Right Sided Infective Endocarditis

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Overview

• Review of a Patient Case

• Background on Infective Endocarditis

• Review treatment for native valve endocarditis caused by Staphylococci

• The use of daptomycin in Infective Endocarditis

• Conclusion
# Patient DP

34 year old man presenting to ED

<table>
<thead>
<tr>
<th>CC</th>
<th>Right sided chest pain x 2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPI</td>
<td>Pt presents with 2 day history of intermittent non radiating right sided substernal chest pain with associated shortness of breath. Patient states he was febrile at home, denied neck or arm pain, dysuria, flank pain, nausea, vomiting, diarrhea, or any sick contacts.</td>
</tr>
<tr>
<td>PMH</td>
<td>Bursitis</td>
</tr>
</tbody>
</table>
| SH     | Homeless, occasionally stays with friends  
+ IDU: heroin  
+ Cocaine use  
+ Narcotic use (hydrocodone/acetaminophen)  
+ smoker, 1 ppd x 10 years  
+ Occasional EtOH |
| FH     | Mother died of lupus at age 34   |
| Allergies | NKDA                                   |
| Immunizations: unknown |
Patient DP

PE on admission
Ht: 5’8”   Wt: 171 lb (77.3 kg)   BMI: 26 kg/m²

<table>
<thead>
<tr>
<th>Temp</th>
<th>Pulse</th>
<th>BP</th>
<th>RR</th>
<th>O2 Sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.7</td>
<td>113</td>
<td>79/45</td>
<td>26</td>
<td>92%</td>
</tr>
</tbody>
</table>

- **Gen**: Diaphoretic, appears uncomfortable
- **HEENT**: Pinpoint pupils, EOMI
- **Resp**: CTAB
- **CV**: Tachycardic, S1, S2, (-) MRG
- **Abd**: Soft, non tender
- **Ext**: Scarring from IVDU
- **Skin**: Dry mucous membranes
- **Neuro**: AAO x 3, no focal deficits
RBC: 3.36 \times 10^6/\mu L
ESR: 52 mm/hr
CRP: > 200 mg/L
LA: 1.4 mmol/L
AST/ALT: 21/24 IU/L
Alk Phos: 111 IU/L
Bili T/D/I: 0.7/0.3/0.4
Alb: 1.9 mmol/L
Ca: 7.1 mg/dL
Corrected Ca: 8.78 mg/dL
CPK: 42 IU/L
Troponin: <0.04 \times 3 ng/ml
Lipase: 10 IU/L
EKG: T wave inversions in lead 3
CrCl: 59 ml/min (111 ml/min)
Hospital Course

- ED: 5L NS raised BP to 101/55. Started on empiric antibiotic therapy with vancomycin and piperacillin/tazobactam. Blood cultures drawn 9/21 in ED.

- Inpatient: Original blood cultures came back with growth at 10 hours of gram-positive cocci in clusters x 2.

- ECHO: Normal LV, EF 55-60% 2 x 1 cm vegetation on tricuspid valve with resultant moderate to severe tricuspid regurgitation. Non mobile echo density on pulmonic valve. Erratically moving echo density within pulmonary artery. RV dilated with preserved RV function.

- Patient switched to daptomycin due to concern of worsening kidney function/acute kidney injury.
## Inpatient Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl 0.9%</td>
<td>5L total</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.5 grams IV BID</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>3.375 mg IV Q6H</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>650mg IV</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>650mg Q4-6 hr prn</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Morphine</td>
<td>2-4mg IV Q4H prn</td>
<td>Pain/opioid withdrawal</td>
</tr>
<tr>
<td>Heparin</td>
<td>5,000 units SC Q8H</td>
<td>DVT ppx</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5mg po x 2</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1-2mg IV HS prn</td>
<td>Difficulty sleeping/anxiety</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>80mg IV Q8H</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>2g IV Q4H</td>
<td>Endocarditis</td>
</tr>
</tbody>
</table>
Right Sided Infective Endocarditis
Right Sided Infective endocarditis (IE)

Epidemiology

• 5% to 15% hospital admissions for acute infection
• Incidence: 1.5 to 3.3 cases per 1000 person-years
• Higher among HIV-seropositive IDU (13.8 cases per 1000 person-years)
• Most common risk factor for development of recurrent native valve IE; 43% of 281 patients

Most common pathogen: Staphylococcus aureus.

