Antimicrobial Update: A focus on bacterial sinusitis, skin and soft tissue infections

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Disclosure

• No real or potential conflict of interest to disclose
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives

• Having completed the learning activities, the participant will be able to:
  – Identify factors influencing the choice of an antimicrobial.
  – Recognize the efficacy of standard and newer antibiotics for the treatment of infections common in primary and acute health care.
Are the bugs winning? Is this a new problem?

In Late 1920s
Sir Alexander Fleming

- 1st to suggest that *penicillium* mold must secrete antibacterial substance, 1st to isolate active substance which he named penicillin

Sir Alexander Fleming
June 26, 1945, New York Times

- “... the microbes are educated to resist penicillin and a host of penicillin-fast (resistant organisms is bred out...)
Sir Alexander Fleming
June 26, 1945, New York Times
(continued)

• In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

What facilitates resistance?

• Time
• Exposure
  – Unnecessary doses
  – Long tx period
• Under dosing
  – Leaves behind more resistant bugs
Empiric Antimicrobial Therapy

• The decision-making process where the clinician chooses the agent based on patient characteristics and site of infection.

Questions to Ask Prior to Choosing an Antimicrobial

• What is/are the most likely pathogen(s) causing this infection?
• What is the spectrum of a given antimicrobial's activity?
• What is the likelihood of resistant pathogen?
• What is the danger if there is treatment failure?

Mechanisms of Bacterial Resistance

Altered membrane permeability
(Many organisms via multiple mechanisms)

Enzyme destruction
(Beta-lactamase produced to inactivate penicillins, produced by organisms such as *H. influenzae*, *M. catarrhalis*, MSSA; extended spectrum beta-lactamase produced to inactivate penicillins and cephalosporins such as *Klebsiella pneumoniae*)

Binding site alteration
Methicillin-resistant *S. aureus* (MRSA), drug-resistant *S. pneumoniae* (DRSP)
Alteration in Target Site
Altered Penicillin-binding Proteins (PBPs)

Without antibiotic:
- Actively growing *S. pneumoniae*
- PBPs facilitate cell wall formation for new cell

Antibiotic binds to PBPs:
- Cannot make adequate cell wall, growth stops

Susceptible *S. pneumoniae*

Antibiotic cannot bind to altered PBPs, growth continues (antibiotic resistance)

Alteration in Ribosomal Target Sites
*S. pneumoniae* vs. Macrolides
Methylation of Ribosomes

Normal Macrolide MOA:
- Macrolide binds to ribosome of *S. pneumoniae* and inhibits bacterial protein synthesis

Macrolide Resistance:
- *S. pneumoniae* acquires gene that results in methylation of the ribosomes. Macrolide unable to bind to altered ribosomes and cannot interfere with protein synthesis

The Beta-lactam Ring:
Vulnerable or Not?

- Penicillin

\[
\text{Penicillin} \quad \text{Cephalosporin}
\]
True or false?

• In a study of antimicrobial prescribing among primary care providers, clinicians in high volume practices and those who were in practice longer were more likely to prescribe antibiotics inappropriately.
  
  Source: CMAJ • October 9, 2007; 177 (8).

TRUE

Updated Treatment Guidelines for ABRS in Children and Adults

Chow, A., et al.,
IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults,
Acute Rhinosinusitis Syndrome (ARS)
Defining the Terms

• Inflammation of the mucosal lining of nasal passage and paranasal sinuses lasting up to 4 weeks, caused by allergens, environmental irritants, and/or infection (viruses {majority}, bacteria and fungi)

Acute Rhinosinusitis (ARS)
Defining the Terms
(continued)

| Acute bacterial rhinosinusitis (ABRS or ABS) | Secondary bacterial infection of paranasal sinuses usually following viral URI, relatively uncommon in adults and children. 
Less than 2% of viral URIs are complicated by ABRS. |

Is antimicrobial needed in ABRS therapy?

• Meta-analyses of antibiotic treatment vs. placebo in ABRS
  - Number needed to treat (NNT) (95% CI)
    • In adults=13 (9–22)
    • In children=5 (4–15)
  - Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults
**Bacterial Pathogens Associated with ABRS**

- **Streptococcus pneumoniae**
  - Gm pos diplococci
  - DRSP rate nationally=25%
    - Adults=38%
    - Children=21–33%
  - Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

- **Haemophilus influenzae**
  - Gm negative rod-shaped bacterium
  - ~30% beta-lactamase production rate nationwide
  - Nontypable strains cause ABRS
    - Adults=36%
    - Children=31–32%
  - Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

