Epidemiology and management of *Staphylococcus aureus* Bloodstream Infection

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Overview

- Introduction
- Brief case
- Bloodstream infection (BSI) general aspects and definitions
- The “special” case of *S. aureus* BSI
- Epidemiology
- Diagnosis
- Management
- Case review and conclusion
Conflict of Interest

- No conflicts
Objectives

• Review the definitions for identifying the presence of and classifying bloodstream infections (BSI)
• Recognize the spectrum of clinical disease and complications associated with *Staphylococcus aureus* BSI
• Review the epidemiology of *Staphylococcus aureus* BSI
• Discuss the management of *Staphylococcus aureus* BSI
Case

- 80 year old woman past history of chronic back pain and osteoarthritis
- General weakness, malaise, and fever
- ER found to have fever to 39 degrees C, no focal findings on exam
- WBC 20, and pyuria. CT Abdo/pelvis unremarkable.
- Admitted and treated with piperacillin/tazobactam for suspected pyelonephritis
Case continued

- Blood and urine cultures grow MSSA
- 7 days iv therapy completed feels better but not back to baseline and kept in as inpatient
- Repeat urine culture shows Cipro sensitive *Klebsiella pneumoniae* and started on that drug
- No dysuria. No fever. No focal back tenderness.
Case continued

- ID called and blood cultures ordered
- Echo-cardiogram, bone scan, cefazolin 2g IV q8h
- Development of leg weakness
- Urgent MRI epidural abscess
- Cloxacillin 2g IV q4h and neurosurgical consult
- Declines surgery
- Long complicated hospital stay and eventual death
Bloodstream infection definitions

• A positive blood culture is mandatory for a diagnosis of BSI
• However, not all positive blood cultures are BSI’s
  • Contamination
  • Bacteremia
  • Transient bacteremia
  • Bloodstream infection (BSI)
Bloodstream infection definitions

• A degree of subjective assessment is required
  • common contaminants coagulase negative staphylooccci, Bacillus, Micrococcus, Corynebacterium, and Propionibacterium species

• Blood must be sent and cultured appropriately (before antibiotics)
  • 1 set = 1 venipuncture and 2 bottles (aerobic and anaerobic)
  • 2 sets (ie 4 bottles) per patient standard
BSI definitions

• Traditional nosocomial versus community-acquired BSI
  • Focus on establishing most likely location of acquisition
  • Subjective component and significant inter-observer variation
  • Infection prevention and control

• Hospital-onset BSI versus community-onset BSI
  • Define by first culture positive after or before 48 hours of admission
  • Objective but lacks detail
  • Clinical management and surveillance
BSI definitions

- Shifts in healthcare provision to community setting
  - Recent admission
  - Specialized care
  - Hemodialysis
  - Chemotherapy
  - Nursing home residents
- Older, different organism distribution, more co-morbidities, more resistant, and higher mortality (Lenz *BMC Infect Dis* 2012)
Laupland and Church *Clin Microbiol Rev* 2014

The diagram illustrates the classification of bloodstream infections (BSIs) based on their etiology and setting. The pyramid is divided into four main categories:

- **Transient bacteremia/fungemia** is the foundation of the pyramid, representing contamination.
- **Hospital-onset (HO)** BSI is the top layer, indicating infections that develop in patients already hospitalized.
- **Infection-associated** BSIs are the middle layer, suggesting infections that start within a hospital setting.
- **Community-onset (CA)** BSI is the bottom layer, referring to infections that start outside a hospital environment.

Additional layers indicate the progression from blood culture positive to viable bacteria/fungi in blood, highlighting the infection's progression and potential causes.
Primary or secondary BSI

- Is BSI an independent entity or just a marker of infection somewhere else?

- **Primary**-vascular catheter-associated only or **no focus** of infection

- **Secondary**-evidence of infection **focus** at a defined body site

- Influences management
The “special” case of *S. aureus* BSI

- Sticky and “abscessogenic”
- Enterotoxins/superantigens
- BSI will alter management for focal infections
- Propensity to acquire resistance
  - Methicillin-sensitive (MSSA)
  - Methicillin-resistant (MRSA)
Epidemiology

