Life Threatening Infections, Antibiotic Selection, and Antibiotic Resistance

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Trauma & Acute Care Surgery Fellow
Surgery Grand Rounds
10.11.10
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
Bacterial proteases cleave tissue planes

Local necrosis $\rightarrow$ sepsis $\rightarrow$ MOF
NSTI

Diagnosis

• Overlying skin often unaffected

• Pain (extremity, perineum) out of proportion to exam

• Edema and tenderness extend beyond rim of cellulitis

• Crepitus specific but not sensitive

• Clostridial species → anemia & jaundice (hemolysis)

• Myonecrosis → ↑ CPK
**LRINF Score**

- **Range 0-13**
- **< 6 → unlikely**
- **6-8 → likely**
- **> 8 → 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>≥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>

CCM 2004;32:1535
NSTI Diagnosis

- Diagnostic imaging (XRAY, CT, MRI) specific but insensitive; should not delay initiation of therapy based on physical exam
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**
  - Carbapenem
  - Piperacillin-tazobactam
  - +/- vancomycin
  - Clinda vs. PCN G for streptococcal NSTI

- **Supportive ICU care**

- **HBO, IVlg of unproven benefit**
NSTI
Summary

- Rare, elusive, lethal
- Diagnosis rests on clinical exam with low threshold for surgical intervention
- Usually polymicrobial → 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

1. Draw Cultures
2. Broad-spectrum Antibiotics
3. Interpret Cultures

- Continue
- De-escalate
- Escalate

100% Sensitivity 100% Specificity
Inadequate Antimicrobial Therapy Associated with Increased Mortality

- Dupont (2001)
- Kolleff (1999)
- Luna (1997)
- Rello (1997)
- Ruiz (2000)

Mortality (%)

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 heath care 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>🟡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>🟡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
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<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
</tr>
<tr>
<td>Pip/tazo</td>
<td></td>
<td></td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
</tr>
<tr>
<td>Vanco</td>
<td></td>
<td></td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td></td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
<td>🟡</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
<td>🟡</td>
<td>🟡</td>
<td></td>
<td>🟡</td>
<td></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
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)
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>
<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>ABW</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>IBW</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>( \frac{52}{1 + [196.4 \times e^{-0.025 \times ABW} - 53.66]/100} )</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>ABW</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>IBW + (0.40 \times</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>IBW + (0.40 \times</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 emperic coverage

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

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

• Recent resurgence with positive outcomes
β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials

Mical Paul, Ishay Benuri-Silbiger, Karla Soares-Weiser, Leonard Leibovici

- 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
Antibiotic Resistance
Antibiotic Resistance Continues to Increase in ICUs and is a Major Healthcare Issue

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Jan–Dec 2003 No. of Isolates</th>
<th>% increase in resistance (2003 vs 98-02*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin/enterococci</td>
<td>2048</td>
<td>12%</td>
</tr>
<tr>
<td>Methicillin/S. aureus</td>
<td>4100</td>
<td>11%</td>
</tr>
<tr>
<td>Methicillin/CNS</td>
<td>3336</td>
<td>1%</td>
</tr>
<tr>
<td>3rd Ceph/E. coli**</td>
<td>1355</td>
<td>0%</td>
</tr>
<tr>
<td>3rd Ceph/K. pneumoniae**</td>
<td>1068</td>
<td>47%</td>
</tr>
<tr>
<td>Imipenem/P. aeruginosa</td>
<td>1392</td>
<td>15%</td>
</tr>
<tr>
<td>Quinolone/P. aeruginosa</td>
<td>1825</td>
<td>9%</td>
</tr>
<tr>
<td>3rd Ceph/P. aeruginosa</td>
<td>2119</td>
<td>20%</td>
</tr>
<tr>
<td>3rd Ceph/Enterobacter spp.</td>
<td>1411</td>
<td>-6%</td>
</tr>
</tbody>
</table>

% Resistance

- 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 infection control and compliance
- 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%
- Severe Sepsis: 8%
- Septic Shock: 3%
- Sepsis Only: 4%

3708 ICU admissions

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></td>
<td></td>
<td></td>
<td>Broad-spectrum AB: OR 4.12</td>
</tr>
<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 effective 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
SCIP *Infection Quality Measures*

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, acinetobacter*)
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

• 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