ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

Agenda

Welcome and Introductions

Antibiotic Challenges in the Management of ABSSSIs  G. Ralph Corey
Presentation and Panel Discussion

Community-Acquired Pneumonia: Continuing Questions and Controversies  Thomas M. File Jr
Presentation and Panel Discussion

The AI Team: Antibiotic Stewardship that Ensures Optimal Outcomes  Michael J. Rybak
Presentation and Panel Discussion

Questions & Answers  All Faculty

AI, anti-infection

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# ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

## Faculty and Disclosures

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
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</thead>
<tbody>
<tr>
<td>Thomas M. File Jr, MD, MSc, MACP, FIDSA, FCCP (Chair)</td>
<td>Professor, Internal Medicine; Master Teacher Chair, Infectious Disease Section Northeast Ohio Medical University Rootstown, OH Chair, Infectious Disease Division Summa Health System Akron, OH</td>
</tr>
<tr>
<td>G. Ralph Corey, MD</td>
<td>Gary Hock Distinguished Professor of Global Health</td>
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<td></td>
<td>Vice-Chair of Education and Global Health Director, Hubert-Yeargan Center for Global Health</td>
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<tr>
<td></td>
<td>Professor of Medicine, Pathology, and Infectious Diseases</td>
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<td></td>
<td>Duke University Medical Center Durham, NC</td>
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<tr>
<td>Michael J. Rybak, PharmD, MPH, FCCP, FIDSA</td>
<td>Professor of Pharmacy and Medicine Director, Anti-Infective Research Laboratory</td>
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<tr>
<td></td>
<td>Department of Pharmacy Practice</td>
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<td>Eugene Applebaum College of Pharmacy</td>
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<td>Wayne State University Detroit, MI</td>
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Consultant: Astellas Pharma US, Inc; Bayer AG; Daiichi Sankyo Co, Ltd; Cubist Pharmaceuticals; Durata Therapeutics, Inc; Forest Laboratories, Inc; GlaxoSmithKline; Merck & Co, Inc; Pfizer, Inc; Tetraphase Pharmaceuticals Research Support: Boehringer Ingelheim GmbH; Gilead Sciences, Inc; Pfizer Inc; Tibotec Pharmaceuticals

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## Continuing Medical Education (CME) Information

### Educational Objectives

Upon proper completion of this activity, participants should be better able to:

- Describe the prevalence of causative pathogens in ABSSSIs and the susceptibility of antibiotics approved to treat them.
- Incorporate evidence-based practices, including 2013 Joint Commission/CMS Core Measures, when managing patients with CABP in the hospital setting.
- Discuss novel, team-centered approaches for implementing antimicrobial stewardship practices in the hospital setting.
ANTIBIOTIC CHALLENGES IN THE MANAGEMENT OF ABSSSIs: IS THERE A PLACE FOR NEWER AGENTS?
Ralph Corey, MD
Vice-Chair for Education and Global Health
Professor of Medicine
Division of Infectious Diseases
Duke University School of Medicine
Durham, NC

5 Steps to Diagnosis and Treatment of Skin and Skin Structure Infections

1. Make sure it is an infection
2. Search for exposures and atypical pathogens
3. Define the severity and depth of infection
4. Define patient’s immune status
5. Treat for Staphylococcus (including MRSA–always!) and Streptococcus (not including enterococcus)
   - Not every antibiotic that kills staph also kills strep
   - Be aware of local patterns of resistance
1. MAKE SURE IT IS AN INFECTION

Stasis Dermatitis

Photo courtesy of Ralph Corey, MD. All rights reserved.
Fixed Drug Eruption

Cutaneous manifestation of an adverse drug reaction

Is this ABSSSI?

• Yes
• No
2. SEARCH FOR EXPOSURES AND ATYPICAL PATHOGENS
Bites: You Are What You Eat

• Dog: *Capnocytophaga*
• Cat/lion: *Pasteurella*
• Bear: *Staphylococcus aureus*!
• Snake: oral flora = fecal flora of the rat it just ate!

Other Causes

• Water contamination
  — Fresh water: *Aeromonas*
  — Salt water: *Erysipelothrix, Vibrio vulnificus, Mycobacterium marinum*
• Trauma
  — Clostridia, *Pseudomonas*
• Many others
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Staphylococcal Exposures

- MRSA transmission between cows and humans
- Transmission of PVL-positive MRSA strain between dogs and humans
- MRSA in horses and horse personnel
- MRSA in pet cats and owners

PVL, Panton-Valentine leukocidin cytotoxin

What is your presumptive etiologic diagnosis?

