Life Threatening Infections, Antibiotic Selection, and Antibiotic Resistance

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University of Colorado School of Medicine
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Surgical Grand Rounds, 10.10.11
Necrotizing Soft Tissue Infections (NSTI)
Necrotizing Soft Tissue Infections

• **Epidemiology**
  – Rare but lethal bacterial infection of skin and soft tissue
  – Outcome correlated strongly with time to definitive therapy and adequacy of debridement
  – Protracted, complicated, expensive hospitalization

• **Nomenclature**
  – Necrotizing cellulitis
  – Necrotising fasciitis
  – Necrotising myositis
  – Fournier’s gangrene: perineal source
## NSTI Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Organisms</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (80%)</td>
<td>Polymicrobial</td>
<td>25%</td>
</tr>
<tr>
<td>Type II</td>
<td>Group A Streptococcus</td>
<td>25%</td>
</tr>
<tr>
<td>Type III</td>
<td>Clostridial spp.</td>
<td>75%</td>
</tr>
<tr>
<td>Fornier’s</td>
<td>Polymicrobial</td>
<td>75%</td>
</tr>
</tbody>
</table>
NSTI
Pathophysiology

• **Primary**
  - Vibrio vulnificus
  - Clostridium septicum

• **Secondary**
  - Trauma
  - Surgical incisions
  - Neglected sSSTIs

• **Severity**
  - Innoculum
  - Virulence
  - Foreign body/ischemic tissue
  - Impaired host defenses
NSTI
Pathophysiology

Bacterial proteases cleave tissue planes → Local necrosis → sepsis → MOF
NSTI
Diagnosis

- Overlying skin often unaffected
- Pain out of proportion to exam
- Edema and tenderness extend beyond rim of cellulitis
- Crepitus specific but not sensitive
- Clostridial species \(\rightarrow\) anemia & jaundice (hemolysis)
- Myonecrosis \(\rightarrow\) ↑ CPK
LRINEC Score

- Range 0-13
- < 6 $\rightarrow$ unlikely
- 6-8 $\rightarrow$ likely
- > 8 $\rightarrow$ very likely
- At a cutoff of 6, PPV = 92% and NPV = 96%
- Not a substitute for clinical judgment

<table>
<thead>
<tr>
<th>Value</th>
<th>LRINEC score, points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein, mg/L</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>&gt;150</td>
<td>4</td>
</tr>
<tr>
<td>WBC count, cells/mm³</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
</tr>
<tr>
<td>15-25</td>
<td>1</td>
</tr>
<tr>
<td>&gt;25</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td></td>
</tr>
<tr>
<td>&gt;13.5</td>
<td>0</td>
</tr>
<tr>
<td>11-13.5</td>
<td>1</td>
</tr>
<tr>
<td>&lt;11</td>
<td>2</td>
</tr>
<tr>
<td>Sodium level, mmol/L</td>
<td></td>
</tr>
<tr>
<td>&gt;135</td>
<td>0</td>
</tr>
<tr>
<td>&lt;135</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
<td></td>
</tr>
<tr>
<td>≤1.6</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1.6</td>
<td>2</td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td></td>
</tr>
<tr>
<td>≤180</td>
<td>0</td>
</tr>
<tr>
<td>&gt;180</td>
<td>1</td>
</tr>
</tbody>
</table>
NSTI
Diagnostic imaging

- Specific but insensitive
- If positive, usually too late
- Should not delay initiation of therapy based on physical exam
- The morbidity secondary to a missed diagnosis justifies a relatively high false negative rate at exploration
NSTI
Treatment

• Surgical emergency

• Debridement to include margin of healthy tissue

• Re-exploration within 24 hours until infection controlled

• Multiple coverage options
NSTI
Treatment

• Broad spectrum antibiotics
  1. Vancomycin
  2. Broad-spectrum GN agent (e.g., carbapenem, pip/tazo)
  3. Clinda vs. PCN G

• Supportive ICU care

• HBO, IVIg of unproven benefit
NSTI
Summary

• Rare, elusive, lethal

• Diagnosis rests on clinical exam with low threshold for surgical intervention

• Usually polymicrobial $\rightarrow$ Broad spectrum antibiotics until organism isolated

• Vigilant follow up until eradication of infection

• **Pitfalls**
  – Diagnostic delay
  – Inadequate debridement
Antibiotic Selection
General Principals

- Timely initiation of broad spectrum therapy, followed by timely discontinuation of unnecessary therapy
- Know the host
- Know the bugs (local antimicobiogram)
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

