Adult Medicine PRN Focus Session—An Update to the Management of Acute Bacterial Skin and Skin Structure Infections: What is the Utility of the New Agents?

Activity Number: 0217-0000-16-120-L01-P, 1.50 hours of CPE credit; Activity Type: An Application-Based Activity

Monday, October 24, 2016
1:30 p.m. to 3:00 p.m.
Great Halls 1 & 2

Moderator: Kurt Wargo, Pharm. D., BCPS
Regional Dean and Associate Professor of Pharmacy, Wingate University Hendersonville Health Sciences Center, Hendersonville, North Carolina

Agenda

1:30 p.m. Acute Bacterial Skin and Skin Structure Infections: A Review of The Pathophysiology and Epidemiology and Relevance of Current Guidelines
Douglas N. Fish, Pharm. D., FCCP, BCPS
Professor and Chair, Department of Clinical Pharmacy, Department of Pharmacy, University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado

2:00 p.m. The Treatment of ABSSSIs Caused by MRSA: Should New Agents Be First-line Therapy?
Sandy J. Estrada, Pharm. D., BCPS
Pharmacy Clinical Specialist, Infectious Diseases; PGY2 Infectious Diseases Program Director, Lee Memorial Health System, Fort Meyers, Florida

2:30 p.m. The Treatment of ABSSSIs Caused by MRSA: If It Ain’t Broke, Don’t Try and Fix It!
Katherine T. Lusardi, Pharm. D., BCPS, AQ-ID
Antimicrobial Stewardship Pharmacist, UAMS Medical Center, Little Rock, Arkansas

Conflict of Interest Disclosures
Sandy J. Estrada: Clinical Investigator: (The Medicines Company), Speaker’s Bureau: (The Medicines Company, Theravance, Merck)
Douglas N. Fish: Consultancies: (Theravance), Grants: (Merck)
Katherine T. Lusardi: Stocks: (Gilead Sciences, Inc)
Kurt Wargo: no conflicts to disclose

Learning Objectives
1. Discuss the pathophysiology and epidemiology of ABSSSIs.
2. Apply the most current guideline recommendations to the treatment of their patients.
3. Describe new agents approved since the release of 2014 guidelines.
4. Compare and contrast the new agents for the treatment of ABSSSIs caused by MRSA.
5. Determine the role of new agents in the treatment of ABSSSIs caused by MRSA.
6. Discuss advantages of new agents over older alternatives.
7. Compare and contrast advantages and disadvantages of new agents in relation to older alternatives.
8. Compare and contrast costs associated with new agents compared to older alternatives.
9. Develop plans to optimize old alternatives in order to achieve similar outcomes to the new agents.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Acute Bacterial Skin and Skin Structure Infections: A Review of the Pathophysiology and Epidemiology, and Relevance of Current Guidelines

Douglas N. Fish, PharmD, FCCP, BCPS-AQ ID
Skaggs School of Pharmacy and pharmaceutical Sciences,
Anschutz Medical Campus
Aurora, Colorado
October 24, 2016

Learning Objectives

• Discuss the pathophysiology and epidemiology of Acute Bacterial Skin and Skin Structure Infections (ABSSSIs)
• Apply the most current guideline recommendations to the treatment of patients
• Describe agents approved since the release of the 2014 IDSA guidelines

Epidemiology of ABSSSIs

• ED visits for ABSSSIs increased from 1.2 million to 3.4 million between 1992 and 2005
• May account for up to 7-10% of all hospital admissions
• Hospital admissions due to ABSSSIs increased in U.S. from 675,000 to 870,000 between 2000 and 2004 (29% increase)
  • In UK, three-fold increase in hospitalizations for abscesses and cellulitis from 1991-2006
  • In Australia, 48% increase in hospitalizations due to cutaneous abscesses from 1999-2008
• Many potential complications including thrombophlebitis, abscess, osteomyelitis, septic arthritis, sepsis
  • 10-34% of all S. aureus bacteremias originate from ABSSSI

Pathophysiology of ABSSSIs

• Skin infections occur as a result of breaches in the skin barrier, either macroscopic or microscopic
• S. aureus infections best characterized
• Neutrophils and macrophages involved in primary response to bacterial invasion
• Host response evaded by multiple bacterial mechanisms including:
  • Blocking of leukocyte chemotaxis
  • Sequestration of host antibodies
  • Formation of polysaccharide capsules or biofilms to escape leukocyte detection
  • Resisting destruction after ingestion by phagocytes

Conflict of Interest

• Advisory Board: Theravance
• Grant Funding/Research Support: Merck
### Pathophysiology of ABSSSIs

- Multiple virulence factors in *S. aureus* including:
  - Panton-Valentine Leukocidin (PVL) in CA-MRSA = lyases WBCs
  - Alpha-hemolysin = toxin forms pores in human cells, facilitates penetration of skin layers, associated with more severe cutaneous lesions
  - Phenol-soluble modulins (PSMs) = proteins lyse cells including leukocytes and erythrocytes, facilitate colonization and invasion
  - Arginine catabolic mobile element (ACME) = provides protection against microbical compounds produced by skin
  - Regulatory locus referred to as acm controls the expression of PVL, alpha-hemolysin, PSMs, and other toxins

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### Etiology of ABSSSIs

- Retrospective study performed in patients at Kaiser Permanente of Northern California between 2006 and 2009
  - Over 3 million covered lives in the system
  - 648,699 infections among 495,458 unique patients
  - 52% female, 78% adults, mean ± 50 age = 41 ± 23
  - Hospitalization in 6% of patients
  - Only 23% of patients cultured, but 58% of cultures were positive
    - 2% of patients with positive blood cultures
    - 39% of blood isolates were *S. aureus*
    - 41% of *S. aureus* isolates were MRSA

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### Overview of the Skin and Skin Structures

- **Epidermis**
  - Avascular proliferative layer, constantly regenerating protein and lipid
  - About as thick as a sheet of paper

- **Dermis**
  - Contains blood vessels, lymphatics, and fibroblasts
  - Eccrine sweat glands, sebaceous glands, and hair follicles originate here

- **Subcutaneous tissue**
  - Effective cushion and energy storage reserve of variable thickness
  - Directly overlies fascia and muscle tissues

Skin and skin structure infections may include any and all layers of the skin as well as fascia and muscle