- MRSA
- Anthrax
- Capnocytophaga
- Other

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3. Define the severity and depth of infection
Patient Evaluation

- Evaluate the systemic effects on the patient
  - BP, heart rate, respiratory rate, severity of pain
- Do not miss
  - Necrotizing fasciitis
  - Gas gangrene
  - Sepsis
- Determine need for source control

Necrotizing Fasciitis

Photo courtesy of Henry F. Chambers, MD. All rights reserved.
Necrotizing Fasciitis

An unresponsive 61-year-old female with a history of diabetes presented with shock, serum glucose >1000 mg/dL...
4. **Define Patient’s Immune Status**
Immune Status

• Leukopenia
  – Fungus (*Aspergillus*, mucor): black fungus
  – Bacteremia: ecthyma (*Pseudomonas*, MRSA)

• Diabetes
  – Mixed gram-negative/anaerobic (foot)
  – Group B streptococcus
  – Fungal coverage (mucor)

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Ecthyma Gangrenosum

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5. TREAT FOR *Staphylococcus* AND *Streptococcus*
Empiric Coverage

• Treat for *Staphylococcus* (including MRSA—always!) and *Streptococcus* (not including *Enterococcus*)
  — Remember: not every antibiotic that kills staph also kills strep
  — Consider local patterns of antibiotic resistance

*S aureus*: A Unique Organism

Reprinted with permission from Lowy FD. *N Engl J Med*. 1998;339(8):520-532. © 1998 Massachusetts Medical Society. All rights reserved.
CA-MRSA Outbreaks

What is this lesion?

- Spider bite
- Furnicle

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ABSSSIs: “Spider Bites” to Furuncles

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Cellulitis

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TREATMENT OF MRSA ABSSSI
Key Issues

In addition to efficacy/safety
- Oral therapy: bioavailability
- Abbreviated courses of Rx
- Once daily or weekly dosing: compliance
- Rapid onset of action
  - FDA-mandated early outcomes

Antibiotics Commonly Used Off-Label for MRSA ABSSSI

- TMP/SMX
- Clindamycin
- Tetracyclines

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FDA-Approved MRSA ABSSSI Antibiotics

- Vancomycin
- Linezolid
- Daptomycin
- Telavancin
- Tigecycline
- Ceftaroline

Vancomycin

Disadvantages

- Slow bactericidal activity\(^1\)
- Poor tissue penetration\(^1\)
- Increasing resistance\(^1\)
  - hVISA, VISA, VRSA
  - Increasing MICs
  - Bacteremia prolonged\(^2\)

hVISA, heterogeneous vancomycin-intermediate *S. aureus*; MIC, minimum inhibitory concentration; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*

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**Linezolid**

**Advantages**
- Excellent tissue penetration; protein binding $=31\%$\(^1\)
- Oral and IV formulations\(^2\)

**Disadvantages**
- Bacteriostatic against gram-positive pathogens\(^2\)
- FDA warning on increased risk of death when used to treat CR-BSI\(^3\)
- Newly described resistance (Cfr methyltransferase, others)
- Toxicity\(^2\)
  - Bone marrow suppression
  - Peripheral neuropathy/optic neuritis (after prolonged course)
  - Lactic acidosis, serotonin syndrome

CR-BSI, catheter-related blood stream infection


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**Daptomycin**

**Advantages**
- Rapidly bactericidal, concentration dependent killing\(^1,2\)
- Kills without lysis\(^3\)
- Effective in BSI

**Disadvantages**
- Potential for myotoxicity\(^1\) and eosinophilic pneumonia
- Development of treatment-emergent resistance\(^3\)

BSI, blood-stream infection

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Telavancin

Advantages
• Rapidly bactericidal, concentration-dependent killing\(^1,2\)
• Effective in both ABSSSIs and HAP/VAP\(^3\)

Disadvantages
• Renal toxicity with increased mortality (HAP/VAP)\(^1,3\)
• Risk of fetal toxicity\(^3\)

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

Tigecycline

Advantages
• Broad spectrum, active against MRSA, β-lactamase producing gram-negative (eg, *Acinetobacter*)\(^1\)
• Noninferior efficacy in ABSSI\(^2,3\)

Disadvantages
• Bacteriostatic\(^4\)
• Low serum concentrations\(^5\)
• Failed HAP/VAP trial\(^6\)
• Significant incidence of nausea, vomiting\(^2,3,7\)
• FDA warning of increased risk of death\(^8\)

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Ceftaroline

**Advantages**
- Broad-spectrum 5th generation cephalosporin
- Bactericidal against gram-positive pathogens, including:
  - *S. aureus* MRSA (MIC<sub>90</sub> 1.0 μg/mL)

**Disadvantages**
- Q 12 h dosing
- Eosinophilic pneumonia


MRSA ABSSSI Antibiotics in Development

- Oritavancin
- Dalbavancin
- Tedizolid
- Radezolid
- Delafloxacin
- 322 GSK
- Pleuromutilin BC-3781
- Avarofloxacin

