Infectious Disease Year in Review 2016

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Overview

Pertinent issues and topics that were relevant to the field of Infectious Disease over the past year

*Endocarditis*

*Zika*

*HAP/VAP*

*Candida/Fungal guideline changes*

*Infection Control and Stewardship/Outbreaks*
Updates in Endocarditis Management
Diagnosing Endocarditis

Echo still imaging test of choice

- TTE favored first now, despite clinical suspicion
- 3d > 2d Echo (more Sensitive may overestimate veg size)
- Possible role for cardiac CT, cardiac MRI
- FDG PET-CT, SPECT imaging

Diagnosing IE (continued)

TTE always done now

TEE should follow TTE if clinical concern for IE is high

If TEE negative, repeat in 3-5 days (NOT 7-10)

FOCUS IS ON TRANSFERRING PATIENT TO APPROPRIATE REF CENTER

➔ MULTIDISCIPLINARY TEAM
Treatment

DO EVERYTHING EARLY!

Start antibiotic treatment early (empiric → focused)
- *Enterococcus faecalis* → ceftriaxone/ampicillin ok (*Unclear: Enterococcus faecium*)
- Prophylaxis- No changes proposed

If indicated, do surgery early
- Left sided IE:
  - CHF, fungal pathogen, EKG changes (AV block), abscess or destruction of valve, persistent /enlarging vegetation, ongoing emboli, veg >10 mm, >5-7 days of bacteremia despite correct Abx, relapsing PV IE

- Right sided IE: Same considerations
  - Valve repair favored over replacement
  - Reasonable to avoid OR when possible with injection drug user
Updates in Zika
Zika Virus

Part of the *Flaviviruses* family

- First isolated-Uganda, 1947, rhesus monkey

Transmission

- Insect: *Aedes* mosquitoes
- **Sex** *(Foy, BD et al. *EID*, 2011)*
- Blood Transfusion
- Vertical  
  *(mother ➔ child)*
How Zika Has Spread Over Time

Source: http://www.storybench.org/spread-zika-virus-roundup-visualizations/
Symptoms of Zika virus

Incubation: 3-12 days

80% Asymptomatic (Duffy, MR et al. *NEJM*, 2009)
• Micronesia Outbreak 2007

20% Symptomatic (Again from Duffy paper)
• Fever, rash, joint pains, conjunctivitis, myalgias, HA (~1 week)
• Pregnancy
Diagnosing Zika

Viral RNA testing (RT-PCR) - during 1st 7 days of illness, test of choice

Zika IgM antibody ELISA testing - may be present >3 days after onset of illness, not reliable <7 days of illness

- Lasts for months once positive
- Cross reacts with other flaviviruses (Dengue, WNV, Yellow fever, St Louis encephalitis) - problem, especially if hx of vaccination to other flaviviruses → Plaque reduction neutralization test (PRNT), done by CDC
- Blood, CSF, amniotic fluid, urine
Pregnant woman with history of travel to an area with ongoing Zika virus transmission

Test for Zika virus infection

Positive or inconclusive for Zika virus infection

- Consider serial fetal ultrasounds
  - Consider amniocentesis for Zika virus testing

Negative for Zika virus infection

- Fetal ultrasound to detect microcephaly or intracranial calcifications
  - Microcephaly or intracranial calcifications present
    - Retest pregnant woman for Zika virus infection
    - Consider amniocentesis for Zika virus testing
  - Microcephaly or intracranial calcifications not present
    - Routine prenatal care
Zika-Advice for Patients

If travelling to area with Zika ➔ DEET/Picaridin/Permethrin spray (ok in pregnancy), bed nets, long sleeved clothing, limit travel (especially if pregnant or thinking)

Condoms and/or avoid sex if concerns for exposure (CDC 7/2016):

<table>
<thead>
<tr>
<th>Zika symptoms:</th>
<th>female</th>
<th>male</th>
</tr>
</thead>
<tbody>
<tr>
<td>wait 8 weeks</td>
<td>wait 6 months</td>
<td></td>
</tr>
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</table>

| No symptoms: | wait 8 weeks | wait 8 weeks |


UPMC Travel Clinic can help locally.
Zika-Treatment

None currently available!