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### Classifications of Skin Infections

- **Primary**: involve areas of previously healthy skin, usually involve only one pathogen
- **Secondary**: occur in areas of previously damaged skin, often polymicrobial
- **Complicated**: involve deeper skin structures (e.g. fascia, muscle), require significant surgical intervention, and/or occur in patients with compromised immune function (e.g. diabetes, HIV infection)
ABSSSI Classification: Uncomplicated vs. Complicated

<table>
<thead>
<tr>
<th>Uncomplicated (Primary)</th>
<th>Complicated (Secondary)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial:</strong></td>
<td></td>
</tr>
<tr>
<td>- Impetigo</td>
<td>Acute wound infections:</td>
</tr>
<tr>
<td>- Erysipelas</td>
<td>- Traumatic</td>
</tr>
<tr>
<td>- Cellulitis</td>
<td>- Bite-related</td>
</tr>
<tr>
<td><strong>Hair follicle associated:</strong></td>
<td>- Post-operative</td>
</tr>
<tr>
<td>- Folliculitis</td>
<td>Chronic wound infections:</td>
</tr>
<tr>
<td>- Furunculosis</td>
<td>- Diabetic foot infections</td>
</tr>
<tr>
<td><strong>Abscess:</strong></td>
<td>- Venous stasis ulcers</td>
</tr>
<tr>
<td>- Carbuncle</td>
<td>- Pressure sores</td>
</tr>
<tr>
<td>- Other cutaneous abscesses</td>
<td>Perianal cellulitis ± abscess</td>
</tr>
</tbody>
</table>

S. aureus implicated pathogen

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Uncomplicated (%)</th>
<th>Complicated (%)</th>
<th>MRSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caruncle</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Furunculosis</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Etiology of ABSSSIs: Kaiser Permanente, 2006-2009

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>MRSA (%)</th>
<th>MSSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caruncle</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Furunculosis</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Patient Case #1

J.J. is a 44-year-old male who presents to the ED with a swollen and painful right lower leg after scratching it on a barbed wire fence. The right calf has a 6 x 4 cm lesion without a well demarcated border which is diffusely red, erythematous, warm to the touch, and painful. No ulcers, blisters, drainage, or areas of necrosis are noted. His PMH is noncontributory and he has NKDA. He has a fever of 100.2°F, otherwise no other systemic findings. J.J. is diagnosed with cellulitis of the right lower leg.

Which of the following antibiotic regimens would be MOST appropriate for treatment of J.J.'s infection?

- a. Oral cephalexin x 5 days
- b. Oral trimethoprim/sulfamethoxazole x 10 days
- c. Intravenous vancomycin x 7 days
- d. Intravenous cefazolin x 10 days

SSTI Management Definitions

- **Nonpurulent SSTIs:**
  - Mild infection: no focus of purulence or systemic signs of infection
  - Moderate infection: systemic signs of infection (temperature >38°C, tachycardia (heart rate >90 beats per minute), tachypnea (respiratory rate >24 breaths per minute) or abnormal white blood cell count [<12 000 or <400 cells/µL])
  - Severe infection: failure of oral antibiotics or systemic signs of infection, or those who are immunocompromised, or those with clinical signs of deeper infection such as bilevel, skin sloughing, hypotension, or evidence of organ dysfunction

- **Purulent SSTIs:**
  - Mild infection: incision and drainage
  - Moderate infection: systemic signs of infection as above
  - Severe infection: patients who have failed incision and drainage plus oral antibiotics, those with SIRS and hypotension, or immunocompromised patients

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Published June 18, 2014
Management of ABSSSIs: IDSA 2014 Guidelines

Nonpurulent Infections
(Examples: Cellulitis, erysipelas, nontuberculous infections)

Mild Infection

Moderate Infection

Severe Infection

Outpatient Treatment of ABSSSI

- For non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended in mild infections
  - β-Lactam (e.g. PCN, VK, cephalexin, dicloxacillin) 500 mg PO QID
  - Clindamycin 300-450 mg PO TID
- IV therapy with similar agents for moderate infections
- Empiric coverage for MRSA is recommended in patients who do not respond to β-lactam therapy
  - May also be considered in those with systemic toxicity, IVDUs, penetrating trauma
- Duration of therapy = 5 days

Patient Case #1 Revisited

J.J. is a 44 year-old male who presents to the ED with a swollen and painful right lower leg after scratching it on a barbed wire fence. The right calf has a 4 x 6 cm lesion without a well demarcated border which is diffusely red, erythematous, warm to the touch, and painful. No ulcers, blisters, drainage, or areas of necrosis are noted. His PMH is noncontributory and he has NKDA. He has a fever of 100.2°F, otherwise no other systemic findings. J.J. is diagnosed with cellulitis of the right lower leg.

Which of the following antibiotic regimens would be MOST appropriate for treatment of J.J.'s infection?

a. Oral cephalaxin x 5 days
b. Oral trimethoprim/sulfamethoxazole x 10 days
c. Intravenous vancomycin x 7 days
d. Intravenous cefazolin x 10 days

Patient Case #2

Y.K. is a 69 year-old female presents with an erythematous area on her left upper arm which is warm to the touch and edematous. The affected area is approximately 4 in² with poorly defined borders, and has an area in the center which is ulcerated and draining a brownish, purulent fluid. Her temperature is 102.3°F and WBCs are elevated at 12,000; her other vital signs are normal. Her medical history is significant for HTN, DL, and depression. She has NKDA.