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**ORITAVANCIN**

**Advantages**
- Rapidly bactericidal against gram positive cocci, including MRSA¹
- SOLO I and II in ABSSSI met efficacy endpoints²
  - MRSA cure in severe ABSSSI with single IV infusion
  - Noninferior to multiple doses of vancomycin IV Q 12 h
- Long half-life³

**Disadvantages**
- Long half-life³

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**DALBAVANCIN**

**Advantages**
- Long half-life supports weekly dosing¹
- Bactericidal against gram-positive cocci, including MRSA³
- In ABSSSI studies noninferior to linezolid¹,²
- Long half-life³

**Disadvantages**
- Long half-life³
- Requires 2 doses, results in mandatory follow-up³

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Tedizolid

Advantages
• Activity against major gram-positive pathogens
• Available as IV or PO
  – Oral: qd dosing; 6 d was noninferior to linezolid Q 12 h for 10 d
  – IV: qd dosing for 6 d was noninferior to linezolid Q 12 h for 10 d
• No cfr resistance reported

Disadvantages
• Toxicity for extended therapy unknown

The BIG Question Now

Which serious staphylococcal infections will these new compounds “take on”?
• HAP/VAP
• Prosthetic joint infections
• Bloodstream infections (± IE)
• Less commonly considered problems
  – Meningitis
  – Endophthalmitis
  – Gastroenteritis

IE, infectious endocarditis


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Conclusions

• Infections of skin and skin structures can be tricky
   1. Make sure you are dealing with infection
   2. Search for exposures and atypical pathogens
   3. Define severity and depth of infection
   4. Define patient’s immune status
   5. THEN treat for staph (always include MRSA) and strep

• Use the most effective and safest antibiotic for each patient!

COMMUNITY-ACQUIRED PNEUMONIA: CONTINUING QUESTIONS AND CONTROVERSIES

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The Impact of CAP in the United States

- Leading cause of morbidity and mortality\(^1-4\)
  - \(\approx 50,000\) deaths/y, especially elderly and patients with comorbidities\(^1,5\)
  - #1 cause of mortality due to infection in US\(^6\)
- Annual incidence\(^7\)
  - General population: 1-12 cases/1,000
  - \(\geq 65\) y/o: 25-44 cases/1,000
- Annual prevalence: >4 million cases\(^3\)
  - \(\approx 1.1\) million admissions/y, 40% 1-y mortality\(^4,5\)
  - \(\approx 80\%\) treated as outpatients\(^8\)
- Annual cost of treatment >$17 billion\(^3\)


Are Present CAP and HCAP Definitions the Best Way to Define Risk of MDR Infection?\(^1\)

2005 Guidelines for Nosocomial Pneumonia: HCAP Etiology

- Risk factors for MDR pathogens causing HCAP
  - Hospitalized ≥2 d in preceding 90 d
  - Nursing home/extended care facility residence
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with MDR pathogen

- Treat for MDR pathogens
  - But this is an overgeneralization; updated guidelines are under development

- Designation of HCAP—poor predictor of resistant pathogens
- Current definition needs further modification so adequate coverage can consistently be provided while avoiding excessive antibiotic use

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Which Scoring Tool Best Predicts Clinical Response, Long-term Outcomes?

- PSI
- CURB-65
- CRB-65
- SMART COP
- SCAP

“...In regards to the best scoring tool to predict clinical response and long term outcomes, Pneumonia Severity Index (PSI) is probably a more accurate score to predict a wide range of clinical outcomes.”

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PSI, Pneumonia Severity Index; CURB-65, Confusion, elevation of blood Urea nitrogen, Respiratory rate, low Blood pressure, age ≥65 y; CRB-65, Confusion, Respiratory rate, low Blood pressure, age ≥65 y; SMART COP, low Systolic blood pressure, Multilobar chest X-ray involvement, low Albumin, high Respiratory rate, Tachycardia, Confusion, poor Oxygenation, low arterial pH; SCAP, Severe Community-Acquired Pneumonia

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Guidelines and Quality Measures: Do They Improve Outcomes of Patients with CAP?

- "...body of evidence supporting the positive effects of guidelines on outcomes in patients with CAP is extraordinary"¹
  - Recent meta-analysis concluded guideline compliance more important than choice of antimicrobials²
- "...no evidence that...pay-for-performance program led to a decrease in 30-d mortality"³
  - 30-d mortality (2003–2009)³
  - Pay-for-performance hospitals: 11.71%
  - Non-pay-for-performance hospitals: 11.85% (95% CI, –0.67–0.38)


CMS 2014 CAP Quality Measures for Inpatients

- Empiric antimicrobials according to guidelines
  - Exceptions: pathogen-directed therapy, clinical trials, diagnostic uncertainty
- CAP mortality
- 30-d readmission rate for pneumonia*

*Complements Core Measures as part of the Hospital Readmissions Reduction Program—hospitals with higher than expected 30-d readmission rates for AMI, heart failure, and pneumonia will incur penalties against their total Medicare payments beginning in FFY 2013.