(Crit Care Med 2006; 34:1589–1596)
Antibiotic Selection
Suspected Infection

100% Sensitivity 100% Specificity

Draw Cultures → Broad-spectrum Antibiotics → Interpret Cultures

Continue → De-escalate → Escalate
Inadequate Antimicrobial Therapy Associated with Increased Mortality

Mortality (%)

0 20 40 60 80 100

Ruiz (2000)
Rello (1997)
Luna (1997)
Kollef (1999)
Dupont (2001)

Inadequate initial antibiotic treatment
Adequate initial antibiotic treatment


Antibiotics are not a substitute for source control
Which Antibiotic(s)?

- Likely organisms
- Activity of antimicrobial agents
- Bactericidal vs bacteriostatic therapy
- Resistance issues
- Patient tolerability
- Compatibility with other treatment
Risk Factors for MDR Organisms

• Hospitalization > 48 hours
• Immunosuppression
• Postoperative infection
• Recent antibiotic therapy
• Recent (< 30 days) contact with healthcare environment
• Residence in skilled nursing care or long term care facility
## Antibiotic Selection
### Covering the Gamut

<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
<th>Enteric GNR</th>
<th>Anaerobes</th>
<th>Pseudo</th>
<th>C. diff</th>
<th>ESBL Kleb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pip/tazo</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vanco</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
# Antibiotic Selection
## Ventilator Associated Pneumonia

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR organisms unlikely</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>MRSA likely</td>
<td>Vanomycin, ceftriaxone</td>
</tr>
<tr>
<td>Pseudomonas likely</td>
<td>Vancomycin, pip/tazo</td>
</tr>
<tr>
<td>PCN allergy</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Linezolid, pip/tazo</td>
</tr>
<tr>
<td>Acinetobacter likely</td>
<td>Vancomycin, polymixin B</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Vanco, pip/tazo, flucononazole</td>
</tr>
</tbody>
</table>
Antibiotic Selection
Dosing

• Inadequate dosing results in both clinical failure and resistance

• Associated with poor outcomes

• Vancomycin = 15 mg/kg q12 h; drive trough > 20

• Gentamicin 7 mg/kg daily; amikacin 20 mg/kg daily

• Levofloxacin 750 mg; ciprofloxacin 400 mg every 8 h

• Piperacillin/tazobactam 4.5g every 6 h
Continuous-Infusion Beta-lactams

- Takes full advantage of a drug’s exposure potential in the context of in vitro potency
- No alteration in dose, dosing schedule, or toxicity
- Opportunity to improve efficacy of selected therapy while minimizing resistance
Special Situations
Obesity

• $\uparrow$ Adipose:lean mass alters $V_d$
  – Lipophilic drugs $\rightarrow$ ABW vs. IBW
  – Hydrophilic drugs $\rightarrow$ IBW vs. ABW

• $V_d$ and Cr clearance highly unpredictable
  – Measure Cr clearance
  – follow serum concentrations whenever possible

Table 3. Dosing weights in obese patients for selected drugs used commonly in critical illness

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>ABW</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>ABW</td>
</tr>
<tr>
<td>Single-dosage</td>
<td>IBW</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>IBW</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>$\frac{52}{1} + \left[196.4 \times e^{-0.025 \times ABW} - 53.66\right]/100$</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>ABW</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>IBW + $(0.40 \times [ABW - IBW])$</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>IBW + $(0.40 \times [ABW - IBW])$</td>
</tr>
<tr>
<td>Drotrecogin alfa (activated)</td>
<td>ABW</td>
</tr>
</tbody>
</table>

ABW, actual body weight; IBW, ideal body weight.
Special Situations

“Double Coverage”

• Differentiate from broad spectrum empiric coverage

• Theory of antimicrobial synergy
  – Improved killing
  – Prevention of resistance

• Early meta-analysis in immunocompromised patients showed no benefit and possible harm

• Recent resurgence with positive outcomes
• 64 trials 7586 patients (1981-2001)

• No mortality difference

• Clinical failure slightly more common with combination therapy (OR=0.87 [0.78-0.97], p=0.03)

• No advantage when specifically treating pseudomonas

• Decreased nephrotoxicity with monotherapy (OR 0.36 [0.28,0.47], p<0.01)
Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis

Anand Kumar, MD; Ryan Zarychanski, MD; Bruce Light, MD; Joseph Parrillo, MD; Dennis Maki, MD; Dave Simon, MD; Denny Laporta, MD; Steve Lapinsky, MD; Paul Ellis, MD; Yazdan Mirzanejad, MD; Greg Martinka, MD; Sean Keenan, MD; Gordon Wood, MD; Yaseen Arabi, MD; Daniel Feinstein, MD; Aseem Kumar, PhD; Peter Dodek, MD; Laura Kravetsky, BSc; Steve Doucette, MSc; the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group
Special Situations
Fungal infection

• 3rd most common cause of ICU bloodstream infection

• Differentiation of colonization from invasive infection is difficult
  – Fungemia
  – Isolated from ≥ 2 sites
  – Immunosuppression
  – Failure to improve despite source control and antimicrobial therapy
Special Situations
Fungal infection

- Empiric therapy indicated in select situations:
  - Septic shock + prior prolonged antibiotic exposure
  - Septic shock + immunosuppression
  - Recurrent GI perforation or anastomotic leak

**Critical Care Medicine. 27(6):1066-1072, June 1999.**
Newer Agents
Linezolid

- Alternative therapy for VAP caused by gram-positive bacteria (MRSA)
- Achievable concentrations in bronchial secretions exceed those in serum
- Dosing adjustment not needed for renal or hepatic insufficiency
- Enteral administration has equivalent bioavailability.
- Clinical equivalence of linezolid and vancomycin in the treatment of VAP caused by gram-positive pathogens; post hoc logistic regression analysis of reported a significantly increased likelihood of clinical cure for linezolid
- Favorable cost effectiveness analyses
Tigecycline
(Glycylcyclines)

- Broad spectrum of activity against gram positives, gram negatives, and anaerobes

- Avoidance of common tetracycline resistance mechanisms (ribosomal protection, efflux pump)

- Dose 100 mg IV then 50 mg IV q12H; no adjustment necessary for renal or mild-mod hepatic impairment

- Comparable clinical cure rates to carbapenems for cIAI and Vanco/aztreonam for cSSTI

- Not active against *Pseudomonas*
Moxifloxacin

- Quinolone with broad range of activity, including gram positives (MRSA), enteric gram negatives, and anaerobes

- Dosing
  - 400 mg IV/PO QD
  - no adjustment for renal or hepatic impairment

- Primary surgical indications = cSSI and cIAI


- Misses MRSA and probably most pseudomonas
Daptomycin

- Binds to and rapidly depolarizes cell membrane of gram positive bacteria (bacteriocidal)
- Highly effective against most gram-positive bacteria, including isolates resistant to methicillin, vancomycin, and linezolid
- No mechanisms of resistance identified
- Current primary indication is for cSSI
- Dosing 4 mg/kg qd (q48 if CrCl < 30 ml/min)
- Major toxicity = rhabdo (0.2%, self-limited, follow CPKs)
Antibiotic Resistance
Antibiotic Resistance Continues to Increase in ICUs and is a Major Healthcare Issue

**Graph:**
- **Vancomycin/enterococci:** 28.5%
- **Methicillin/S. aureus:** 59.5%
- **Methicillin/CNS:** 89.1%
- **3rd Ceph/E. coli***:** 5.8%
- **3rd Ceph/K. pneumoniae**:** 21.1%
- **Imipenem/P. aeruginosa:** 29.5%
- **Quinolone/P. aeruginosa:** 31.9%
- **3rd Ceph/P. aeruginosa:** 31.1%
- **3rd Ceph/Enterobacter spp.:** 80%

<table>
<thead>
<tr>
<th>Jan–Dec 2003 No. of Isolates</th>
<th>% increase in resistance (2003 vs 98-02*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2048</td>
<td>12%</td>
</tr>
<tr>
<td>4100</td>
<td>11%</td>
</tr>
<tr>
<td>3336</td>
<td>1%</td>
</tr>
<tr>
<td>1355</td>
<td>0%</td>
</tr>
<tr>
<td>1068</td>
<td>47%</td>
</tr>
<tr>
<td>1392</td>
<td>15%</td>
</tr>
<tr>
<td>1825</td>
<td>9%</td>
</tr>
<tr>
<td>2119</td>
<td>20%</td>
</tr>
<tr>
<td>1411</td>
<td>-6%</td>
</tr>
</tbody>
</table>

*January through December 2003
*1998 through 2002 (+/- standard deviation)*
Increase in Resistant Nosocomial Infections: MRSA

http://www.cdc.gov/drugresistance/healthcare/ha/slideset.htm
Factors Contributing to Antibiotic Resistance

- Increased severity of illness
- Severely immunocompromised patients
- New devices and procedures
- Resistance in the community
- Ineffective source control
- Inappropriate antibiotic usage
- Greater antibiotic usage
Strategies to Minimize Antibiotic Resistance

- Limit initiation of antimicrobial therapy
- Limit duration of prophylactic therapy
- Limit duration of empiric therapy
- Limit duration of targeted therapy
- Choice of antibiotic class
- Antibiotic rotation
Most febrile ICU patients do not have an infection.