Y.K. is diagnosed with cellulitis. Following incision & drainage, what is the most appropriate empiric antibiotic treatment for this patient?

a. Oral dicloxacillin x 10 days
b. Oral trimethoprim/sulfamethoxazole x 5 days
c. Intravenous vancomycin x 7 days
d. Intravenous cefazolin x 10 days

Etiology of ABSSSIs: Kaiser Permanente, 2006-2009

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>% of Episodes</th>
<th>MRSA</th>
<th>β-hemolytic Streptococci</th>
<th>Other Gram +</th>
<th>F. coli</th>
<th>Other Gram +</th>
<th>Anaerobic Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>6%</td>
<td>81</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>&lt;5</td>
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<tr>
<td>Folliculitis</td>
<td>14%</td>
<td>88</td>
<td>32</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>10</td>
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<tr>
<td>Impetigo</td>
<td>8%</td>
<td>88</td>
<td>13</td>
<td>18</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td>80</td>
<td>27</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Carbuncle/ Erysipelas</td>
<td>6%</td>
<td>91</td>
<td>56</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Wound Infection</td>
<td>3%</td>
<td>52</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>ABSSSI</td>
<td>1%</td>
<td>68</td>
<td>18</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>31</td>
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Management of ABSSSIs: IDSA 2014 Guidelines

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2014 IDSA Guidelines: Outpatient Treatment of ABSSSI

- Empirical therapy for MRSA is recommended for purulent cellulitis (e.g., cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess) in outpatients
- Antibiotics include:
  - TMP-SMX 1-2 DS tabs PO BID
  - Doxycycline 100 mg PO BID
  - Alternative agents include minocycline (200 mg x 1, then 100 mg PO BID)
- Duration of therapy = 5 days

Patient Case #2 Revisited

Y.K. is a 69 year old female presents with an erythematous area on her left upper arm which is warm to the touch and edematous. The affected area is approximately 4 in² with poorly defined borders, and has an area in the center which is ulcerated and draining a brownish, purulent fluid. Her temperature is 102.3°F and WBCs are elevated at 12,000; her other vital signs are normal. Her medical history is significant for HTN, DL, and depression. She has NKDA.

Y.K. is diagnosed with cellulitis. Following incision & drainage, what is the most appropriate empiric antibiotic treatment for this patient?

- a. Oral dicloxacillin x 10 days
- b. Oral trimethoprim/sulfamethoxazole x 5 days
- c. Intravenous vancomycin x 7 days
- d. Intravenous cefazolin x 10 days

Management of ABSSSIs: IDSA 2014 Guidelines

- Purulent Infections
  - Mild Infection
    - Incision & Drainage
  - Moderate Infection
    - Incision & Drainage Specimens for C/S
    - Oral Antibiotics: TMP/SMX
  - Severe Infection
    - Incision & Drainage Specimens for C/S
    - Empiric IV Antibiotics: Vancomycin
      - Linezolid
      - Daptomycin
      - Telavancin
      - Ceftazidime

Patient Case #3 Revisited

F.S., a 49 year-old male, presents to the ED with cellulitis on his back. The lesion is a 3 cm-diameter abscess with necrotic edges, a 4 cm halo of erythema, and warm to the touch of yellowish purulent material. Two similar, smaller lesions are also present. The PMH is significant for hypertension, T2DM, and obesity. F.S. has a temperature of 101.9°F and WBC of 14,500. F.S. was initially seen by his PCP 5 days ago for a self-reported “spider bite” on his back; at that time an I & D of a 1 x 2 cm abscess was performed and he was started on PO clindamycin.

Which of the following antibiotic regimens would be most appropriate for F.S at this time?

- a. Oral amoxicillin/clavulanate x 10 days
- b. Intravenous vancomycin x 5 days
- c. Oral trimethoprim/sulfamethoxazole x 7 days
- d. Intravenous cefazolin x 10 days

Treatment of ABSSSI in Hospitalized Patients

- Empiric antibiotics for hospitalized patients with complicated infections (e.g., deeper infections, surgical/traumatic wound infection, major abscesses, cellulitis, infected ulcers/burns) should cover MRSA pending culture results:
  - Vancomycin 30-40 mg/kg/d
  - Dosed to troughs of 15-20 mg/L
  - Linezolid 600 mg IV/PO Q12H
  - Daptomycin 4 mg/kg IV Q24H
  - Telavancin 10 mg/kg IV Q24H
  - Ceftaroline 600 mg IV Q12H
- Duration of therapy = 7-14 days

Stevens DL et al. Clin Infect Dis 2014 Sep 1;61(5) 1-2, 2016 ACCP Annual Meeting
Antibiotic Options for Treatment of MRSA ABSSSIs in Hospitalized Patients

• Traditional “older” agents
  • Vancomycin – approved 1958
  • Clindamycin – approved 1968
  • Quinupristin/dalfopristin (Synercid) – approved 1999
  • Linezolid (Zyvox) – approved 2000
  • Daptomycin (Cubicin) – approved 2003
  • Tigecycline (Tygacil) – approved 2005

• Newer agents
  • Telavancin (Vibativ) – approved 2009
  • Ceftaroline (Teflaro) – approved 2010
  • Dalbavancin (Delvance) – approved May 23, 2014
  • Tedizolid (Sivextro) – approved June 20, 2014
  • Oritavancin (Orbactiv) – approved August 6, 2014

ABSSSI Pathophysiology, Epidemiology, and Current Guidelines: Key Takeaways

• ABSSSIs are among the most common infections & increasing in both frequency and severity
• MRSA remains a key pathogen, being more common in purulent and complicated infections
• The 2014 IDSA guidelines base need for empiric antibiotics and specific drug selection on purulent vs. nonpurulent infection, severity, and risk of MRSA
• Newer agents for the treatment of ABSSSI are either not well defined or not addressed at all in the 2014 IDSA guidelines, creating controversy regarding appropriate roles
The Treatment of ABSSSIs caused by MRSA: Should New Agents be First Line Therapy

Sandy J. Estrada, Pharm.D., BCPS (AQID)
Lee Memorial Health System
Fort Myers, FL
10/24/2016

Conflict of Interest

• Speaker’s Bureau: Merck, Theravance, The Medicines Company
• Research Funding: The Medicines Company

Learning Objectives

• Compare and contrast the new agents for the treatment of ABSSSIs caused by MRSA
• Determine the role of new agents in the treatment of ABSSSIs caused by MRSA
• Discuss advantages of new agents over older alternatives

Why Do We Need New Agents?