• Second most common cause of BSI overall (Laupland Clin Microbiol Infect 2014)
  • *Escherichia coli* 30 per 100,000
  • *Staphylococcus aureus* 21 per 100,000
  • *Streptococcus pneumoniae* 10 per 100,000
Overall case fatality rate MSSA 20.2% and MRSA 22.3%
Laupland *CMI* 2013
<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>No. of patients with ISA infection ((n = 226))</th>
<th>Annual incidence, per 100,000</th>
<th>Relative risk (95% confidence interval)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>24</td>
<td>7692</td>
<td>257.2 (161.0–393.6)</td>
<td>&lt;.001</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>3</td>
<td>4918</td>
<td>150.0 (30.5–441.1)</td>
<td>&lt;.001</td>
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<tr>
<td>Human-immunodeficiency-virus infection</td>
<td>4</td>
<td>778</td>
<td>23.7 (6.4–61.4)</td>
<td>&lt;.001</td>
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<tr>
<td>Solid organ transplantation</td>
<td>3</td>
<td>683</td>
<td>20.7 (4.2–61.3)</td>
<td>&lt;.001</td>
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<tr>
<td>Heart disease</td>
<td>114</td>
<td>362</td>
<td>20.6 (15.8–27.0)</td>
<td>&lt;.001</td>
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<tr>
<td>Cancer</td>
<td>47</td>
<td>348</td>
<td>12.9 (9.1–17.8)</td>
<td>&lt;.001</td>
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<tr>
<td>Illicit intravenous drug use</td>
<td>13</td>
<td>321</td>
<td>10.1 (5.3–17.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>31</td>
<td>241</td>
<td>8.2 (5.4–12.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48</td>
<td>192</td>
<td>7.0 (5.0–9.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>16</td>
<td>200</td>
<td>6.4 (3.6–10.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>26</td>
<td>120</td>
<td>3.9 (2.5–5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2</td>
<td>80</td>
<td>2.4 (0.3–8.7)</td>
<td>.3</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>5</td>
<td>74</td>
<td>2.2 (0.7–5.3)</td>
<td>.1</td>
</tr>
</tbody>
</table>

**NOTE.** ISA, invasive Staphylococcus aureus.
S. aureus BSI western interior

- Overall incidence 2010-2016 (per 100,000)
  - MRSA 6.3
  - MSSA 22.2
S. aureus BSI western interior

• In-hospital case fatality
  • MRSA 23%
  • MSSA 17%

• Focus of infection
  • No focus 28%
  • Bone and joint 24%
  • Endovascular 18%
  • Soft tissue 13%
  • Respiratory 12%
  • Other 3%
Diagnosis-Number of cultures

- Consider any positive blood culture for *S. aureus* a BSI
  - Erroneous use of number of sets positive to classify as BSI not uncommon (ie confused with coag negative staphylococci)
- Persistently positive blood cultures (Kullar *Clin Infect Dis* 2014)
  - Positive blood cultures despite 7 days of therapy
    - More likely endovascular or deep-seated focus
    - Metastatic infection development
    - Risk for post-treatment relapse
    - 2-3 fold higher mortality
Diagnosis-Echocardiography

• Approximately 5-15% of patients will have endocarditis
• Transthoracic approximately 50% sensitive but highly specific
• Transesophageal (TEE) estimated 95%+ sensitive
• TEE on all patients?
• Complicated scoring systems (Palraj Clin Infect Dis 2015)
Diagnosis-Clinical

• Clinical and diagnostic imaging search for a focus
  • Respiratory
  • Bone and joint
  • Intra-abdominal/pelvic
Source control

- Abscess=drain the pus
- Remove the line (Fowler Clin Infect Dis 1998)
- Evacuate the empyema
- Washout the joint
Antibiotherapy

- MSSA
  - Cloxacillin
  - Cefazolin
- MRSA
  - Vancomycin
  - Daptomycin
  - Linezolid
- Adjuncts and combination therapy
Cefazolin or cloxacillin for MSSA

- No RCT’s but increasing observational studies
- Concerns cefazolin
  - high inoculum cefazolin resistance (Nannini AAC 2009)
  - broader spectrum
  - lack of CSF penetration
- McDanel *CID* 2017
  - 3,167 patients, 37% cefazolin versus 63% nafcillin/oxacillin
  - 37% reduction in 30-day and 23% reduction in 90-day mortality after adjustment (20% vs. 25% CFR)
  - Odds of recurrence =1.13; 95% CI 0.94-1.36
From: Comparative Effectiveness of Cefazolin Versus Nafcillin or Oxacillin for Treatment of Methicillin-Susceptible Staphylococcus aureus Infections Complicated by Bacteremia: A Nationwide Cohort Study
Clin Infect Dis | © The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
**Comparison of Cefazolin versus Oxacillin for Treatment of Complicated Bacteremia Caused by Methicillin-Susceptible *Staphylococcus aureus***

**TABLE 3**

Adverse drug events with cefazolin or oxacillin for complicated MSSA bacteremia

<table>
<thead>
<tr>
<th>Outcome or parameter</th>
<th>No. (%) among patients treated with:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Oxacillin</td>
</tr>
<tr>
<td>All adverse drug events</td>
<td>12 (13)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>6 (6)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>1 (1)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Discontinued due to adverse event</td>
<td>9 (10)</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>
Vancomycin and MRSA

- Vancomycin has been the standard drug of choice since MRSA was first identified
- Vancomycin has a number of potential problems
  - Renal dysfunction
  - Penetration
  - Dosing and need for TDM
  - No oral bioavailability
  - Vast anecdotes of dislike
Vancomycin reduced susceptibility