• Community-acquired oxacillin-resistant strains, coagulase-negative staphylococci, Beta-Hemolytic streptococci, fungi, aerobic gram-negative bacilli, including Pseudomonas aeruginosa, polymicrobial
Right Sided Infective endocarditis (IE)

- The Duke Criteria: sensitivity and specificity > 80%

- General: Fever, rigors, night sweats, anorexia, weight loss, or arthralgia
- Cardiac: Murmur
- Skin Lesions: Osler’s nodes, Janeway lesions, splinter hemorrhages, petechiae, clubbing
- Eyes: Roth spots
- Other: Splenomegaly, neurological, renal

Right Sided IE: pleuritic chest pain, pulmonary findings, tricuspid insufficiency
- Septic pulmonary emboli eventually present in 87% of cases
- 35% of IDUs with IE demonstrate heart murmurs on admission

Infective Endocarditis. Circulation 2005; 111: e394-e434
Pathogenesis
## Treatment: Native valve Endocarditis caused by Staphylococci

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Route</th>
<th>Duration</th>
<th>Strength of Recomendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin-susceptible: Nafcillin or oxacillin with Optional addition of gentamicin sulfate</td>
<td>12g/24 h IV in 4-6 equally divided doses</td>
<td>6 weeks</td>
<td>1A</td>
<td>6 weeks for complicated right-sided IE and for left-sided IE; 2 weeks for uncomplicated right-sided IE</td>
</tr>
<tr>
<td></td>
<td>3mg/kg per 24h IV/IM in 2 or 3 equally divided doses</td>
<td>3-5 days</td>
<td></td>
<td>Clinical benefit not yet established. Dosage should be adjusted to achieve peak serum concentration of 3–4 mcg/mL and trough serum concentration of &lt; 1 mcg/mL when 3 divided doses are used</td>
</tr>
<tr>
<td>Oxacillin-resistant Vancomycin</td>
<td>30mg/kg per 24 h IV in 2 equally divided doses</td>
<td>6 weeks</td>
<td>1B</td>
<td>Adjust vancomycin dosage to achieve 1-h serum concentration of 30–45 mcg/mL and trough concentration of 10–15 mcg/mL</td>
</tr>
</tbody>
</table>

Infective Endocarditis. Circulation 2005; 111: e394-e434
Vancomycin

- Current standard for MRSA associated IE
- Longer duration of therapy
- Suboptimal outcomes for MSSA
- Slow clinical response
Daptomycin

• Indication:
  • 4mg/kg Q24H x 7-14 days: complicated skin and skin structure infections
  • 6mg/kg Q24H x 2-6 weeks: Staphylococcus aureus bacteremia, including right-sided IE caused by MSSA or MRSA

• MOA: Binds to bacterial cell membranes and causes a rapid depolarization of membrane potential, causing inhibition of DNA, RNA, and protein synthesis; results in bacterial cell death.

• Rapid bactericidal activity in vitro against most gram-positive bacteria
• Role in treatment of staphylococcal endocarditis not clearly defined

Cubicin (daptomycin)[package insert]. Cubist Pharmaceuticals, Inc
Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

- Open label, randomized, non inferiority trial
- 44 sites in four countries
- August 28, 2002 to February 16, 2005

- Analysis: modified intention-to-treat population and per protocol
- Block randomization 1:1 daptomycin or standard therapy

- Interventions:
  - Daptomycin 6 mg/kg IV once daily
  - Standard therapy
    - Vancomycin 1g Q12H
    - Antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) 2g Q4H
Study Design

Inclusion Criteria:
- 18 years of age or older
- One or more blood cultures that were positive for S. aureus within two days before initiating study medication.