• MRSA Rates remain high nationally
• Increased Vancomycin MICs
• Higher vancomycin doses increase nephrotoxicity
• Vancomycin tolerance affects susceptibility of other agents

Newly Approved Antimicrobials

• Telavancin
  • Approved: September 11, 2009
  • Label expansion for concurrent S. aureus bacteremia
• Dalbavancin
  • Approved: May 23, 2014
  • Tedizolid phosphate
  • Approved: June 20, 2014
• Oritavancin
  • Approved: August 6, 2014
• All indicated to treat ABSSSI

Case

• ZT is 38 year old male with a history of non-healing surgical wound on his left foot
  • Culture from 3 weeks ago grew MRSA
  • Vancomycin MIC 2 mcg/ml, Linezolid MIC 2 mcg/ml
  • Patient completed 10 days of oral linezolid
• PMH: Diabetes, obesity
• PSH: Left second toe amputation
• Social history: non-contributory except that he is a business owner and is reluctant to be hospitalized or come for daily iv antimicrobial infusion
• At office visit today, there is purulent drainage from the wound and no significant improvement from the last visit
• Would you consider a “new” ABSSSI antimicrobial for ZT?
The Old or the New: Factors to Consider

- Guidelines
- Primary Literature
- Resistance
- Pharmacoeconomics
- Patient Satisfaction

Tedizolid

Tedizolid phosphate is rapidly converted to tedizolid by serum phosphatase in vivo.

Parameter | Tedizolid 200 mg daily | Cmax 1.8 mcg/ml | Tmax (oral) 3 hours | AUC0-inf 21.6 mcg x hr/ml | Protein binding 85-90% | Half-life 11 hours | Volume of distribution 108 L | Elimination 10% urine 82% feces | Bioavailability 91%

Comparative Pharmacokinetics

Tedizolid is approximately 4-8x more potent than linezolid.

- Linezolid
- 600 mg PO BID x 10 days

Enhanced Activity in vitro with Tedizolid

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC &gt; mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus MSSA</td>
<td>0.25-0.50</td>
</tr>
<tr>
<td>Staphylococcus aureus MRSA</td>
<td>2.0</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.25-0.50</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>0.25-0.50</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.25-0.50</td>
</tr>
<tr>
<td>Enterococcus faecalis Non-VRE &amp; VRE</td>
<td>0.5</td>
</tr>
<tr>
<td>Enterococcus faecium Non-VRE &amp; VRE</td>
<td>0.5</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>1.0</td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>1.0</td>
</tr>
</tbody>
</table>

In vitro stability against some linezolid resistant isolates.

Less GI Toxicity with Tedizolid in Phase III Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Tedizolid N=652</th>
<th>Linezolid N=652</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>20 (3.0)</td>
<td>29 (4.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (2.0)</td>
<td>21 (3.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (2.3)</td>
<td>35 (5.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (1.8)</td>
<td>20 (3.1)</td>
</tr>
<tr>
<td>Irritation</td>
<td>65 (9.8)</td>
<td>75 (11.4)</td>
</tr>
</tbody>
</table>

Tedizolid 200 mg PO daily x 6 days vs Linezolid 600 mg PO BID x 10 days
Telavancin Summary

**Features and Properties**
- Indication: Complicated skin and skin structure infections in adults, including patients with concurrent S. aureus bacteremia.
- Resistant Spectrum of Activity: MRSA, VISA/VISA, DAP-NS LR-SA.

**Dosage and Administration**
- **Dose:** 10 mg/kg
- **Frequency:** Daily
- **Preparation and administration:** IV: D5W 250 mL; 1 hour infusion
- **Dose correction for CrCl:**
  - **CrCl 10-30 ml/min:** 10 mg/kg Q48h
  - **CrCl 10-30 ml/min:** 10 mg/kg Q24h

**Telavancin In vitro Activity against Methicillin-Resistant S. aureus (MRSA)**

**ATLAS 1&2: Telavancin Phase 3 Studies in cSSSI**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Telavancin MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (M)</td>
<td>0.06</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.06</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.06</td>
</tr>
<tr>
<td>Vancomycin ≤5 µg/mL</td>
<td>0.06</td>
</tr>
<tr>
<td>Vancomycin ≥2 µg/mL</td>
<td>0.06</td>
</tr>
<tr>
<td>Daptomycin 16.5 µg/mL</td>
<td>0.06</td>
</tr>
<tr>
<td>Daptomycin 5.2 µg/mL</td>
<td>0.06</td>
</tr>
<tr>
<td>Multidrug resistant</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Primary objective:**
- To compare the efficacy and safety of VIBATIV to vancomycin in the treatment of adult with complicated Gram-positive cSSSI with emphasis on patients with infections due to MRSA at a test-of-cure (TOC) visit 7-14 days after completion of therapy.

**Comparisons:**
- Telavancin 10 mg/kg IV Q24h
- Vancomycin ≤5 µg/mL Q24h
- Treatment duration: 7-14 days

**References:**
ATLAS 1&2: Cure Rates

<table>
<thead>
<tr>
<th></th>
<th>Pooled clinical cure rates from Phase 3 clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

ATLAS 1&2 Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>VIBATIV 10 mg/kg</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=929</td>
<td>N=535</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>33 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Foamy urine</td>
<td>13 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 %</td>
<td>13 %</td>
</tr>
</tbody>
</table>

Dalbavancin Summary

**Features and Properties**

**Indication**
- Complicated skin and skin structure infections in adults

**Mechanism of action**
- Glycopeptide antibacterial inhibits peptidoglycan synthesis

**Resistant Spectrum of Activity**
- MRSA, VISA/VISA, DAP-NS SA/Ent, LR-Ent

**Dosage and administration**
- Dose: 1000mg day 1; 500mg day 8 or 1500 mg day 1
- Frequency: Once weekly
- Preparation and administration: D5W only (1-5 mg/ml) 30 minute IV infusion
- Renal Adjustment: (CrCl <30 ml/min) 750mg day 1; 375 mg day 8 OR 1175 mg IV x 1

Dalbavancin Activity Against Gram Positive Pathogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>Dalbavancin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0.06</td>
<td>3</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.06</td>
<td>2</td>
</tr>
<tr>
<td>VISA</td>
<td>1.00</td>
<td>14</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.12</td>
<td>0.5</td>
</tr>
<tr>
<td>Vibrio group streptococci</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>0.06</td>
<td>2</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td>VanA VRE</td>
<td>32-128</td>
<td>512</td>
</tr>
<tr>
<td>VanB/C VRE</td>
<td>0.10-1</td>
<td>512</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Listeria species</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