- **Moraxella catarrhalis**
  - Gram negative with ≥90% beta-lactamase production rate
    - Adults=16%
    - Children=8–11%
  - Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults
Empiric Antimicrobial Therapy in ABRS:
Gram positive with DRSP Risk
Gram Negative with Beta-lactamase Production Risk

Algorithm for the Management of Acute Bacterial Rhinosinusitis

- Signs and symptoms either:
  a) Persistent and not improving (≥10 days);
  b) Severe (≥2−4 days), or
  c) Worsening or “double-sickening” (≥3−4 days)

- Risk for resistance
  - Age <2 or >65 y, daycare
  - Prior antibiotics within the past month
  - Prior hospitalization past 5 days
  - Comorbidities
  - Immunocompromised
  - Symptoms persisting and not improving

- Symptomatic treatment

- Complete 5−7 days of antimicrobial therapy

- Failure to improve after 3−5 days

- Refer to specialist

- CT or MRI to investigate noninfectious causes or suppurative complications

- Sinus or meatal cultures for pathogen-specific therapy

- Refer to specialist

- Evidence-based Practice
Symptomatic Treatment in ABRS

- Saline nasal irrigations
- Intranasal corticosteroids when ABRS is accompanied by allergic rhinitis
- Topical or systemic decongestants for patient sense of congestion relief

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

Source: Clinical Infectious Diseases
http://cid.oxfordjournals.org/
### Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Adults

<table>
<thead>
<tr>
<th>Indication</th>
<th>First-line (Daily dose)</th>
<th>Second-line (Daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial empiric therapy</td>
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</tr>
<tr>
<td>Amoxicillin-clavulanate 500 mg/125 mg PO TID</td>
<td>Amoxicillin-clavulanate 2000 mg/125 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td></td>
<td>Or</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate 875 mg/125 mg PO BID</td>
<td>Doxycycline 100 mg PO BID or 200 mg PO daily</td>
<td></td>
</tr>
</tbody>
</table>

(continued)

- High dose (HD, 3–4 g/d) amoxicillin needed against DRSP
- Clavulanate as a beta-lactamase inhibitor, allows amoxicillin to have activity against beta-lactamase producing organisms such as *H. influenzae, M. catarrhalis*

(continued)

- Doxycycline- DRSP treatment failure risk, activity against gm negative organisms, stable in presence of beta-lactamase
  - Pregnancy risk category D
Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Adults (continued)

- β-lactam allergy (Allergy to antimicrobials with beta-lactam ring such as penicillins, cephalosporins)
  - Doxycycline 100 mg PO BID
  - Doxycycline 200 mg PO daily
  - Levofloxacin 500 mg PO daily
  - Moxifloxacin 400 mg PO daily

- Respiratory fluoroquinolones (FQ) - Activity against DRSP, gram-negative organisms, stable in presence of beta-lactamase

- Risk for antibiotic resistance or failed initial therapy
  - Amoxicillin-clavulanate 2000 mg/125 mg PO BID
  - Levofloxacin 500 mg PO daily
  - Moxifloxacin 400 mg PO daily
Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Adults (continued)

- All options with activity against DRSP, gram-negative organisms, stable in presence of and/or active against beta-lactamase

![Image of text](https://example.com/image)

Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children

<table>
<thead>
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<th>Second-line (Daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial empirical therapy</td>
<td>Amoxicillin-clavulanate 45 mg/kg/day PO BID</td>
<td>Amoxicillin-clavulanate 90 mg/kg/day PO BID</td>
</tr>
</tbody>
</table>

Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children (continued)

- Risk for antibiotic resistance or failed initial therapy
  - Amoxicillin-clavulanate 90 mg/kg/day PO BID
  - or
  - Clindamycin 30–40 mg/kg/day PO TID plus cefixime 8 mg/kg/day PO BID or cefpodoxime 10 mg/kg/day PO BID
  - or
  - Levofloxacin 10–20 mg/kg/day PO every 12–24 h

*Resistance to clindamycin (~31%) is found frequently among Streptococcus pneumoniae serotype 19A isolates in different regions of the United States.*

Source: Chow, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults
Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children
(continued)

<table>
<thead>
<tr>
<th>β-lactam allergy</th>
<th>Levofloxacin 10–20 mg/kg/day PO every 12–24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I hypersensitivity</td>
<td>Or Clindamycin* (30–40 mg/kg/day PO TID) plus cefixime (8 mg/kg/day PO BID) or cefpodoxime (10 mg/kg/day PO BID)</td>
</tr>
<tr>
<td>Non–type I hypersensitivity</td>
<td></td>
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</tbody>
</table>

*Resistance to clindamycin (~31%) is found frequently among Streptococcus pneumoniae serotype 19A isolates in different regions of the United States [94].
Source: Chew, A., et al., IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

Where are the $4 drugs?