- SIRS Only: 59%
- No SIRS: 26%
- Sepsis Only: 4%
- Severe Sepsis: 8%
- Septic Shock: 3%

Rangel-Frausto JAMA 273: 117, 1995
Antibiotic Exposure Greatly Increases Risk of Subsequent Resistant Infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Setting</th>
<th>Findings and Odds Ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velmahos</td>
<td>2002</td>
<td>Prophylaxis of severely injured trauma patients</td>
<td>Abx &gt; 24 h: OR 2.13</td>
</tr>
<tr>
<td>Harbarth</td>
<td>2000</td>
<td>Surgical prophylaxis following CABG</td>
<td>Abx &gt; 48 h increases gram-negative resistance: OR 1.6</td>
</tr>
<tr>
<td>Kollef</td>
<td>1999</td>
<td>Resistant pathogens in nosocomial MICU and SICU infections</td>
<td>Prior Abx exposure: OR 3.39</td>
</tr>
<tr>
<td>May</td>
<td>2006</td>
<td>ICP monitor prophylaxis in trauma</td>
<td>Broad-spectrum prophylaxis increased subsequent resistant infections</td>
</tr>
</tbody>
</table>
Prophylactic Antibiotics - Appropriate Duration of Therapy

• Single dose therapy is as affective as multiple doses in majority of studies.
  – Longer therapy indicated in some cases
    • usually related to inadequate data
  – No studies indicate treatment longer than 72 hrs is beneficial
  – No studies support continuing therapy for drains/tubes

AJHP 1999; 56:1839-88
Measures specific to surgical prophylaxis:

1. Prophylactic antibiotics received within 1 hour prior to surgical incision
2. Appropriate prophylactic antibiotic selection for surgical patients
3. Prophylactic antibiotics discontinued within 24 hours after surgery end time
4. Postoperative serum glucose 6 AM control in cardiac patients
5. Appropriate hair removal
6. Immediate postoperative normothermia for CRS patients
7. Postoperative wound infection diagnosed during index hospitalization

Days of Antibiotics and Risk of MRSA-Pooled Odds Ratios

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

- 401 patients from 51 French ICUs; VAP diagnosed bronchoscopically by quantitative microbiology

- Mortality, vent-days, ICU days, and recurrent infection equivalent

- Recurrence with MDR organism less likely in 8 day group

- Higher re-infection rate if initial organism non lactose fermenting GNR (*pseudo*, *acineto*)
Antibiotic Class and Resistance

- Certain classes of antibiotics have greater likelihood of selecting for resistance

  - Broad-spectrum cephalosporins
    - MRSA, VRE, C. difficile, ESBLs, Acinetobacter

  - Fluoroquinolones
    - MRSA, MDR gram-negatives

  - Vancomycin
    - MRSA, VRE

  - Clindamycin
    - C. difficile
Antibiotic Rotation Strategies Appear to Contribute to a Reduction in Gram-Negative Resistant Pathogens

<table>
<thead>
<tr>
<th>MDR Pathogen Group</th>
<th>IRR (95% CI; p-value)</th>
<th>Infection Rate Relative Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Pathogens</td>
<td>0.24 (0.13 to 0.42; p&lt;0.0001)</td>
<td>-76%</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>0.33 (0.14 to 0.80; p=0.014)</td>
<td>-67%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>0.10 (0.02 to 0.41; p=0.001)</td>
<td>-90%</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>0.28 (0.11 to 0.76; p=0.012)</td>
<td>-72%</td>
</tr>
</tbody>
</table>

MDR = resistance to 3 or more AB classes; IRR = Incidence Rate Ratio

Negative Binomial Regression Model: Multidrug resistant Infection rate – count variable; Patient-days - exposure variable; AB rotation – predictor variable

Summary

• Most febrile patients do not need antibiotics; treat patients, not fevers

• Antibiotics are not a substitute for source control

• When initiating antibiotics, hit them early, hard, and with big doses

• Practice timely de-escalation/discontinuation

• Make informed decisions regarding antibiotic selection based on knowledge of the host, local environment, and suspected infection

