2012 Infectious Diseases Update

MRSA, VRE, and MDRO

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Disclosure: Dr. Spach has no significant financial interest in any of the products or manufacturers mentioned.
Antimicrobial Resistance: Outlines

• MRSA
• VRE
• NDM-1
Methicillin-Resistant *Staphylococcus aureus* (MRSA)
Beta-Lactams: Mechanism of Action

- Penicillin Binding Proteins
- Transpeptidation
- Carboxypeptidation
- Beta-Lactam
- Cell Membrane
- Cell Wall
- DNA
- Staphylococcus aureus
Beta-Lactams: Mechanism of Action

Cell Wall Synthesis

Cell Membrane

Penicillin Binding Proteins

Staphylococcus aureus

DNA

Beta-Lactam
MRSA: Resistance to Beta-Lactams

- Altered Penicillin Binding Protein
  - PBP 2a

- Beta-Lactam
  - DNA
  - mecA
  - PBP 2a
MRSA

Community-Acquired
USA-300

Hospital-Acquired
USA-100
MRSA USA 300 “Superbug”: Key Features

- Emergence in Community
- Virulent Pathogen
- Multi-Drug Resistance
MRSA USA 300 Toxin Production

MRSA

Phenol-soluble modulins (PSMs)

Alpha-hemolysin

Panton Valentine Leukocidin (PVL)
Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children

Catherine Liu, Arnold Bayer, Sara E. Cosgrove, Robert S. Daum, Scott K. Fridkin, Rachel J. Gorwitz, Sheldon L. Kaplan, Adolf W. Karchmer, Donald P. Levine, Barbara E. Murray, Michael J. Rybak, David A. Talan, and Henry F. Chambers

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A 28-year-old woman presents with a 5 x 5 cm boil on her back. She has no known medical problems. She is afebrile and the lesion is erythematous, slightly tender, and soft in the middle. She had a similar abscess about 1 year ago caused by MRSA.
Case History: Skin & Soft Tissue

- You suspect MRSA. How would you manage this abscess?

A. Hot compresses
B. Antibiotics
C. Incision and drainage
D. Incision and drainage + antibiotics
2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

• Simple Abscess or Boil
  - Incision and Drainage

“For simple abscesses or boils, incision and drainage alone is likely adequate, but additional data are needed to further define the role of antibiotics, if any, in this setting.”

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

Simple Abscess or Boil: Evidence Summary

- Observational Studies: 80-90% cure rate with I & D alone
- Retrospective Studies (n = 2): suggest improved cure rate if antibiotic used
- Randomized Controlled Trials (n = 2): antibiotics did not improve cure rate, but prevented new lesions in short term

Case History: Skin & Soft Tissue

- A 28-year-old man presents with an abscess on his hand and fever (T = 38.6°C). He has diabetes, but no other medical problems. The patient says this is a spider bite, but he has a history of 2 prior MRSA infections.
Case History: Skin & Soft Tissue

- You suspect MRSA. How would you manage this?

A. Hot compresses
B. Antibiotics
C. Incision and drainage
D. Incision and drainage + antibiotics
2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- Simple Abscess or Boil
  - Incision and Drainage

- Complicated Abscess
  - Incision and drainage + antimicrobial therapy

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- Complicated Abscess
  - Severe or extensive disease or rapid progression of cellulitis
  - Signs and symptoms of systemic illness
  - Associated comorbidities or immunosuppression
  - Extremes of age
  - Abscess in area difficult to drain (eg, face, hand, genitalia)
  - Associated septic phlebitis
  - Lack of response to incision and drainage alone

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

• Empiric Therapy for Out-Patient Management
  - TMP-SMX: 1-2 DS tabs PO BID
  - Clindamycin: 300-450 mg PO TID
  - Doxycycline: 100 mg PO BID
  - Minocycline: 200 mg x1, then 100 mg PO BID
  - Linezolid: 600 mg PO BID

• If Also Covering for Group A Streptococcus
  - TMP-SMX + Amoxicillin: 500 mg PO TID
  - Clindamycin
  - Doxycycline/Minocycline + Amoxicillin: 500 mg PO TID
  - Linezolid

2010 IDSA Practice Guidelines
Therapy for CA-MRSA Skin & Soft Tissue Infection

- **Empiric Therapy for Hospitalized Patient**
  - Vancomycin: 15-20 mg/kg IV q 8-12 h (do not exceed 2 g/dose)
  - Linezolid: 600 mg IV or PO BID
  - Daptomycin: 4 mg/kg IV QD
  - Telavancin: 10 mg/kg IV QD
  - Clindamycin: 600 mg IV or PO TID

**Notes:**
(1) for most non-obese adults, vancomycin 1g IV every 12 hours without trough monitoring adequate for treatment of SSTI
(2) after IDSA guidelines developed, FDA-approved Ceftaroline: 600 mg IV q12 h for acute SSTI, including MRSA.