**Similar Early Response Rates with Dalbavancin**

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin 2 Doses</th>
<th>Vancomycin/Linezolid</th>
<th>Absolute Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion spread</td>
<td>83.3%</td>
<td>81.8%</td>
<td>1.5 (-4.6 to 7.6)</td>
</tr>
<tr>
<td>DISCOVER 1</td>
<td>76.6%</td>
<td>78.3%</td>
<td>-1.7 (-4.4 to 1.0)</td>
</tr>
<tr>
<td>Both Trials</td>
<td>79.7%</td>
<td>79.8%</td>
<td>0.1 (-4.5 to 4.2)</td>
</tr>
</tbody>
</table>

**Early 20% reduction of infection area**

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin 2 Doses</th>
<th>Vancomycin/Linezolid</th>
<th>Absolute Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCOVER 1</td>
<td>89%</td>
<td>90.9%</td>
<td>-1.0 (-4.7 to 2.7)</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>87.6%</td>
<td>85.9%</td>
<td>1.7 (-3.2 to 6.7)</td>
</tr>
<tr>
<td>Both Trials</td>
<td>88.6%</td>
<td>88.1%</td>
<td>0.6 (-2.9 to 4.1)</td>
</tr>
</tbody>
</table>

**Dalbavancin: One Dose vs Two Doses**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Doses</th>
<th>Absolute Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-72h response</td>
<td>81.4%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Day 14 clinical success</td>
<td>84%</td>
<td>84.8%</td>
</tr>
<tr>
<td>Day 28 clinical success</td>
<td>84.5%</td>
<td>85.1%</td>
</tr>
</tbody>
</table>
**Limited and Comparable Adverse Effects Profile**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Dalbavancin N=1178 (%)</th>
<th>Comparator* N=1224 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous adverse effect</td>
<td>109 (6.1%)</td>
<td>80 (6.5%)</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>53 (2.7%)</td>
<td>35 (2.8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>98 (5.5%)</td>
<td>78 (6.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50 (2.8%)</td>
<td>37 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79 (4.4%)</td>
<td>72 (5.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>83 (4.3%)</td>
<td>59 (4.8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>46 (2.7%)</td>
<td>30 (2.4%)</td>
</tr>
<tr>
<td>Purpur</td>
<td>38 (2.1%)</td>
<td>41 (3.3%)</td>
</tr>
<tr>
<td>ALT &gt; 3x ULN</td>
<td>52 (0.8%)</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>

*Comparators include: Vancomycin, Linezolid, Cefazolin, and Cephalexin

---

**Oritavancin Summary**

**Indication**
- Complicated skin and skin structure infections in adults

**Mechanism of action**
- Glycopeptide antibacterial, inhibits peptidoglycan synthesis

**Resistant Spectrum of Activity**
- MRSA, VISA/VISA, VRSA/VRE, DAP-NS SA/Ent, LR-SA/Ent

**Dosage and administration**
- **Dose**: 1200mg once
- **Frequency**: One time dose
- **Preparation and administration**: D5W 1000 mL only, 3-hour IV infusion
- **Renal Adjustment**: (CrCl <30 ml/min: None)

---

**Oritavancin Mechanism of Action**

- Oritavancin exhibits three distinct mechanisms of action:
  - Binds to peptidoglycan precursors to inhibit transglycosylation step of cell wall biosynthesis
  - Binds to peptide bridging segments to inhibit cross-linking
  - Disrupts bacterial membrane integrity, leading to depolarization, permeabilization and cell death

---

**Oritavancin in vitro Activity**

<table>
<thead>
<tr>
<th>MIC</th>
<th>mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus MSSA</td>
<td>0.12</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.12</td>
</tr>
<tr>
<td>VRSA</td>
<td>1.0</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.25</td>
</tr>
<tr>
<td>Streptococcusagalactiae</td>
<td>0.65</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.908</td>
</tr>
<tr>
<td>Enterococcus faecalis Non-VRE</td>
<td>0.06</td>
</tr>
<tr>
<td>VRE</td>
<td>1.0</td>
</tr>
<tr>
<td>Enterococcus faecium Non-VRE</td>
<td>0.03</td>
</tr>
<tr>
<td>VRE</td>
<td>0.3</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>1.0</td>
</tr>
</tbody>
</table>

---

**Potential Affects on Concomitant Medications**

- Despite the absence of hepatic metabolism, oritavancin affects CYP 450 system
  - Non-specific weak inhibitor
    - Warfarin AUC increased 33%
    - Ratio of omeprazole to 5-OH-omeprazole increased 13%
  - Contraindication
    - Use of IV heparin within 48 hours of oritavancin administration
    - aPTT remains falsely elevated
Non-Inferior Clinical Outcomes with Single Dose

• **SOLO I**

<table>
<thead>
<tr>
<th>Modified Intention-to-Treat</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early response at 48-72 hours</td>
<td>86%</td>
<td>75.6%</td>
</tr>
<tr>
<td>Investigator-assessed clinical cure, GUT</td>
<td>79.6%</td>
<td>68.8%</td>
</tr>
<tr>
<td>Early lesion size reduction 24%</td>
<td>86.9%</td>
<td>82.6%</td>
</tr>
</tbody>
</table>

**Clinical Evaluation Population**

| Early response at 48-72 hours | 87.3% | 86.1% |
| Investigator-assessed clinical cure, EOT | 90.6% | 88.7% |
| Early lesion size reduction 20% | 91.9% | 93.2% |

EOT = End of therapy after 7-10 days


Limited and Comparable Adverse Effects Profile

<table>
<thead>
<tr>
<th></th>
<th>Oritavancin N=976 (%)</th>
<th>Vancomycin N=983 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>36 (3.7)</td>
<td>32 (3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>97 (9.9)</td>
<td>103 (10.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (4.6)</td>
<td>46 (4.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24 (2.7)</td>
<td>26 (2.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>43 (4.4)</td>
<td>66 (6.7)</td>
</tr>
<tr>
<td>Infusion site phlebitis</td>
<td>24 (2.5)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>19 (1.9)</td>
<td>34 (3.0)</td>
</tr>
<tr>
<td>Abscess (limb &amp; subcutaneous)</td>
<td>37 (3.8)</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>27 (2.8)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>18 (1.9)</td>
<td>15 (1.0)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>24 (2.5)</td>
<td>15 (1.1)</td>
</tr>
</tbody>
</table>