Exclusion Criteria:
- CrCl < 30ml/min, significant hepatic insufficiency
- Osteomyelitis, pneumonia, refractory shock
- Polymicrobial bacteremia
- S. aureus with reduced susceptibility to vancomycin (MIC > 4 μg/ml)

Primary outcome: Clinical success rate in each of the two treatment groups in the modified intention-to-treat population at the visit 42 days after the end of therapy.

Patient Characteristics

- 246 patients randomly assigned
  - 120 to daptomycin and 115 to standard therapy
  - Standard therapy: 62 patients received antistaphylococcal penicillins (50 nafcillin, 9 flucloxacillin, 3 oxacillin), and 53 received vancomycin

- Median age: 50 years, 40% females, 20% injection drug users
- 8.3% vs 11.3% with septic pulmonary emboli
- MRSA: 45 in daptomycin (37.5%) and 44 in standard therapy (38.3%)

# Patient Characteristics

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Daptomycin (n=120) #(%)</th>
<th>Standard Therapy (n=115) #(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated bacteremia</td>
<td>32 (26.7)</td>
<td>29 (25.2)</td>
</tr>
<tr>
<td>Complicated bacteremia</td>
<td>60 (50)</td>
<td>61 (53)</td>
</tr>
<tr>
<td>Uncomplicated right-sided endocarditis</td>
<td>6 (5)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Complicated right-sided endocarditis</td>
<td>13 (10.8)</td>
<td>12 (10.4)</td>
</tr>
<tr>
<td>Left-sided endocarditis</td>
<td>9 (7.5)</td>
<td>9 (7.8)</td>
</tr>
</tbody>
</table>

Results

- Primary outcome: Overall success in modified intention to treat population
  - 44.2% in daptomycin group
  - 41.7% in standard therapy group
  - Absolute difference in success rates: 2.4% (-10.2 to 15.1)
- MSSA:
  - 44.6% in daptomycin group
  - 48.6% in standard therapy group
  - Absolute difference in success rates: -4% (-20.3 to 12.3), P=0.74
- MRSA:
  - 44.4% in daptomycin group
  - 31.8% in standard therapy group
  - Absolute difference in success rates: 12.6% (-7.4 to 32.6), P=0.28
- Success at end of therapy:
  - 61.7% in daptomycin group
  - 60.9% in standard therapy group
  - Absolute difference in success rates: 0.8% (-11.7 to 13.3)

Application in Clinical Practice

Strengths:
• Randomized
• Does have comparable efficacy to standard therapy in treatment of MRSA and MSSA infections

Limitations:
• Open label
• Study groups were heterogenous: several different types of infections
• Compared to standard therapy, did not break down results for different regimens.
• Lack of statistical significance does not mean non inferiority- success rates not even that high

Conclusions: Would not yet recommend daptomycin over vancomycin in a patient with IE, especially with known pulmonary septic emboli

Patient DP

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/23</td>
<td>Patient not improving, occasional hemoptysis</td>
</tr>
<tr>
<td>9/24</td>
<td>Susceptibility cultures came back as MSSA. Therapy streamlined to nafcillin and gentamicin. CT Chest: Numerous patchy/nodular areas of consolidation throughout each lung. R &gt; L pleural effusion. Raised concern for septic pulmonary emboli.</td>
</tr>
<tr>
<td>9/25</td>
<td>Repeat CT chest showed worsening bilateral pleural effusions. Thoracentesis done. Exudative based on Lights criteria.</td>
</tr>
<tr>
<td>9/26</td>
<td>TEE showed 2.4 x 1.6cm tricuspid valve mass with moderate to severe regurgitation and suspected perforated tricuspid. Patient transferred to RIH for surgical review.</td>
</tr>
</tbody>
</table>
References