A 31-year-old man presents with an cellulitis on his left hand. On examination, he is afebrile and there is no focal abscess identified. He had no known medical problems.
How would you manage this?

A. Ciprofloxacin
B. TMP-SMX
C. Amoxicillin-clavulanic acid
D. Amoxicillin-clavulanic acid + TMP-SMX
2010 IDSA Practice Guidelines

Therapy for CA-MRSA Skin & Soft Tissue Infection

- Simple Abscess or Boil
  - Incision and Drainage

- Complicated Abscess
  - Incision and drainage + antimicrobial therapy

- Nonpurulent Cellulitis (and no abscess)
  - Empiric therapy for beta-hemolytic streptococci

## Oral Antibiotics and Antimicrobial Activity
### MRSA and Group A Streptococcus

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MRSA</th>
<th>Group A Streptococcus</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td>++++</td>
<td>+</td>
<td>Rash most common adverse effect</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>+++</td>
<td>+</td>
<td>Good choice for MRSA if allergic to TMP-SMX</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>+++</td>
<td>++++</td>
<td>Poorly tolerated and 4x/day dosing</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>-</td>
<td>++++</td>
<td>No activity against MRSA</td>
</tr>
<tr>
<td>Linezolid</td>
<td>++++</td>
<td>++++</td>
<td>Highly effective but very expensive</td>
</tr>
</tbody>
</table>
Case History: Recurrent MRSA

- A 36-year-old woman presents with her third episode of MRSA skin and soft tissue infection in the past 6 months.
- In addition to treating the current problem, what strategies might be effective in preventing further infections?

“Most experts define recurrent disease as 2 or more discrete skin and soft tissue episodes at different sites over a 6-month period.” - IDSA Guidelines 2010
Staphylococcus aureus colonization
2010 IDSA Practice Guidelines
MRSA Decolonization

• Nasal Decolonization
  - Mupirocin: bid x 5-10 days

• Topical Body Decolonization
  - Chlorhexidine: once daily x 5-14 days
  - Dilute bleach bath*: 2x/week x 3 months

• Oral Antimicrobials (if topical therapy fails)
  - Consider active agent + Rifampin

* Dilute bleach bath = 1 teaspoon per gallon of water
[or ¼ cup per ¼ tub or 13 gallons of water] for 15 minutes twice weekly for 3 months

Case History: MRSA Bacteremia

- A 67-year-old woman undergoes abdominal surgery and has a central intravenous catheter for short term TPN. She develops fever and blood cultures grow *Staphylococcus aureus*, resistant to methicillin. The central venous catheter is removed.

- Should an ECHO be performed?
- If vancomycin is used, what trough should you aim for?
- How long a treatment course is needed?
2010 IDSA Practice Guidelines
Therapy for MRSA Bacteremia

• ECHO recommended for all; TEE preferred
• Vancomycin mainstay of therapy, but less effective with MSSA
• Daptomycin 6 mg/kg/day is alternative to vancomycin
• Addition of gentamicin or rifampin NOT recommended
• Recommend Vancomycin trough of 15-20 ug/ml
• Duration for uncomplicated* bacteremia: 14 days
• Duration for complicated bacteremia: 4-6 weeks

Uncomplicated bacteremia: absence of endocarditis; no implanted prostheses, follow-up blood cultures negative at day 2-4, fever resolves within 72 hours of starting therapy; and no metastatic site of infection

Daptomycin vs Comparator for MSSA & MRSA Bacteremia & Endocarditis

**Study Design**

- **Methods**
  - Adults with known/suspected bacteremia or endocarditis (n = 236)
  - Randomized, open-label

- **Regimens: MSSA**
  - Daptomycin: 6 mg/kg IV qd
  - Nafcillin + Gentamicin (first 4 days or until blood cultures negative x 48h)

- **Regimens: MRSA**
  - Daptomycin: 6 mg/kg IV qd
  - Vancomycin + Gentamicin (first 4 days or until blood cultures negative x 48h)

**Success 42 Days Post Treatment**

FDA Linezolid Warning
Linezolid vs. Vancomycin for IV Catheter Bacteremia

Study Design

- Methods
  - Adults with IV catheter-related bacteremia
  - N = 736
  - Randomized, open-label

- Regimens
  - Linezolid: 600 mg IV or PO q12h
  - Vancomycin*: 1g IV q 12h

*Patients could switch to oxacillin or dicloxacillin if MSSA identified

Patients could receive concomitant therapy for gram-negative infections

Death Rate (up to day 84)

Source: FDA Letter March 16, 2007
Empiric Therapy for Hospitalized Patient

“When compared with vancomycin, none of these newer agents have demonstrated superiority in the primary outcome of clinical cure.”