Long Acting Lipoglycopeptides: Potential Impact on Transitions of Care

<table>
<thead>
<tr>
<th>Scenario: Assumes 1st line treatment only, equal efficacy 88.9%</th>
<th>Dalbavancin/Oritavancin: 14 days outpatient (no inpatient admission)</th>
<th>Vancomycin: 3 days inpatient + Linezolid (oral): 11 days outpatient</th>
<th>Daptomycin: 3 days inpatient, 11 days outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Cost (Inpatient)</strong></td>
<td>Weekly x 2 or Once</td>
<td>Once</td>
<td>Three times daily</td>
</tr>
<tr>
<td><strong>Drug Cost (Outpatient)</strong></td>
<td>Weekly x 2 or Once</td>
<td>Once</td>
<td>Three times daily</td>
</tr>
<tr>
<td><strong>Inpatient medical</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Outpatient medical</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Activity against VISA</strong></td>
<td>Likely</td>
<td>Likely</td>
<td>Likely</td>
</tr>
<tr>
<td><strong>Activity against VRSA</strong></td>
<td>No</td>
<td>Likely</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>GI effects, hypomagnesemia, cost</td>
<td>Nausea, cost</td>
<td>Nephrotoxicity, QT effects, teratogenicity, cost</td>
</tr>
</tbody>
</table>

Cost Comparison by Key Components

<table>
<thead>
<tr>
<th>Dalbavancin</th>
<th>Vancomycin + Linezolid</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3,887</td>
<td>$8,345</td>
<td>$12,676</td>
</tr>
</tbody>
</table>

Utilization of Long-Acting Lipoglycopeptides: Real World Experience

Real World Experience Utilizing Oritavancin to Discharge Patients with ABSSSI

• Study Design
  • Multicenter, retrospective chart review of 151 patients discharged from seven hospitals
  • January – December 2015
• On label utilization only included
• Clinical outcomes and adverse events were assessed
• 151 patients were evaluated

© American College of Clinical Pharmacy
Real World Experience Utilizing Oritavancin to Discharge Patients with ABSSSI

Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, range)</td>
<td>78 (27-92)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 (37%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>43 (41%)</td>
</tr>
<tr>
<td>Psychiatric Disorder</td>
<td>19 (17%)</td>
</tr>
<tr>
<td>Antibiotic Naive</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>IVAB Naive</td>
<td>50 (48%)</td>
</tr>
</tbody>
</table>

Culture Results

Prior Antibiotic Exposure

Results

- 10 patients (6.6%) were readmitted at 30 days
- 4 admissions (2.6%) were attributable to infection
- 2 patients for gram-negative infection
- 2 patients for abscess drainage
- 1 MSSA
- 1 culture negative
- No patients required additional gram positive antimicrobial therapy
- No serious safety events (1 nausea, 1 diaphoresis, 1 headache, 1 abdominal cramping)

Dalbavancin Real World Experience

- Study Design
  - Multi-center retrospective database and chart review of dalbavancin utilization at 6 physician owned infusion centers
  - July 2014-March 2015
  - Clinical outcomes and adverse events were assessed
  - All indications were included (on and off-label utilization)
  - 105 patients were assessed

Variable | Value
--- | ---
Gender, male | 57 (45%)
Age (mean, range) | 52 (13-92)
Diabetes | 39 (37%) |
Obesity | 43 (41%) |
Psychiatric Disorder | 19 (17%) |
Antibiotic Naive | 13 (12%) |
IVAB Naive | 50 (48%) |

Culture Results

Prior Antibiotic Exposure

Results

- Clinical success rate of 87% in cellulitis cases
- Admission/readmission not assessed
- 60 day infection recurrence: 9% (all indications)
- 10 patients required discontinuation due to adverse event
  - 1 GI distress
  - 6 Urticaria
  - 1 dyspnea
  - 2 anaphylaxis

Case

- ZT is 38 year old male with a history of non-healing surgical wound on his left foot
  - Culture from 3 weeks ago grew MRSA
  - Vancomycin MIC 2 mcg/ml, Linezolid MIC 2 mcg/ml
  - Patient completed 10 days of oral linezolid
  - PMH: Diabetes, obesity
  - PSH: Left second toe amputation
  - Social history: non-contributory except that he is a business owner and is reluctant to be hospitalized or come for daily iv antimicrobial infusion
  - At office visit today, there is purulent drainage from the wound and no significant improvement from the last visit

Would you consider a "new" ABSSSI antimicrobial for ZT?
Role in Therapy - Discussion

- Tedizolid
  - Reduce duration of therapy
  - Preserved activity against linezolid resistant organisms
  - Less MAOI activity

- Telavancin
  - Patients with concurrent bacteremia
  - Preserved activity against resistant organisms
  - Once daily option for outpatient setting

Role in Therapy - Discussion

- Dalbavancin/Oritavancin
  - Shift IV therapy more into the outpatient setting
  - Limit/reduce hospitalizations and healthcare costs
  - Awaiting data on treatment of more serious infections
The Treatment of ABSSSIs Caused by MRSA: If It Ain’t Broke, Don’t Try to Fix It!

Katherine Lusardi, PharmD, BCPS-AQ ID
UAMS Medical Center, Hospital Pharmacy
Little Rock, AR
24 October 2016

Learning Objectives

1. Compare and contrast advantages and disadvantages of new agents in relation to older alternatives.
2. Compare and contrast costs associated with new agents compared to older alternatives.
3. Develop plans to optimize old alternatives in order to achieve similar outcomes to the new agents.

Conflict of Interests

• Shareholder in Gilead Sciences, Inc.

Audience Response

• Area of practice?
  • Hospital, OP, ED
• 340b Hospitals?
• Who has ED programs in place where this would work?
• Who wishes they could have effective ED avoidance programs?

