Candidemia: Lessons learnt from Asian studies for intervention

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Candidemia

• Affects >250,000 people/year worldwide with > 50,000 deaths
• Incidence reported to be between 2 and 14 cases per 100,000 persons in population-based studies and 6.87 cases per 1000 ICU patients
• Mostly in ICUs and those with extreme age
• Cited as the 4th most common bloodstream infection
• Mortality 25-60%

Pathogenesis of Candidemia

- Antibiotics
- Colonization
- Barrier disruption
  - GI surgery
  - Vascular access
  - Mucosal barrier injury
  - Neutropenia

Candidia species

Candidemia (candida BSI)
Disseminated Candidiasis

- Skin lesions
- Chorioretinitis
- Hepatosplenic abscess
Risk Factors for Candidemia

Healthcare-related
- Critical illness, especially long-term ICU stay
- Abdominal surgery, especially with anastomotic leakage
- Broad-spectrum antibiotics
- Central vascular catheter / total parenteral nutrition
- Hemodialysis
- Solid organ transplantation
- Glucocorticoid / chemotherapy

Host-related
- Acute necrotizing pancreatitis
- Hematologic malignancies
- Solid-organ tumors
- Neonates - low birth weight, and preterm infants
- Candida colonization, particularly if multifocal (colonization index >0.5 or corrected colonization index >0.4)

Candidemia in Asia

Risk Factors for Candidemia in Developing Countries

• The risk factors and underlying diseases for candidemia are **SIMILAR** in both developed and developing countries
• A multi-center study from India, candidemia occurred in
  • Younger age
  • Less co-morbidities
  • Much earlier post-ICU admission (median 8 days post-ICU admission compared to 23 days in USA)
• May be due to early colonization of Indian patients

## Incidence of Candidemia in Asian Countries and Developed Countries

<table>
<thead>
<tr>
<th>Countries</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>0.30</td>
</tr>
<tr>
<td>Canada</td>
<td>0.45</td>
</tr>
<tr>
<td>UK</td>
<td>1.87</td>
</tr>
<tr>
<td>Australia</td>
<td>0.21</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.32</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.049</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Countries</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Asia</td>
<td>0.39-14.2</td>
</tr>
<tr>
<td>China</td>
<td>0.38</td>
</tr>
<tr>
<td>India</td>
<td>1.94</td>
</tr>
<tr>
<td>Thailand</td>
<td>1.31</td>
</tr>
<tr>
<td>Singapore</td>
<td>0.12-0.33</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2.93</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*per 1000 discharges/admissions

Relatively higher incidence in Asian countries

Candidemia in Asian and Developed Countries

• Incidence increased 5 fold globally in the last 10 years
• Developing countries → 4–15 times higher than developed countries
• The incidence of candidemia
  • Asia: from 0.026 to 4.2 cases per 1000 admissions
  • Developed countries: from 0.03 to 1.87 cases per 1000 admissions
  • ICUs of developing countries: 2.2 to 41.0 cases per 1000 admissions
  • ICUs of developed countries: 0.24–6.87 cases per 1000 admissions
• Over all crude mortality rate
  • Developed countries < 50%
  • Developing countries >50%
Why More Candidemia in Asians

- Limited awareness in fungal diseases
- Overuse and/or misuse of antibiotics and corticosteroid
- Suboptimal infection control
  - Lack of infrastructure, staff training, sanitation, surveillance programs, and compliance of healthcare workers
- Management largely based on clinical assessment and empirical therapy
  - Lack of accurate diagnostic methods and species identification
  - Inefficient implement of guidelines
- Immunogenetics
  - The majority of patients in the ICU do not acquire invasive candidiasis, even if they share similar risk factors
  - Single nucleotide polymorphisms (SNPs) in toll-like receptor 1–interferon-γ pathway – associated with candidemia → No data in Asians