### CABP: JC/CMS Antimicrobial Recommendations by Site of Care²

<table>
<thead>
<tr>
<th>Inpatient, Non-ICU</th>
<th>Inpatient, ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactam (IV or IM) + macrolide (IV or po) –OR–</td>
<td>Macrolide (IV) + β-lactam (IV) –OR– antipseudomonal β-lactam (IV)</td>
</tr>
<tr>
<td>Anti-pneumococcal quinolone monotherapy (IV or po) –OR–</td>
<td>Antipseudomonal quinolone (IV) + either β-lactam (IV) –OR– antipseudomonal β-lactam (IV)</td>
</tr>
<tr>
<td>β-lactam (IV or IM) + doxycycline (IV or po) –OR– Tigecycline monotherapy (IV) –OR– Macrolide monotherapy (IV or po)</td>
<td></td>
</tr>
</tbody>
</table>

*If aged <65 y with no risk factors for drug-resistant Pneumococcus.*


### CABP: New Antimicrobials

- **Tigecycline IV**
  - Glycylcycline (derivative of minocycline): broad spectrum including *S pneumoniae*, atypicals¹
  - Approved for ABSSSI, CABP, intra-abdominal infections²
    - CABP: comparable to levofloxacin¹
    - HAP/VAP: comparable to imipenem for HAP; inferior for VAP³,⁴
  - Listed as option for CABP admitted to general ward
    - 100 mg initially, then 50 mg Q 12h²
    - Adverse effects: nausea, vomiting²

- **Ceftaroline IV**
  - Prodrug, broad-spectrum cephalosporin⁵
  - Bactericidal in CABP infections vs *S pneumoniae*, *S aureus* (MSSA), *H influenzae*, *K pneumoniae*, *K oxytoca*, *E coli*⁶
  - Approved for CABP, ABSSSI; 600 mg q 12 h⁶

MSSA, methicillin-susceptible *S aureus*

**Ceftaroline vs Ceftriaxone in Patients with CABP**

- N=1228 adults, mean age 61 y; PSI III/IV
- Clinical cure for *S. pneumoniae*: ceftaroline 59/69 (85.5%) vs ceftriaxone 48/70 (68.6%)
  - *Ceftaroline has greater affinity for penicillin-binding protein 2x*

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**DIAGNOSTIC TESTS**

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What is the Benefit of CAP Biomarkers in Patient Management?

Biomarker procalcitonin (PCT) guides reduction in hospital antibiotic treatment of CAP without increasing mortality risk

<table>
<thead>
<tr>
<th>Trials of PCT to Guide Therapy Duration in CAP Hospital Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Christ-Crain M et al²</td>
</tr>
<tr>
<td>Schuetz P et al³</td>
</tr>
<tr>
<td>Bouadma L et al⁴</td>
</tr>
</tbody>
</table>


PCT for Antimicrobial Stewardship When Treating RTIs

<table>
<thead>
<tr>
<th>PCT value</th>
<th>&lt;.01 µg/L</th>
<th>&lt;.025 µg/L</th>
<th>≥0.25 µg/L</th>
<th>&gt;0.5 µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection?</td>
<td>Very unlikely</td>
<td>Unlikely</td>
<td>Likely</td>
<td>Very likely</td>
</tr>
<tr>
<td>Antibiotic recommendation</td>
<td>Strongly discouraged</td>
<td>Discouraged</td>
<td>Encouraged</td>
<td>Strongly encouraged</td>
</tr>
<tr>
<td>F/U</td>
<td>Reassess and recheck PCT after 6-24h if no clinical improvement</td>
<td>Recheck PCT every 2-3 d to consider early stop antibiotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When to overrule</td>
<td>Consider antibiotic if patient is clinically unstable or at high risk for adverse outcomes (PSI IV-V) or has strong evidence for bacterial pathogen</td>
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</tbody>
</table>

RTI, respiratory tract infection
Role of Newer Molecular Tests in CAP Management

- Standard culture methods (blood, sputum)
  - Low yield, time to results
- Gram stain, urinary antigen testing
  - \textit{S. pneumoniae}, \textit{Legionella} spp
- Newer molecular tests (PCR, MALDI-TOF)\textsuperscript{4-6}
  - Potential for more rapid diagnosis, greater sensitivity
  - Allows for pathogen-directed therapy

PCR, polymerase chain reaction; MALDI-TOF, matrix-assisted laser desorption/ionization Time of Flight mass spectrometry


Enriched PCR Detection of CAP Pathogens

Table 2. Bacterial Yield in the Study Population and the Contribution of Different Methods to the Determination of Etiology with Respect to Their Different Specificity