- Amoxicillin
  - Clinical limitations?
- Ciprofloxacin
  - Clinical limitations?
- TMP-SMX
  - Clinical limitations?
- Cephalexin
  - Clinical limitations?

Community-acquired MRSA
CA-MRSA vs. HC-MRSA

- Genetically different from HC-MRSA
  - Not an “escapee” from LTC or the hospital
  - Some are from older strain, known as phage type 80/81.
  - Was first discovered in neonatal infections in Australia in 1953 and went on to cause serious outbreaks of skin lesions, sepsis and pneumonia worldwide
  - Often in young people and children

True or false?

- Skin lesions infected by CA-MRSA often occur spontaneously on intact skin.
- All CA-MRSA strains can cause necrotizing infection.

**FALSE**

- Skin lesions infected by CA-MRSA often occur spontaneously on intact skin. **FALSE**
- All CA-MRSA strains can cause necrotizing infection.
True or false?
• Skin lesions infected by CA-MRSA often occur spontaneously on intact skin. **FALSE**
• All CA-MRSA strains can cause necrotizing infection. **FALSE**

Necrotizing Infection Risk
• CA-MRSA strains
  - Majority carry a leukocyte-destroying cytotoxin, Panton-Valentine leukocidin (PVL) toxin
The first mention of MRSA...

• ...in healthcare literature appeared in what year?
  A. 1960
  B. 1972
  C. 1985
  D. 1994

The first mention of MRSA...

• ...in healthcare literature appeared in what year?
  A. 1960
  B. 1972
  C. 1985
  D. 1994

The first mention of MRSA... (continued)

• The mechanism(s) of transmission of CA-MRSA include(s):
  A. Skin contact.
  B. Droplets.
  C. Exposure to contaminated objects.
  D. All of the above.
The mechanism(s) of transmission of CA-MRSA include(s):
A. Skin contact.
B. Droplets.
C. Exposure to contaminated objects.
D. All of the above.

MRSA’s Mechanism of Resistance
- Methicillin=Penicillin form stable in presence of beta-lactamase
- MRSA implies resistance by mechanism other than beta-lactamase production

MSSA Methicillin-sensitive *S. aureus*
- Implies *S. aureus* strain where mechanism is beta-lactamase production
CA-MRSA
According to the CDC, who gets it?

- Close physical contact with others
  - Athletes
  - Military recruits
  - Children
  - Men who have sex with men
  - Prison inmates
- Select ethnic groups
  - Pacific Islanders, Alaskan Natives, Native Americans

References

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

Available at http://cid.oxfordjournals.org/content/early/2014/06/14/cid.ciu296.full.pdf+html
You see a 36 yo man with no chronic health problems...
•...who presents with 2 furuncles, each around 3 cm in diameter, in upper thigh on the right. These have been present × 3 d, slightly increasing in size during this time. He is without fever or other systemic symptoms.

According to Sanford Guide Recommendations,...
•...you perform an I & D and then advise the following:
  A. Warm soaks to the area until clear.
  B. A systemic antibiotic empirically.
  C. A topical antibiotic.
  D. An culture and sensitivity of the lesion contents and prescribe a systemic antibiotic based on these results.
For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. Additional data are needed to further define the role of antibiotics, if any, in this setting.

Antibiotic therapy is recommended for abscesses associated with the following conditions:
- Severe or extensive disease (involving multiple sites of infection)
- Rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness
- Associated comorbidities
Antibiotic Therapy in MRSA

• Antibiotic therapy is recommended...(cont.)
  – Immunosuppression
  – Extremes of age
  – Abscess in an area difficult to drain (face, hand, and genitalia)
  – Associated septic phlebitis, and lack of response to incision and drainage alone

(continued)

• For outpatients with purulent cellulitis (cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess), empirical therapy for CA-MRSA is recommended pending culture results.

(continued)

• Length of therapy
  – Five to 10 days of therapy is recommended but should be individualized on the basis of the patient’s clinical response.
Per Sanford Guide in MRSA-SSTI
5–10 d Course

- TMP-SMX DS 1 tablets BID
  - 2 tabs with BMI≥40 kg/m²) BID
  - Or
- Doxycycline or minocycline 100 mg BID
  - Or
- Clindamycin 300 mg TID
  - 450 mg TID with BMI≥40 kg/m²

Or

If no response with aforementioned therapies after 2–3 days
- Investigate possible complications
- Consider vancomycin 1 gm IV q12h
- or linezolid 600 mg PO q12h

Linezolid (Zyvox®)

- Mechanism of action
  - Inhibits protein synthesis by preventing formation of ribosome complex that initiates protein synthesis
  - Binds to a unique binding site so avoids issue of cross resistance to other antimicrobials
• For outpatients with nonpurulent cellulitis (cellulitis with no purulent drainage or exudate and no associated abscess), empirical therapy for infection due to β-hemolytic streptococci is recommended.
**IDSA: Antibiotic Therapy in CA-MRSA, Outpatient Setting**

- If coverage for both β-hemolytic streptococci and CA-MRSA is desired, options include the following:
  - Clindamycin alone; or TMP-SMX; or a tetracycline such as doxycycline in combination with a β-lactam (amoxicillin); or linezolid alone.