Candida Studies in Asia

25 centers in 6 countries:
China, Hong Kong, Singapore, India, Taiwan, Thailand

From July 2010 to June 2011

1601 episodes of candidemia
1910 isolates

10 centers in 7 countries:
Brunei, Korea, Philippines, Singapore, Taiwan, Thailand, Vietnam

From 2013-2015
861 isolates
Species Distribution of *Candida* in Asia

- *Candida albicans*, 41.36%
- *Candida tropicalis*, 25.45%
- *Candida glabrata*, 13.93%
- *Candida famata*, 0.89%
- *Candida dubliensi*, 0.10%
- *Candida catenulate*, 0.05%
- *Candida intermedia*, 0.26%
- *Candida krusei*, 1.94%
- *Candida parapsilosis*, 12.15%
- *Candida pararugosa*, 0.05%
- *Candida pelliculosa*, 0.73%
- *Candida sake*, 0.21%
- *Candida haemulonii*, 0.37%
Species Distribution of *Candida* in Asia

Species Distribution of *Candida* in Asia
Antifungal Susceptibility of *Candida* in Asia
Antifungal Susceptibility of *Candida* Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Amphotericin B</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S to R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S-DD to R</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
<td>S</td>
</tr>
<tr>
<td><em>C. guilliermondii</em></td>
<td>S to R</td>
<td>S to R</td>
<td>S to r</td>
<td>S to r</td>
<td>S</td>
<td>S to R</td>
</tr>
<tr>
<td><em>C. auris</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

S-DD, Susceptible dose-dependent; I, Intermediate; S, Susceptible

Previous fluconazole exposure is important

Candida auris: An Emerging Fungal Pathogen

- Found in 16 countries in 4 continents within 5 years
- Canada, Colombia, Germany, India, Israel, Japan, Kenya, Kuwait, Norway, Pakistan, Spain, South Africa, South Korea, the United Kingdom, and Venezuela, United States

- Cause of emergence
  - Unknown
  - May be antifungal selective pressure
  - DNA fingerprint study suggested that it emerged independently in multiple regions

Identification of *Candida* into Species Level: Where we are?

10 responses:
India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1
Routine Techniques for Identification

Turnaround time 1-5 days

10 responses:
India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1
Antifungal Susceptibility Test: Where we are?

10 responses: India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1

Turnaround time 1-5 days
Our Future Direction

Need to implement and develop diagnostic tools to make it available widely with shorter turnaround time (for both identification and antifungal susceptibility)
Antifungal Treatment of Invasive Candidiasis

IDSA 2016

• **Echinocandins** - strong recommendation; high-quality evidence

• **Fluconazole** - strong recommendation; high-quality evidence in **selected** patients
  - Not critically ill
  - Unlikely fluconazole-resistant

• **Lipid amphotericin B** - strong recommendation; high-quality evidence for alternative

• **Voriconazole** - strong recommendation; moderate-quality evidence

ESCMIID 2012

• **Echinocandins** – Al

• **Liposomal AMB** – BI

• **Voriconazole** – BI

• **Fluconazole** – CI

Empirical Antifungal Agents for Candidemia

10 responses:
India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1
Echinocandins in National Formulary Drug List

10 responses:
India 2, Thailand 2, Malaysia 2, Indonesia 1, Philippines 1, Singapore 1, Taiwan 1
Candidemia in Asian Countries

- Similar risk factors as western countries
- Higher incidence
- Different species distribution – more *C. tropicalis* in tropical countries
- Increased antifungal resistance
- Lack of diagnostic facilities and antifungal susceptibility testing
- Limited access to antifungal agents
What Should Be Our Strategies to Improve Management in Candidemia?

- Development and improvement of mycology laboratory
- Improvement of infection control
- Local epidemiology studies
- Antifungal treatment
  - Education – appropriate drug
  - Availability of antifungal agents
  - Prophylaxis in specific cases
  - Antifungal stewardship
- Source control
  - Surgery, remove prosthesis/catheter
Thank you