• Judicious antibiotic use with halt the emergence of resistant organisms and save lives
Life Threatening Infections, Antibiotic Selection, and Antibiotic Resistance

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Staff Surgeon, Denver Health Medical Center

Surgical Grand Rounds, 10.10.11
U Penn School of Medicine
Philadelphia, PA

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New York, NY

Denver Health Medical Center
Denver, CO
Bactericidal/Bacteriostatic Antimicrobials vs MSSA/MRSA

**Bactericidal**
- Aminoglycosides
- Daptomycin
- Vancomycin
- Quinupristin-dalfopristin (MSSA only)

**Bacteriostatic**
- Linezolid
- TMP-SMX

DORIPENEM

- Spectrum similar to imipenem and meropenem
- In vitro, enhanced activity against and a lower propensity to select for resistance in P. aeruginosa\(^1,2\)
- MIC\(_{90}\) for resistant Enterobacteriaceae (CTZ-R Citrobacter and Enterobacter and ESBL+ Klebsiella and E. coli) are 1-2 and 2-4 dilutions lower than meropenem and imipenem, respectively\(^1\)
- Distributes well to tissue, including CNS\(^3\)
- In animals, lower potential for CNS toxicity compared to imipenem\(^4\)
- Stability in solution allows for prolonged infusion\(^5\)

# Carbapenems: MIC<sub>90</sub> (mcg/mL)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Doripenem&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Ertapenem</th>
<th>Meropenem</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible S. aureus (&lt;i&gt;n=498&lt;/i&gt;)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.06</td>
<td>0.5</td>
<td>0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus (&lt;i&gt;n=1275&lt;/i&gt;)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>8</td>
<td>32</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Klebsiella spp., ESBL+ (&lt;i&gt;n=34&lt;/i&gt;)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.06</td>
<td>0.25</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Enterobacter spp., CTZ-resistant (&lt;i&gt;n=33&lt;/i&gt;)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.12</td>
<td>4</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>B. fragilis (&lt;i&gt;n=81&lt;/i&gt;)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Other &lt;i&gt;Bacteroides fragilis&lt;/i&gt; group species (&lt;i&gt;n=84&lt;/i&gt;)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1 – 2 (&lt;i&gt;n=110&lt;/i&gt;)</td>
<td>1 - 2</td>
<td>0.5</td>
<td>0.5 – 1</td>
</tr>
</tbody>
</table>

• Breakpoint criteria for meropenem and imipenem; breakpoints not assigned to doripenem
**Doripenem Phase III**

Complicated intra-abdominal infection\(^1,2\)

- Doripenem demonstrated non-inferiority to meropenem in both studies

- **Malafia et al:**
  - Clinical response rate for ME at TOC: 83.3% (D) vs. 83% (M)
  - Microbiologic response at TOC: 83.3% (D) vs. 83.4% (M)

- **Lucasti et al:**
  - Clinical cure rate for ME at TOC: 86.7% (D) vs. 86.6 (M)
  - Clinical cure rates were comparable between the CE and ME treatment groups, at TOC and early follow-up, respectively

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1. Malafaia O et al. Presented at the 46th ICAAC; Sept 27-30, 2006; San Francisco, CA. poster L-1074b; 2, Lucasti C et al. Presented at the 1007 ECCMID, Munich, Germany, Poster #834;
Doripenem Phase III

Nosocomial Pneumonia (in progress)

• Randomized, open-label study in non-ventilated nosocomial pneumonia (NP) or early ventilator-associated pneumonia (VAP)
  – Doripenem 500 mg IV q8h (1 h infusion) vs. piperacillin-tazobactam 4.5 g IV q6h, with optional switch to levofloxacin PO after study day 3
  – Adjunctive amikacin for Pseudomonas; MRSA coverage optional
  – Duration of therapy: 7 to 14 days (IV + oral)

• Randomized, open-label study in ventilator-associated pneumonia (VAP)
  – Doripenem 500 mg IV q8h (4 h) vs. imipenem 500 mg q6h or 1g q8h IV only
  – Prolonged doripenem infusion
  – Adjunctive if P. aeruginosa, MRSA
Common Antibiotic-Resistance Mechanisms

- Ribosomal protection
- Macrolide and tetracycline efflux pumps
- PBP alterations (target site modifications)
- Beta-lactamases (including extended spectrum beta-lactamases)
- DNA gyrase mutations
**Tigecycline Indications**