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>No. (%) of patients with positive sampling (n = 106)</th>
<th>Blood culture (n = 106)</th>
<th>Plural fluid culture (n = 123)</th>
<th>Urine antigen testing (n = 123)</th>
<th>BAL fluid protocol respiratory culture (n = 130)</th>
<th>Culture and PCR from respiratory sample for \textit{S. pneumoniae} (n = 106)</th>
<th>Culture and PCR from respiratory sample for \textit{Legionella} (n = 106)</th>
<th>Culture and PCR from respiratory sample for non-pneumococcal \textit{S. pneumoniae} (n = 106)</th>
<th>Culture and PCR from respiratory sample for non-\textit{S. pneumoniae} (n = 106)</th>
<th>Non-pneumococcal \textit{S. pneumoniae} (n = 106)</th>
<th>\textit{S. aureus} (n = 106)</th>
<th>M. tuberculosis (n = 106)</th>
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</thead>
<tbody>
<tr>
<td>\textit{S. pneumoniae}</td>
<td>27 (25.5)</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>9</td>
<td>16</td>
<td>18</td>
<td>16</td>
<td>16</td>
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<td>16</td>
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<tr>
<td>\textit{M. tuberculosis}</td>
<td>15 (14.1)</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>9</td>
<td>16</td>
<td>18</td>
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<td>16</td>
<td>16</td>
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<tr>
<td>\textit{K. pneumoniae}</td>
<td>10 (9.4)</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>9</td>
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<td>16</td>
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<tr>
<td>\textit{M. abscessus}</td>
<td>8 (7.5)</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>9</td>
<td>16</td>
<td>18</td>
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<td>16</td>
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<tr>
<td>\textit{E. coli}</td>
<td>8 (7.5)</td>
<td>10</td>
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<td>9</td>
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<td>16</td>
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<tr>
<td>\textit{K. oxytoca}</td>
<td>6 (5.6)</td>
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<td>10</td>
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<td>16</td>
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<td>16</td>
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<tr>
<td>\textit{P. aeruginosa}</td>
<td>6 (5.6)</td>
<td>10</td>
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<td>\textit{S. maltophilia}</td>
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<td>\textit{B. cereus}</td>
<td>3 (2.6)</td>
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<td>\textit{C. jeikeium}</td>
<td>2 (1.9)</td>
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<td>10</td>
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<td>\textit{A. baumannii}</td>
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<td>16</td>
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<tr>
<td>\textit{M. catarrhalis}</td>
<td>1 (0.9)</td>
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<tr>
<td>\textit{H. influenzae}</td>
<td>1 (0.9)</td>
<td>10</td>
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<td>16</td>
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<tr>
<td>\textit{A. viscosum}</td>
<td>1 (0.9)</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>9</td>
<td>16</td>
<td>18</td>
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</tr>
<tr>
<td>\textit{H. parainfluenzae}</td>
<td>1 (0.9)</td>
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<td>13</td>
<td>16</td>
<td>9</td>
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</tr>
<tr>
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<td>0 (0.0)</td>
<td>10</td>
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<tr>
<td>\textit{M. phenolicum}</td>
<td>0 (0.0)</td>
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<tr>
<td>\textit{M. fortuitum}</td>
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<tr>
<td>\textit{M. chelonei}</td>
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<tr>
<td>\textit{M. luteus}</td>
<td>0 (0.0)</td>
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<td>13</td>
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<td>9</td>
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<td>18</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>77 (72.3)</strong></td>
<td><strong>77</strong></td>
<td><strong>77</strong></td>
<td><strong>77</strong></td>
<td><strong>77</strong></td>
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</tr>
</tbody>
</table>

Among the 38 patients who had complete sampling (conventional + molecular assays), a microbial etiology was determined for 89%.

Empiric Therapy for Atypical Pathogens: Does it Improve CAP Outcomes?

Issues of controversy regarding significance of atypical pathogens

- Clinical relevance of terminology
- Awareness of such pathogens
- Diagnostic testing
- Debate as to the clinical impact of treating these infections
- Perceived contradictory results of published evidence

Empiric Therapy for Atypical Pathogens: Early Outcome Assessment

Early outcome assessment may identify benefit of macrolides

```
<table>
<thead>
<tr>
<th></th>
<th>FOCUS 1 (macrolide)</th>
<th>FOCUS 2 (no macrolide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4 Clinical Stability and Symptom Improvement</td>
<td>76.6</td>
<td>57.6</td>
</tr>
<tr>
<td>Test of Cure</td>
<td>89.1</td>
<td>87.9</td>
</tr>
</tbody>
</table>
```

“Thus, empiric therapy for atypical pathogens does improve outcomes for patients with CAP.”

ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

Fluoroquinolone or β-Lactam + Macrolide

Which has better outcomes in non-ICU CAP?¹

• Reviewed evidence
  — Multiple studies; but different designs
  — Considered “collateral damage”
  — Immunomodulatory effects of macrolides
  — Fluoroquinolone PK and resistance
• Conclusion
  — Neither of the two first-line regimens has been proved to have clear-cut clinical superiority

“The therapeutic decision making should be individualized, taking into account additional patient information such as the presence of drug allergies, local resistance patterns, patient comorbidities, and risk factors for the presence of resistant *S. pneumoniae*”


How Important is MRSA as a Cause of CAP?¹

“MRSA clearly is an important pathogen in CAP. While currently causing a relatively low percentage of CAP cases, the disproportionate frequency of otherwise healthy young people with this infection drives concern and therefore empiric antibiotic therapy.”¹

• EMERGEncy ID Net study (2006-2007)²
  — N=595 CAP patients, pathogen identified in 17%
  — *S. pneumoniae*: 9.6%; MRSA, 2.4%; MSSA: 1.5%;
  — *K. pneumoniae*: 0.7%; *H. influenzae*: 0.3%
• Clinical features suggesting increased risk of CA-MRSA pneumonia¹
  — Cavitory pneumonia
  — Neutropenia
  — Lung necrosis
  — Hemoptysis

MRSA CAP: What is the Best Antimicrobial Therapy?

- Antimicrobials for MRSA pneumonia\(^1\)
  - Appropriate: vancomycin, linezolid
  - Under study: ceftaroline
  - Unclear: clindamycin, trimethoprim/sulfa
- "Linezolid consistently demonstrates better clinical response rates than vancomycin in clinical trials of MRSA pneumonia. Linezolid also suppresses exotoxin production in \textit{in vitro} models, which may be important in CA-MRSA CAP"\(^1\)
  - Zephyr study (HAP/VAP)\(^2\)
    - Clinical response: linezolid, 57.6%; vancomycin, 46.6%; \(P < .05\)
    - No difference in mortality


Do Adjunctive Therapies Improve Patient Outcomes in Severe CAP?

“Adjunctive therapies directed at the host response rather than the pathogens are attractive to improve outcomes.

Corticosteroids, statins, ACE inhibitors, and anticoagulants have been used with some encouraging results, although data are still scarce.

Future research is needed in these areas to decrease mortality due to severe CAP.”

Conclusions

- CAP is very common and serious
- Despite many advances, controversies and questions remain
- New guidelines are under development


Recent journal devoted to current issues in the management of inpatient CAP
ANTIMICROBIAL STEWARDSHIP THAT ENSURES OPTIMAL OUTCOMES

Michael J. Rybak, PharmD, MPH, FCCP, FIDSA
Professor of Pharmacy and Medicine
Director, Anti-Infective Research Laboratory
Department of Pharmacy Practice
Eugene Applebaum College of Pharmacy
Wayne State University, Detroit, MI

Drug Resistance is Rising

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Antibiotic Stewardship in Your Facility Will...

**DECREASE**
- Antibiotic resistance
- *C. difficile* infections
- Costs

**INCREASE**
- Good patient outcomes


CLINICAL AND ECONOMIC COSTS OF RESISTANCE
ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

The Burden of Antimicrobial Resistance

Greater impact of MRSA on clinical and economic outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MSSA&lt;sup&gt;b&lt;/sup&gt; (n=390)</th>
<th>MRSA&lt;sup&gt;b&lt;/sup&gt; (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo mortality&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.5%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Hospital charges&lt;sup&gt;d&lt;/sup&gt; 6-mo median (range)</td>
<td>$6,748 ($0–$35,089)</td>
<td>$26,274 ($4,531–$86,974)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on medical records, accounting systems, and interviews between January 1, 2004 and June 30, 2006
<sup>b</sup>Patients with S. aureus infection within the Minneapolis Veterans Affairs hospital and associated clinics
<sup>c</sup>Within 6 mo of onset
<sup>d</sup>Median 6-mo inpatient unadjusted costs in 2006 US dollars


Attributable Costs of Resistance*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients with ARI (n=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (LOS)</td>
<td>6.4 ± 12.7 d</td>
</tr>
<tr>
<td>Death&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.5%</td>
</tr>
<tr>
<td>Medical costs (mean ± SE)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>$18,588–$29,069</td>
</tr>
<tr>
<td>Total hospital costs&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>$3.4–$5.4 million</td>
</tr>
<tr>
<td>Total societal costs&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>$10.7–$15.0 million</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted attributable mortality. Absolute mortality 18.1% with ARI vs 3.0% without ARI; adjusted OR = 2.16
<sup>b</sup>Economic costs were reported in 2008 US dollars
<sup>c</sup>Variable costs for a base case patient, including medications and blood products
<sup>d</sup>Including labor, benefits, supplies, equipment used, and allocated administrative and support costs for employees and space occupied
<sup>e</sup>Costs of mortality, lost productivity

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Cost Savings if Antimicrobial Resistance Reduced