Larocca RA, et al. Nature, 2016 ➔ single dose of synthetic DNA or inactivated virus vaccine protective in mice

Abbink P, et al. Science 2016 ➔ Inactivated virus, purified Ig from vaccinated monkeys and plasmid DNA virus protective in rhesus monkeys

Plans for Vaccine Development

• NIH Vaccine Research Center (U.S)- 1/2016
• Bharat Biotech International (India)- 2/2016
• Other private companies (worldwide)- 3/2016
  • Inovio Pharma-GLS-5700: first human trial for Zika vaccine (synthetic DNA vaccine)
Updates in HAP/VAP

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

HAP- Pneumonia diagnosed >48 hours after being hospitalized

VAP- A form of HAP in which pneumonia is diagnosed >48 hours after being placed on the vent
No HCAP management included in guidelines (will likely be grouped with CAP instead)

For VAP/HAP

- Clinical assessment/diagnosis alone trumps all adjunctive testing
  - (BAL sTREM-I, Procalcitonin (PCT), CPIS scoring + Clinical assessment)
- Each hospital should generate personalized antibiogram and distribute this to all associated centers/institutions to help guide empiric therapy for HAP/VAP
  - MRSA (vancomycin – linezolid probably equivalent in most setting)
  - Pseudomonas, resistant GN’s (CRE/KPC)
- In majority of cases, 7 days of therapy for HAP/VAP is sufficient (vs 8-15 days)

- De-escalate, de-escalate, de-escalate!
Utility of Biomarkers

No studies specifically comparing use of procalcitonin + clinical assessment to clinical assessment alone in the dx of HAP/VAP

- 6 studies focusing on performance characteristics of PCT in dx of HAP/VAP
- Between 2002-2011
- No consistency in measuring PCT (Kryptor vs immuno-luminometric method
- Cutoffs varied for positive result (0.5-3.9 ng/mL)
- No validated cutoffs established
- Pooled 6 studies → 665 patients, 335 (50%) diagnosed with HAP/VAP
- Sn of PCT+ clinical criteria 67%, Sp 83%

No studies specifically comparing use of sTREM-I + clinical assessment to clinical assessment alone in dx of HAP/VAP

- Again 6 studies isolated focusing on performance characteristics
- Again no consistency in measuring sTREM-I
- Again cutoffs varied (5-900 pg/mL)
- Pooled 6 studies → 208 patients, 108 (52%) diagnosed with HAP/VAP
- Sn sTREM+ clinical criteria 84%, Sp 49%
MRSA/Pseudomonas/MDRs

VAP in the U.S. (Surveillance data)
- Enteric GN’s-20-40%
- Staph aureus- 20-30% (50% MRSA)
- Pseudomonas 10-20% (~1/3 R to cefepime or Zosyn)
- Acinetobacter 5-10% (50-60% of these carbapenem R)

For VAP (empiric):
- Cover MRSA if >10% incidence or + risk factors (Table 2)
- PSA/GN’s-double cover if risk factors or >10% rate of MDR, or antibiogram not available

HAP in the U.S-Meta-analysis of 23 studies
- Enteric GN’s-22%
- Staph aureus- 16% (63% MRSA)
- Pseudomonas-13%

For HAP (empiric):
- Cover MRSA if risk factors or >20% incidence, or high risk of death
- PSA/GN’s-double cover if risk factors or high risk of death

For MDR Gram Negatives:
- If only susceptible to colistin/polymixin B/aminoglycosides, then use combination systemic and inhaled therapy [meta-analysis of 9 studies showed improved outcomes]
## Risk Factors

### Table 2. Risk Factors for Multidrug-Resistant Pathogens

<table>
<thead>
<tr>
<th>Risk factors for MDR VAP</th>
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<tbody>
<tr>
<td>Prior intravenous antibiotic use within 90 d</td>
<td></td>
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<tr>
<td>Septic shock at time of VAP</td>
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<tr>
<td>ARDS preceding VAP</td>
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<tr>
<td>Five or more days of hospitalization prior to the occurrence of VAP</td>
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<tr>
<td>Acute renal replacement therapy prior to VAP onset</td>
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<th>Risk factors for MDR <em>Pseudomonas</em> VAP/HAP</th>
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Abbreviations: ARDS, acute respiratory distress syndrome; HAP, hospital-acquired pneumonia; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*. MDR *Pseudomonas* refers to multidrug-resistant *Pseudomonas*.
7 days now recommended (rather than 8-15 days) for VAP/HAP

**Figure 2.** ORs of mortality. Vertical line is the “no difference” point in mortality between the two arms. Horizontal lines are 95% CI. ■ = OR; the size of each square denotes the proportion of information provided by each trial. ◆ = pooled OR for all trials. df = degrees of freedom; M-H = Mantel-Haenszel.