Old and New

Old
• Clindamycin
• Daptomycin
• Doxycycline
• Linezolid
• Tetracycline
• TMP/SMX
• Vancomycin

New
• Cefaroline
• Dalbavancin
• Oritavancin
• Tedizolid
• Televancin

Old vs. New

One is Silver and the Other Gold
New Agents - Advantages

- "One and done"
- Compliance
- Less line requirements
- Patient assistance options

New Agents - Disadvantages

- Broader coverage than necessary
- Adverse effects
- Drug/lab interactions
- Administration concerns
- Logistics
- Paperwork
- Cost

Old Agents - Advantages

- Practitioner comfort
- Mostly PO options
- Well studied
- Cost
- Mostly generic

Old Agents - Disadvantages

- Adverse effects
- Drug interactions
- Line requirements
- Increasing resistance
- Compliance

Pricing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medispan AWP</th>
<th>ASP Average (range)</th>
<th>Cost/14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oritavancin 1200 mg</td>
<td>438.00</td>
<td>2957.04</td>
<td>2480.00</td>
</tr>
<tr>
<td>Dalbavancin 1000 mg</td>
<td>1344.00</td>
<td>1044.80</td>
<td>1344.00</td>
</tr>
<tr>
<td>Televancin 750 mg</td>
<td>143.10</td>
<td>148.80</td>
<td>1532.80</td>
</tr>
<tr>
<td>Tedizolid 200 mg</td>
<td>371.70</td>
<td>235.40</td>
<td>330.8</td>
</tr>
<tr>
<td>Vancomycin 1000 mg</td>
<td>20.29</td>
<td>5.96</td>
<td>197.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medispan AWP</th>
<th>ASP Average (range)</th>
<th>Cost/14 days</th>
</tr>
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<tbody>
<tr>
<td>Daptomycin 500 mg</td>
<td>543.59</td>
<td>452.00</td>
<td>7610.26</td>
</tr>
<tr>
<td>Linezolid 600 mg</td>
<td>96.00 (IV)</td>
<td>47.33 (PO)</td>
<td>5124.00</td>
</tr>
<tr>
<td>IMC/TMP 5S</td>
<td>1.85</td>
<td>-</td>
<td>103.60</td>
</tr>
<tr>
<td>Clindamycin 300 mg</td>
<td>1.29</td>
<td>-</td>
<td>72.28</td>
</tr>
<tr>
<td>Metronidazole 100 mg</td>
<td>5.53</td>
<td>-</td>
<td>154.84</td>
</tr>
<tr>
<td>Minocycline 100 mg</td>
<td>1.67</td>
<td>-</td>
<td>46.76</td>
</tr>
</tbody>
</table>

New Agents on Trial

- Oritavancin vs vancomycin = non-inferior^2-3
  - SOLO-I & SOLO-III
- Dalbavancin vs vancomycin = non-inferior^4
  - Discover I & Discover II
- Ceftaroline vs vancomycin + aztreonam = non-inferior^5-6
  - Canvas 1 & Canvas 2
- Televancin vs vancomycin = non-inferior^7
  - Atlas 1 & Atlas 2
- Tedizolid vs Linezolid = non-inferior^8-9
  - Establish 1 & Establish 2

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/MedicareDrugAvgSalePrice/2016ASPFiles.html
Study Comparators²⁻⁹

- Outcomes assessed
  - New agents were all non-inferior
  - Early treatment response
  - Follow up to 28 days, readmission not assessed
  - Change in ABSSSI trial design

- Study structure
  - Different, but limited comparators
  - For long acting agents, >45% of patients in studies were treated inpatient
  - Mean hospitalization 8+ days

Optimization of Older Agents

Appropriate Assessment is Key

- Some infections are not serious enough
  - Role of antibiotics
  - Role of IV antibiotics
- Some infections are too serious
  - Role of PD antibiotics
  - Role of ED/CDU/OU
  - Role of hospital admission

Susceptibilities for MRSA¹¹⁻¹⁷

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>National Database</th>
<th>Local (Arkansas) Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>90.3 – 79.8</td>
<td>&lt;</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>90.7 – 100</td>
<td>+</td>
</tr>
<tr>
<td>Linezolid</td>
<td>98.9 – 100</td>
<td>+</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>94.1 – 94.9</td>
<td>&lt;</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>93.8 – 96.3</td>
<td>=</td>
</tr>
<tr>
<td>Trimethoprim (MIC90 &gt; 1)</td>
<td>99.9 – 100</td>
<td>+</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>95.6</td>
<td>&gt;</td>
</tr>
<tr>
<td>Diflucan</td>
<td>98.4</td>
<td>?</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>100</td>
<td>?</td>
</tr>
<tr>
<td>Telavancin</td>
<td>100</td>
<td>?</td>
</tr>
</tbody>
</table>

Appropriate Assessment

- Prospective study of ABSSSI presentations to ED
  - 619 patients enrolled
  - 94 (15.2%) admitted to hospital, Avg LOS = 4 Days
  - More likely to have systemic signs of infection (SIRS), infected wounds, non-abscess based infections
  - Larger infected areas were more likely to be admitted
  - 30 (51.9%) admitted patients had infected areas ≥ 78.5cm²
  - 6.9% of non-admitted patients had infected areas ≥ 78.5cm²
  - Reasons for admission
    - 85% needed IV abx
    - 24.5% needed surgical intervention

Appropriate Treatment

- Subset analysis of a rapid diagnostic prospective clinical trial
- Primary outcomes were failure at 7 days and reported ABSSSI recurrence at 1 and 3 months
- 272 Patients consented and enrolled
  - 1 week failure: 10.2%
  - 1 month recurrence: 22.4%
  - 3 month recurrence: 39.9%
  - Risk of recurrence: contact with pt with ABSSSI, use of packing, history of ABSSSI
Appropriate Treatment

• Prospective study comparing TMP/SMX and doxycycline for MRSA ABSSSI

• 34 Patients enrolled from ED visit, no hospital admissions included
  • Abscesses drained and packed
  • Follow up visit at 2-5 days, phone f/u at 10-14 days and 28-35 days
  • 23 (68%) had MRSA, all were susceptible to TMP/SMX and doxycycline
  • Infection/erythema diameter was 7.2±4.9 cm
  • Primary outcome was failure
  • 3 (9%) had failure at 10-14 days and were hospitalized
  • All failures were in TMP/SMX group, but not significant differences

Appropriate Treatment

• Retrospective comparison between tetracyclines and B-lactams
  • 282 included community onset MRSA ABSSSI
    • 50 received tetracyclines (minocycline, doxycycline)
    • 193 received B-lactams (amoxicillin/clavulanate, cephalaxin)
    • 39% required I&D (half by surgical service)
    • Median lesion diameter 4 cm
  • Overall success was 90.1%:
    • Tetracycline: 96%
    • B-lactam: 87%
    • B-lactam therapy was only independent risk factor for failure