Current ARI rate: 13.5%
Reduced ARI rate: 10%

Savings for 1391 patients:
$1548 per patient


Antimicrobial Stewardship Programs
Issues Related to ASP Implementation

- Restrictions common in academic centers, not community hospitals\(^1,2\)
- Lack of strong scientific evidence to support improved outcomes\(^1,3\)
- Lack of a full-time ID consult service\(^2\)
  - Role of pharmacist, physician, ID fellow unclear and varies\(^1\)
- Limited use of local guidelines\(^1\)
- Limited use of CPOE and CDSS\(^1\)
- Program funding inconsistent\(^1\)
- Administrative support and data analysis inconsistent\(^1\)

CPOE, computerized provider order entry; CDSS, clinical decision support system


Antibiotic Use Evaluation = Antimicrobial Stewardship

1. Assess patient
2. Make diagnosis
3. Select treatment plan

- Are antibiotics needed?
- What are my options?
- Formulary restrictions?
- Will it work?

- Risk stratification (severity, risk factors for MDROs)
- Guidelines (local or national)
- Spectrum of activity and local antibiogram
- Nonscientific inputs: peer opinion, marketing

4. Implement plan
5. Reassess patient
6. Modify plan

- Are antibiotics still needed?
- Can I streamline therapy?
- Specific microbiology
- Convenience and cost

MDROs, multi-drug resistant organisms

ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

Stewardship Strategies: Therapeutic Guidelines and Pathways

- Disease-based treatment guidelines to target
  - Selection: initial empiric therapy and alternatives
  - Dosing: pharmacodynamic optimization
  - Route: IV/PO conversions
  - Duration of therapy, facilitate discharge from hospital
- Must have multidisciplinary involvement and input from all stakeholders (eg, surgery, pulmonary, nurse managers)
- Should account for local resistance patterns


“Back-End Approach”
Prospective audit with intervention and feedback
Formulary restriction and pre-authorization requirements
“Front-End Approach”

Advantages1,2
- Can be customized to facility
- Preserves prescriber autonomy
- Circumvents potential for delays in initiating therapy
- Provides educational opportunities

Disadvantages1,2
- Labor intensive
- Recommendations optional
- Potential for inappropriate exposure

Advantages1,3
- Initial orders funneled through experts
- Can be facilitated through computer surveillance
- Immediate educational opportunities
- Control of antimicrobial use

Disadvantages1,3
- Delays therapy for critically ill patients
- Requires trained personnel
- Loss of prescriber autonomy
- Potential for prescriber to circumvent
- Potential for inappropriate exposure


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**“Back-End Approach”**
- Prospective audit with intervention and feedback
- Formulary restriction and pre-authorization requirements

**“Front-End Approach”**

| Education          | • Most frequently employed intervention
|                   | • Essential element of any ASP
| Guidelines        | • ASP should facilitate development of evidenced-based guidelines
|                   | • Must be tailored to local practice and epidemiology
| Computer Surveillance | • Opportunity for screening information as it becomes available
|                   | • Can develop alerts, reports, and decision support pathways
| Outcomes Measurement | • Determines the impact of new policies
|                   | • Opportunities for research and publication


---

**ASP Improves Clinical Outcomes**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>ASP</th>
<th>Usual practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate Antimicrobial</td>
<td>90</td>
<td>32</td>
</tr>
<tr>
<td>Clinical Cure</td>
<td>91</td>
<td>55</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Antibiotic Resistance</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

University of Pennsylvania Hospital observational study, clinical outcomes with a comprehensive stewardship program compared with usual practice.1,2


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ABSSSI and CABP: Maximizing the Anti-Infective Arsenal to Optimize Patient Outcomes

**ANTIMICROBIAL STEWARDSHIP INTERVENTION: OUTCOMES WITH ABSSSI**

**Epidemiology of Skin and Soft Tissue Infections (SSTIs)**

SSTI Hospitalization by Type of Infection (2009-2011; N=471,550)

- Cellulitis and abscess: 63%
- Impetigo: 7%
- Other infections of the skin: 15%
- Folliculitis: 5%
- Carbuncle and furuncle: 8%
- Other SSTI: 2%

Other infections of the skin: folliculitis.
Other SSTI: erysipelas, mastitis, acute lymphadenitis, hydradenitis, and necrotizing fasciitis.

**Antibiotic Resistance and Treatment Outcomes**

CA-MRSA leads to significantly greater rates of hospitalization, failure of initial therapy, and infection recurrence in patients with cSSSI vs those with CA-MSSA (2003–2005).

