocompromised

Treatment of Candiduria
Do not treat asymptomatic candiduria unless risk factors are present

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Non-immunocompromised

The Bottom Line: Candidemia in the ICU

• Epidemiology supports importance of candidemia, particularly in ICU settings
• Need better diagnostics
• Need practical rules to assess risk
• Antifungals for:
  ✓ Prophylaxis
  ✓ Preemptive and empirical therapy
  ✓ Traditional therapy

Treatment of Candiduria
Do not treat asymptomatic candiduria unless risk factors are present

• Treat
  ✓ Symptomatic patients
  ✓ Neutropenic patients
  ✓ Low birth-weight infants
  ✓ Patients with urological manipulations/ obstructions

• Treatments
  ✓ Remove “hardware” (stents and/or Foley)
  ✓ Fluconazole (200-400 mg/dl)
  ✓ Flucytosine (100mg/kg/d)
  ✓ Lower urinary tract infections: AMB bladder irrigations (rarely useful)
  ✓ Upper urinary tract infections (pyelonephritis): can use azoles and echinocandins