Appropriate Treatment

• Retrospective review of antibiotic therapy for CA-MRSA
  • 531 episodes of CA-MRSA in 492 patients
    • 361 patients with abscesses (~80% had I&D)
    • 312 (6%) received active antibiotics
    • 219 (4%) received inactive antibiotics
    • 45 (8.5%) had treatment failure through follow up days 14-30
  • No association with failure with lesion size
  • Only predictor of failure was inactive treatment
  • Note: 190 pts with inactive treatment still had success

Appropriate Treatment

• Daptomycin – evaluated in Phase 3 trials, at 4mg/kg for cSSTI
  • 10% of patients had MRSA
  • Success compared to
  • Post-marketing patient databases: CORE 2004 & CORE 2005
    • 52-63% of patients had MRSA
    • 667 (66.7%) patients with cSSTI
    • Clinical success rates 93-96%

ED Avoidance: CDU/OU

• 213 pts referred to CDU
  • 39 (18.3%) patients hospitalized
  • 181 patients not enrolled in study
  • 32 (15%) patients discharged on IV abx (ceftriaxone, ampicillin/subbactam, clindamycin, vancomycin)
    • Followed up in 48-72 hours with PCP, wound care, or ID doctor
    • IV LOT 5.4 days
    • 96.0% treatment success rate
  • Conclusion: hospitalization avoided, 109 days moved from IP to OP

ED Avoidance: CDU/OU

• Pediatric ED Evaluation of 8234 cases
  • 2200 Admitted to hospital
    • Mean age 27.3 months
    • 304 Admitted to OU
    • 192 patients evaluable per study
    • Mean age 47 months, less likely to have abscesses
    • 43 (22.4%) Failed OU stay and were admitted from OU with average LOS 2.9 days
      • More likely to present with fever, and more resources used
ED Avoidance: ED vs CDU/OU

- Evaluation of 308 patients with SSTI
  - 219 treated in ED and discharged
  - ED patients were more likely to have abscesses
  - 89 admitted to OU
  - OU patients had more SIRS criteria, more co-morbidities, more cultures done
  - Outcome was 96 h revisit/admission
    - 30 (9.7%) patients: 23 (10.5%) from ED, 7 (7.9%) from OU
    - Secondary outcome was 30 day infection related admission
    - 23 (7.3%) patients, no difference between ED and OU
  - Antibiotics: Clindamycin, cephalaxin, amox/clav, TMP/SMX, doxycycline, linezolid

Case

- Patient LK is a 44 year old male, with a history of uncontrolled diabetes. He has a large (70 cm²) warm, fluctuant area on his leg, and an I&D is performed. The rapid PCR shows MRSA. The patient takes warfarin for afib, fluoxetine for depression, and is allergic to sulfa.
- The patient is admitted to the OU, due to sustained fever (38.1 C) and tachycardia (102) in the ED. The APN orders fluids and a loading dose of vancomycin.
- The patient improves overnight, and the red area does not progress. The patient is stable for discharge, but there is concern about discharging the patient with IV Vancomycin.

What does 10-14 days look like?

<table>
<thead>
<tr>
<th></th>
<th>Sulfamethoxazole 1500 mg</th>
<th>Doxycycline 100 mg</th>
<th>CPF</th>
<th>Sulfamethoxazole 1500 mg</th>
<th>Doxycycline 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>$4,236.94</td>
<td>$140.72</td>
<td>CPF</td>
<td>$4,236.94</td>
<td>$140.72</td>
</tr>
<tr>
<td>Pediatric</td>
<td>$4,837.94</td>
<td>$597.12</td>
<td>CPF</td>
<td>$4,837.94</td>
<td>$597.12</td>
</tr>
<tr>
<td>Acquisition Cost</td>
<td>$4,143.87</td>
<td>$413.12</td>
<td>Acquisition Cost</td>
<td>$1,913.55</td>
<td>$555.84</td>
</tr>
<tr>
<td>Drug Profit</td>
<td>$893.87</td>
<td>$188.18</td>
<td>Drug Profit</td>
<td>$7,894.29</td>
<td>$6,198.26</td>
</tr>
<tr>
<td>For 14 Days</td>
<td>$893.87</td>
<td>$188.18</td>
<td>For 14 Days</td>
<td>$7,894.29</td>
<td>$6,198.26</td>
</tr>
<tr>
<td>Time</td>
<td>$51.06</td>
<td>$14.06</td>
<td>Time</td>
<td>$61.06</td>
<td>$61.06</td>
</tr>
<tr>
<td>14 Days</td>
<td>$51.06</td>
<td>$95.34</td>
<td>14 Days</td>
<td>$61.06</td>
<td>$95.34</td>
</tr>
<tr>
<td>Total</td>
<td>$795.93</td>
<td>$1,777.86</td>
<td>Total</td>
<td>$2,655.35</td>
<td>$4,734.76</td>
</tr>
</tbody>
</table>

CMS 2014 Charges/Payments

<table>
<thead>
<tr>
<th>DRG</th>
<th>Avg. Charges</th>
<th>Avg. Payments</th>
</tr>
</thead>
<tbody>
<tr>
<td>602 – Cellulitis with MCC</td>
<td>10,714.88</td>
<td>9,231.94</td>
</tr>
<tr>
<td>603 – Cellulitis without MCC</td>
<td>6,518.02</td>
<td>5,072.90</td>
</tr>
</tbody>
</table>


What if it doesn’t go perfectly?

- If an OU/CDU patient is admitted to the hospital
  - Patient converts from Observation to Inpatient status
  - 340B pricing does not apply
  - Not all payers cover IP administration of long acting agents
  - Drug cost now comes from DRG reimbursement, not billable line item
ED Avoidance: Limitations

- Heavy on quick turn around paperwork
- Insurance verification
- Coding and billing
- Potential to delay treatment
- If patient is admitted, potential to lose money
- Role of drug restriction

Summary

- New agents are expensive compared to old agents, but may have LOS benefit when used appropriately.
- Effective use of new agents will take well designed protocols that not all hospitals have ready. Many times, old agents will work for plenty of patients.
- No new agent has been prove superior.
- Assess infections appropriately for severity, placing patients into the appropriate treatment environment.
- Utilize agents in situations that justify the high cost of new agents

References