<table>
<thead>
<tr>
<th>cSSSI</th>
<th>cIAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complicated skin and skin structure infections (cSSSI) in adults caused by susceptible strains of:</td>
<td>• Complicated intra-abdominal infections (cIAI) in adults caused by susceptible strains of:</td>
</tr>
<tr>
<td>– <em>E. coli</em></td>
<td>– <em>C. freundii</em></td>
</tr>
<tr>
<td>– <em>E. faecalis</em></td>
<td>– <em>E. cloacae</em></td>
</tr>
<tr>
<td>– <em>S. aureus</em> (including MRSA)</td>
<td>– <em>E. coli</em></td>
</tr>
<tr>
<td>– <em>S. agalactiae</em></td>
<td>– <em>K. oxytoca</em></td>
</tr>
<tr>
<td>– <em>S. anginosus</em> group</td>
<td>– <em>K. pneumoniae</em></td>
</tr>
<tr>
<td>– <em>S. pyogenes</em></td>
<td>– <em>E. faecalis</em>†</td>
</tr>
<tr>
<td>– <em>B. fragilis</em></td>
<td>– <em>S. aureus</em>†</td>
</tr>
</tbody>
</table>

*Vancomycin-susceptible isolates only.
†Methicillin-susceptible isolates only.
Tigecycline: An Expanded Broad Spectrum of In Vitro Activity

<table>
<thead>
<tr>
<th>Tygacil™ (tigecycline) IN VITRO ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positives</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gram negatives</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Resistant gram positives</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Resistant gram negatives</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
</tr>
</tbody>
</table>
Clinical Cure Rates in cSSSI and cIAI

<table>
<thead>
<tr>
<th></th>
<th>Tigecycline</th>
<th>Vancomycin plus aztreonam</th>
<th>Imipenem-cilastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure Rate (%)</td>
<td>87</td>
<td>89</td>
<td>86</td>
</tr>
</tbody>
</table>

Data on file, Wyeth Pharmaceuticals Inc.
<table>
<thead>
<tr>
<th>Infections</th>
<th>Pathogens</th>
<th>AVELOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated Intra-Abdominal Infections</td>
<td>Including polymicrobial infections such as abscess caused by <em>Escherichia coli</em>, <em>Bacteroides fragilis</em>, <em>Streptococcus anginosus</em>, <em>Streptococcus constellatus</em>, <em>Enterococcus faecalis</em>, <em>Proteus mirabilis</em>, <em>Clostridium perfringens</em>, <em>Bacteroides thetaiotaomicron</em>, or <em>Peptostreptococcus</em> species</td>
<td>400 mg IV/PO q24h 5-14 days*</td>
</tr>
<tr>
<td>Community-Acquired Pneumonia</td>
<td><em>Streptococcus pneumoniae</em> (including multi-drug resistant strains [MDRSP**]), <em>Haemophilus influenzae</em>, <em>Moraxella catarrhalis</em>, methicillin-susceptible <em>Staphylococcus aureus</em>, <em>Klebsiella pneumoniae</em>, <em>Mycoplasma pneumoniae</em>, <em>Chlamydia pneumoniae</em></td>
<td>400 mg IV/PO q24h 7 to 14 days</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis</td>
<td><em>S pneumoniae</em>, <em>H influenzae</em>, <em>Haemophilus parainfluenzae</em>, <em>K pneumoniae</em>, methicillin-susceptible <em>Staphylococcus aureus</em>, <em>M catarrhalis</em></td>
<td>400 mg IV/PO q24h 5 days</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Moraxella catarrhalis</em></td>
<td>400 mg IV/PO q24h 10 days</td>
</tr>
</tbody>
</table>
## Antibiotic Activity Against Staphylococci

SECURE Survey, United States 2000-2001

<table>
<thead>
<tr>
<th>Organism</th>
<th>Daptomycin</th>
<th>Linezolid</th>
<th>Q-DA</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>0.25</td>
<td>4.0</td>
<td>0.25</td>
<td>1.0</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.5</td>
<td>4.0</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>MSSE</td>
<td>0.5</td>
<td>2.0</td>
<td>0.25</td>
<td>1.0</td>
</tr>
<tr>
<td>MRSE</td>
<td>0.5</td>
<td>2.0</td>
<td>0.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

MIC$_{90}$ μg/mL

Q-DA=quinupristin-dalfopristin.