(continued)

- The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTI is not recommended.

**Management of SSTIs**

Not Apparent
Necrotizing Myonecrosis/Phlegmasia

<table>
<thead>
<tr>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
</table>
| Intravenous Rx
  - Vancomycin or Piperacillin/Tazobactam
  - Cephalexin or Cefazolin
| Oral Rx
  - Amoxicillin or Clindamycin

<table>
<thead>
<tr>
<th>Moderate</th>
<th>Mild</th>
</tr>
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<tbody>
<tr>
<td>I &amp; D (C &amp; S)</td>
<td></td>
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<tr>
<td>I &amp; D</td>
<td></td>
</tr>
</tbody>
</table>

Emergency Rx
- IV/IM Cefazolin or Piperacillin/Tazobactam

Defined Rx
- MEGA
- TMP-SMX
- Clindamycin
- Doxycycline
You see that same 36 yo man with no chronic health problems...

- ...who has now presented with repeated episodes of furuncles and carbuncles.
- You have eliminated the possibility any underlying immunosuppression or diabetes.

MRSA Decolonization per IDSA

- Consider in selected cases if
  - Recurrent SSTI despite optimizing wound care and hygiene measures
  - Ongoing transmission occurs among household members or other close contacts despite optimizing wound care and hygiene measures.

MRSA Decolonization per IDSA (continued)

- Nasal decolonization with mupirocin BID for 5–10 days
- Oral antimicrobial therapy for active infection only, not for decolonization
  - Caveat on oral antibiotic use if topical decolonization not effective and organism sensitive
• Additional measures
  – Topical body decolonization regimens with skin antiseptic solution (chlorhexidine) for 5–14 days
  – Alternative=Dilute bleach baths
    • Bleach baths- 1 teaspoon (4.9 mL) per gallon (3.8 L) of water [or ¼ cup (59.1 mL) per ¼ tub or 13 gallons (49.2 L) of water] given for 15 min twice weekly

You receive the results of a culture and sensitivity...

• ...on a MRSA-infected skin lesion. The results reveal that the organism is sensitive to clindamycin and resistant to erythromycin.
• Does this influence your treatment plan?

Per IDSA SSTI Guidelines
Treatment of Suspected *S. aureus* Infection

• “…≥50% of methicillin-resistant *S. aureus* (MRSA) strains have inducible or constitutive clindamycin resistance.”
True or false?
• If a SSTI does not improve in 48–72 h with antimicrobial therapy, then infection with a resistant pathogen is likely the only cause.

FALSE

Per IDSA SSTI Guidelines
• “Progression despite receipt of antibiotics could be due to infection with resistant microbes or because a deeper, more serious infection exists than was previously realized.”
Severe Deep Soft Tissue Infection per IDSA SSTI Guidelines

- Often occur later in necrotizing infection
  - Violaceous bullae
  - Cutaneous hemorrhage
  - Skin sloughing
  - Pain disproportionate to physical findings
  - Skin anesthesia
  - Rapid progression
  - Gas in the tissue
Hospitalized Patients
Complicated SSTI: 7–14 d Therapy
• Vancomycin IV
• Linezolid PO or IV
• Daptomycin IV
• Telavancin IV
• Clindamycin PO
  – Add β-lactam with nonpurulent cellulitis if no clinical response

True or false?
• Across North America, brown recluse spider bites are the most common reason for new-onset ulcerating skin lesions.

False
Across North America, brown recluse spider bites are the most common reason for new-onset ulcerating skin lesions.
Brown Recluse Spider Bite

- “Red, white, and blue” sign
- Central blistering with surrounding gray to purple discoloration at bite site surrounded by ring of blanched skin surrounded by large area of redness

Brown Recluse Spider Bite (continued)

- Treatment
  - Local debridement, elevation, loose immobilization
  - At time of bite, ice to limit venom spread helpful
  - Dapsone often prescribed with scant evidence of effectiveness.
• Avoidance
  - Check before putting body part into area where spiders hide (footwear, boxes, other).

Conclusion

End of Presentation
Thank you for your time and attention.

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