MRSA: Mechanism of Action

Altered Penicillin Binding Protein

PBP 2a

Beta-Lactam

DNA

mecA
Vancomycin: Mechanism of Action

Cell Wall Synthesis

Vancomycin

DNA
Daptomycin: Mechanism of Action

1. Ca$^{2+}$-Dependent Binding to Cell Membrane
2. Membrane Depolarization and K$^+$ Efflux
Ceftaroline and MRSA: Mechanism of Action

Altered Penicillin Binding Protein

PBP 2a

Ceftaroline

DNA
Vancomycin-Resistant Enterocococcus
Enterococcus and Antimicrobial Resistance in U.S. Resistance Bases on Species

- *E. faecalis*: fewer than 5% vancomycin resistant
- *E. faecium*: more than 80% vancomycin resistant

VRE: Risk Factors

- Close physical proximity to patient with VRE
- Long period of hospitalization
- Hospitalization in long-term facility
- Surgical Unit or ICU
- Presence of urinary catheter
- Receipt of multiple courses of antibiotics

Impact of Antibiotics & Enterococcus & VRE

Baseline

Increase in Enterococcus

Antibiotics

Gram-Negative Bacilli

Enterococcus

VRE
Impact of Antibiotics & Enterococcus & VRE

Baseline

Increase in Enterococcus

Emergence of VRE

Antibiotics

Vancomycin

Gram-Negative Bacilli  Enterococcus  VRE
Impact of Antibiotics & Enterococcus & VRE

Vancomycin: Mechanism of Action

Vancomycin inhibits the formation of the peptidoglycan layer in the bacterial cell wall by targeting the D-Ala-D-Ala ligase. This enzyme catalyzes the final step in the synthesis of the peptidoglycan precursor, which is a pentapeptide. However, vancomycin binds to the intermediate tripeptide, preventing the ligase from completing the pentapeptide synthesis.

The diagram illustrates the sequence of events:
- Tripeptide Intermediate
  - D-Ala
  - D-Ala
  - D-Ala

- Cell Wall Pentapeptide Precursor
  - D-Ala
  - D-Ala
  - D-Ala
  - D-Ala
  - D-Ala

Vancomycin binds to the tripeptide intermediate, preventing the formation of the pentapeptide.
VRE: Mechanism of Resistance

D-Ala
Δ Ligase
D-X

Tripeptide Intermediate

D-Ala
D-X

Cell Wall Pentapeptide Precursor

D-Ala
D-X

Vancomycin
A 29-year-old woman is in a MVA that requires a prolonged SICU stay. While receiving ceftazidime and vancomycin, she develops a fever of 39.5°C. Urine cultures and blood cultures grow *Enterococcus* resistant to ampicillin, gentamicin, and vancomycin. The species of *Enterococcus* is not yet known.
Case History: Question

- Which of the following likely will have good activity against both vancomycin-resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus faecalis*?

1. Quinupristin-dalfopristin
2. Daptomycin
3. Piperacillin-tazobactam
4. Quinupristin-dalfopristin
5. Linezolid
Agents used to Treat VRE

- Linezolid
- Daptomycin
- Tigecycline
- Quinupristin-Dalfopristin (only for *E. faecium*)
New Delhi Metallo-beta-lactamase -1 (NDM-1)
Alarm over 'unbeatable' enzyme that could make all bacterial diseases resistant to antibiotics

By JENNY HOPE
Last updated at 10:23 AM on 12th August 2010

NDM-1, Superbug Gene, Could Spread Worldwide, Doctors Warn

NDM1 - New Super Bug - The Death Of Us All? 79
NDM-1
Description

- Enzyme produced by bla_{NDM-1} gene
- Metallo-beta-lactamase (carbapenemase)
- Plasmid spread documented
- Primarily found in *Enterobacteriaceae* species
- Inactivates wide range of antibiotics
Mechanisms of Resistance: Beta-Lactamase

- Outer Membrane
- Cell Wall
- Periplasmic Space
- Cell Membrane
- Porin Channel
- Beta-Lactamase
- DNA
NDM-1
An Emerging Superbug

• 2009: First reported in India
• May 2010: reported in UK
• June 2010: 3 cases reported in US (MA, CA, IL)
  - All involved patients who received recent medical care in India
• As of March 2012: total of 13 cases reported in US
NDM-1 Detection

- “Carbapenem resistance and carbapenemase production conferred by $bla_{NDM-1}$ is detected reliably with phenotypic testing methods currently recommended by the Clinical and Laboratory Standards Institute, including disk diffusion testing and the modified Hodge test.”

CDC. MMWR. 2010;59:750.
NDM-1 Laboratory Diagnosis

- Preliminary Positive: Modified Hodge Test
  - Detects carbapenemase in *Enterobacteriaceae* isolates
  - Utilizes meropenem disk

- Confirmatory Test
  - Molecular Analysis (PCR or DNA sequencing)
NDM-1
Treatment

- Tigecycline
- Colistin
- Aztreonam (some isolates susceptible)
End