- Vancomycin susceptible ≤2 ug/mL
- Vancomycin intermediate (VISA) 4-8 ug/mL
- Vancomycin resistant (VRSA) ≥16 ug/mL
- Elevated but not resistant MICs ie “MIC creep”
Vancomycin reduced susceptibility

• Jacob *Int JID* 2013
  • Increased mortality (1.4 RR 95% CI, 1.15-1.71) for MIC ≤1ug/mL versus 1.5-2 ug/mL

• Kalil *JAMA* 2014
  • No difference in outcomes with MIC ≤1ug/mL versus 1.5-2 ug/mL in observational studies

• Baxi *AAC* 2016
  • No difference in outcome among 429 episodes with MIC <2ug/mL versus 2 ug/ml
Daptomycin

- Bactericidal
- IV only but once per day (6-12 mg/kg)
- Adjust dosing if cr cl <30 mL/min
- CK elevation/myositis
- Inactivation by pulmonary surfactant
Daptomycin and *S. aureus* BSI

- **Fowler NEJM 2006**
  - Not inferior to standard therapy with low dose gent plus vancomycin (MRSA) or anti-staphylococcal penicillin (MSSA)

- **Retrospective observational studies of MRSA BSI patients with vancomycin MIC>1 ug/mL**
  - **Moore CID 2012**
    - Clinical failure (31% vs. 17%) and mortality (20% vs.9%) higher with vancomycin as compared to daptomycin
  - **Murray CID 2013**
    - Clinical failure (48% vs. 20%) and mortality (13% vs. 4%) higher with vancomycin as compared to daptomycin
  - **Weston CID 2014**
    - Clinical failure vancomycin versus daptomycin 51% vs. 34%
Linezolid

- Well tolerated (cytopenias, serotonin syndrome)
- Tissue penetration including CNS
- High bioavailability
- Bacteriostatic
- Not inferior to vancomycin but very limited secondary data on BSI (Schorr JAC 2005)
Other *in vitro* active drugs?

- Tetracycline/Tigecycline
- TMP-SMX
- Clindamycin
- Quinolones (levofloxacin, moxifloxacin)
Combination therapies

• Combinations of 2 or more active drugs may be either better or worse than one alone

• Rifampin plus vancomycin
  • Observational studies suggest that this combination may be antagonistic (Tremblay Ann Pharmacother 2015)
  • MRSA endocarditis RCT (Levine Ann Intern Med 1991)
    • No significant difference in duration of bacteremia or cure
    • Small study (42 patients)

• Gentamicin plus cell wall agent
  • May clear bacteremia sooner (1 day) but higher rate of renal dysfunction and no difference in outcome (Cosgrove CID 2009)
Combinations with resistant drugs

- A vast array of studies in recent years evaluating combinations of drugs that alone may not be active
  - Daptomycin plus β-lactams (nafcillin, cefotaxime, amoxicillin-clavulanate, and imipenem) reduce cell net positive surface charge increasing that daptomycin binding to the cell surface (Mehta AAC 2012)
  - Daptomycin plus TMP-SMX (Claeys AAC 2015)
  - Vancomycin plus cephalosporins (Rybak Exp Opin Pharmacother 2013)
Evolving treatments

• IV Fosfomycin plus imipenem (del Rio CID 2014)
• Ceftaroline
• Ceftibiprole
• Tedizolid
Duration of therapy

- Endocarditis standard 6 weeks (4 if tricuspid uncomplicated)
- The default duration of therapy for *S. aureus* BSI is 4-6 weeks of IV administered antibiotics (*ie if endocarditis can’t be ruled out then treat it*)
- Care with community onset cases
- Difficult to treat foci may need further oral therapy (*ie bone and joint*)
Duration of therapy

- Short course therapy if all fulfilled
  - Negative TEE
  - Negative repeat blood culture
  - Rapid clinical response
  - Removable focus
  - No clinical signs of metastasis
  - No indwelling device (i.e., pacemaker)
Case review

- First identification of *S. aureus* in blood cultures should have prompted a clinical search for a focus (urine culture was a red herring)
- TEE
- Repeat blood cultures
- Imaging of spine
- Minimum 4 weeks of IV therapy
- ID consult
Summary

- *Staphylococcus aureus* BSI is a serious condition that is associated with major adverse outcomes
- Second most common but arguably most important etiology of BSI
- Sending blood for culture is necessary to identify *S. aureus* BSIs
Summary

• A clinical and diagnostic imaging search for foci is required in patients who have *S. aureus* BSI
• Core management principles include source control, identification of complicated foci/metastasis, and appropriate anti-biotherapy (drug, dose, duration)
• Infectious diseases consultation is recommended in the management of patients with *S. aureus* BSI
Questions?