*Dimopoulos, et al. Chest 2013- Systematic review/Meta-analysis*

*No differences in mortality, rate of relapses, ICU stay, mechanical vent duration*
Updates in the Management of Candidemia 2015-2016
Changes in guidelines-2009 vs 2016

Changes Since 2009:

• For basically all patients (neutropenic, ICU, etc.) ➔ Use an Echinocandin up front (caspo/mica/anidulafungin)
• Identify the Candida species and obtain susceptibilities for Echinocandins and azoles (if prior exposure)
  • 90% associated with *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis* and *C. parapsilosis*
• If possible: ‘step-down’ to oral regimen (fluconazole/voriconazole preferred) 5-7 days after starting empiric therapy
• **Reminder:** Eye exam w/in 1 week, at least 14 days of tx, remove all lines, and Candida in lungs is almost universally a contaminant!
Double blind non-inferiority study comparing use of Anidulafungin vs fluconazole for invasive Candidiasis in 245 patients

Endpoint: Resolution of symptoms AND fungemia at end of study period, and 2+6 week follow up

Why Echinocandins up front for invasive Candidiasis?

<table>
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<th>End Point</th>
<th>Global Success</th>
<th>Absolute Percent Difference between Treatments (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Fluconazole Group (N=118) no.</td>
<td>Anidulafungin Group (N=127) no. (%)</td>
</tr>
<tr>
<td>End of intravenous therapy</td>
<td>71 (60.2)</td>
<td>96 (75.6)</td>
</tr>
<tr>
<td>End of all therapy</td>
<td>67 (56.8)</td>
<td>94 (74.0)</td>
</tr>
<tr>
<td>2-Week follow-up</td>
<td>58 (49.2)</td>
<td>82 (64.6)</td>
</tr>
<tr>
<td>6-Week follow-up</td>
<td>52 (44.1)</td>
<td>71 (55.9)</td>
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Figure 1. Global Response to Treatment for Prespecified Time Points in the Modified Intention-to-Treat Population.

A successful global response required both clinical success (defined as the resolution of signs and symptoms of invasive candidiasis and no additional systemic antifungal therapy) and microbiologic success (defined as the eradication of candida species present at baseline as determined on follow-up culture, or the presumed eradication if culture data were not available for a patient with a successful clinical response). P<0.02 for the comparison between the anidulafungin group and the fluconazole group at the end of intravenous therapy. P<0.02 for the comparison between the two groups at the end of all therapy and at the 2-week follow-up. At the end of intravenous therapy, 33 patients in each of the two groups (26% in the anidulafungin group and 28% in the fluconazole group) switched to oral fluconazole. For multiple comparisons of the secondary end points, 98.3% confidence intervals (CI) adjusted post hoc were 2.9 to 31.6 at the end of all therapy, 0.4 to 30.4 at the 2-week follow-up, and −3.4 to 27.0 at the 6-week follow-up. The dashed vertical line represents the prespecified margin for noninferiority.
Isavuconazole’s Influence on 2016 guidelines

**Candida**
- Isavuconazole covers most *Candida* species *in vitro* (even fluconazole resistant isolates!)
- ACTIVE-International double-blinded trial: Isavuconazole vs Echinocandin → prelim results suggest Isa is NOT non-inferior
- Do not use a first line for candida

**Aspergillus**
- Alternative to voriconazole for invasive *Aspergillus* infections
- Possible use in salvage therapy (breakthrough on posaconazole ppx)
Updates in Antibiotic Stewardship 2016

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

- All hospitals now required to have Stewardship program by CMS/Joint Commission- 2016
- Guidelines for implementation released this year
Upcoming Challenges 2017 and beyond

Where is the Next big outbreak?

*Candida auris*-potentially resistant to all classes of antifungals

Impact of Zika long term

Long acting HIV regimens

New multidrug-resistant organism treatments

Newer diagnostics

Novel vaccines (including Ebola)