- Hospitalized: 46% for CA-MRSA (n=102) vs 18% for CA-MSSA (n=102) (P < .001)
- Failed Therapy: 39% for CA-MRSA vs 16% for CA-MSSA (P < .001)
- Recurrent Infection: 18% for CA-MRSA vs 6% for CA-MSSA (P < .015)


**Antibiotic Use in ABSSSI**

Vancomycin used as initial therapy in 58% of cSSSI cases in 2009

Parenteral antibiotic use in >10% (by 2009) of adult cases within first 24 h of admission to 100 US hospitals, based on chart review of 22,382 admissions for cSSSI between 1/1/00 and 6/30/09.


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Opportunities for Antimicrobial Stewardship Programs

Opportunity for ASPs
SSTIs Requiring Hospitalization

Study Parameters

- Retrospective chart review of adults discharged with diagnosis of SSTI from 1/107 to 12/31/07
  - 477-bed academic hospital in Denver
  - SSTI classified as cellulitis, cutaneous abscess, or SSTI with additional complicating factors
- Results (N=322)
  - 66 (20%): cellulitis
  - 103 (32%): abscess (incision and drainage in 98%)
  - 153 (48%): complicating factors
    - Common comorbidities in each group: IV drug use, diabetes mellitus, alcohol abuse

Study Findings

- 150 pts had positive cultures from abscess, deep tissue, or blood
  - *S. aureus* or streptococci identified in 145 (97%)
- Duration of antibiotic therapy, (median, d)
  - Cellulitis: 13 (IQR, 10–14 d)
  - Cutaneous abscess: 13 (IQR, 10–16 d)
  - SSTI with complications: 14 (IQR, 11–17 d)
- 30-d treatment failure, recurrence, readmission
  - Cellulitis: 12.1%
  - Cutaneous abscess: 4.9%
  - SSTI with complications: 9.2%

<table>
<thead>
<tr>
<th>Parenteral Antibiotic</th>
<th>Patients (N=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>73%–79%</td>
</tr>
<tr>
<td>Gram positive activity, without MRSA coverage</td>
<td>≤20%</td>
</tr>
<tr>
<td>Broad aerobic gram-negative activity</td>
<td>61%–80%</td>
</tr>
<tr>
<td>Anaerobic coverage</td>
<td>73%–83%</td>
</tr>
</tbody>
</table>

IQR, interquartile range

SSTIs Requiring Hospitalization: Excess Resource Utilization

- ESR or CRP determined in nearly 70% of patients
- Blood cultures for 47%–58% of patients
- Imaging studies in 94% of patients
  - SSTI with complicating factors: 86%
  - Significant association between cellulitis and use of plain film (P < .004) and ultrasound (P < .001)
  - Advanced imaging (CT, MRI) in 20% of all cases
- Yield of imaging studies: 14 (4%) of 322 cases
  - Plain film: 4 (1%)
  - Ultrasound: 1 (0.3%)
  - CT: 7 (2%)
  - MRI: 3 (1%)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein
SSTIs Requiring Hospitalization: Study Conclusions

- Additional therapy results
  - 85% of cellulitis inpatients received MRSA coverage
    - =50% of 66 cases discharged on TMP/SMX
    - Highest rate of failure, 12.1% (8/66)
    - 5/8 (63%) cases of cellulitis failure discharged on TMP/SMX

- Conclusions
  - Substantial healthcare resources used to treat SSTI
  - Some diagnostic testing poorly defined, expensive, unnecessary
  - Many patients received inappropriate broad antibiotic coverage, including gram-negative and anaerobic coverage
  - Duration of hospitalization for treatment appeared excessive, and many patients could have received part of therapy at home

Impact of ASP on Inpatient Treatment of ABSSSI

- Objective
  Observe impact of ASP on ABSSSI treatment and outcomes since ASP implemented 2/2012
  - Appropriateness of antibiotic therapy
  - LOS
  - 30-d readmission rate

- Historic control
  Treatment outcomes of ABSSSI (ICD9 codes 681-682.9) at Summa Health System in 2011
  - Mean LOS: 6.2 d
  - 30-d readmission rate: 6.2%

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Impact of ASP on Inpatient Treatment of ABSSSI (continued)

ASP Intervention Types (N=85)

- Antibiotic regimen change
- De-escalation
- Dose change
- ID consult
- Other

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>2012 (N=62)</th>
<th>2011 (N=1149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS, mean (d)</td>
<td>4.4</td>
<td>6.2</td>
</tr>
<tr>
<td>30-d All-Cause Readmission</td>
<td>6.5%</td>
<td>16.71%</td>
</tr>
<tr>
<td>30-d ABSSSI Readmission</td>
<td>3.33%</td>
<td>6.27%</td>
</tr>
</tbody>
</table>


Summary: Antimicrobial Stewardship Programs

- Driven by increasing antibiotic resistance
  - Limited pipeline
- Needs leaders and training programs
- Requires administration support
- Some components may be forced based on:
  - Future Joint Commission and CMS requirements
- Requires evaluation of ASP impact
  - To improve and develop effective policies
  - Maintain services and resources