When Sticks & Stones Expose Your Bones
Will Gentamicin Save You?
Evaluating the Need for Expanded Gram-Negative Coverage in Prophylaxis of Grade III Open Fractures

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Learning Objectives
1. Define open fracture and classify injuries based on the Gustilo grading system.
2. Discuss clinical practice guideline recommendations made by the Surgical Infection Society and the Eastern Association for the Surgery of Trauma.
3. Review literature to assess recommendations for adding expanded Gram-negative coverage in prophylaxis of Gustilo grade III open fractures.
Assessment Questions

1. The Surgical Infection Society recommends the addition of an aminoglycoside to a first-generation cephalosporin in the prophylaxis of all grade III open fractures.
   A. True
   B. False

2. Which of the following is a potential risk associated with use of an aminoglycoside in prophylaxis of open fractures?
   A. Increased probability of developing future antibiotic-resistant infections
   B. Increased length of time for fracture healing
   C. Increased risk of acute kidney injury
   D. Both A and C

3. Several randomized controlled trials support the addition of aminoglycosides for prophylaxis in grade III open fractures.
   A. True
   B. False

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Faculty (Speaker) Disclosure: Amber N. Welborn has indicated she has no relevant financial relationships to disclose relative to the content of this presentation.
Introduction to Open Fractures

I. Open Fracture\(^1\,\!^2\)
   A. Fracture associated with a break in the skin, often secondary to high-energy injury (See Figure 1)
   B. Enables communication with the fracture and/or its hematoma and the external environment
   C. Environmental exposure generates potential for infection

![Figure 1. Illustration and x-ray image of an open fracture where the end of the broken tibia has torn through soft tissues and is now exposed to the external environment\(^3\)](image)

II. Etiology\(^1\,\!^4\)
   A. Extent of trauma is directly related to the amount of energy delivered via the mechanism of injury
   B. Mechanisms of injury are categorized as follows
      i. Low-energy-energy trauma (~100 foot-pounds of energy)
         1. Torsional injuries
         2. Fall from standing
      ii. Moderate-energy trauma (~300 - 500 foot-pounds of energy)
         1. Skiing injury
         2. Bicycling injury
      iii. High-energy trauma (greater than 2000 foot-pounds of energy)
         1. Motor vehicle accident
         2. Fall from a height
         3. Firearm

III. Epidemiology\(^5\)
   A. Most common causes include crush injuries, falls, and road traffic accidents\(^1\)
   B. A study from the United Kingdom evaluated 2,386 open fractures over a 15-year period
      i. Incidence of 30.7/100,000/year
         1. 69.1% occurring in males with average age of 40.8 years
         2. 30.9% occurring in females with average age of 56 years
      ii. Location of injury (See Figure 2)
         1. Second most common involves tibia/fibula, often caused by high-energy injuries
         2. Open lower limb fractures tend to be more severe than open upper limb fractures
IV. Classification

A. Several different classification systems exist

B. Common goals of classification include
   i. Treatment guidance
      1. Surgical protocols
      2. Antibiotic recommendations
      3. Timing of interventions
   ii. Improving communication and research
   iii. Predicting patient outcomes

C. The Gustilo-Anderson classification system
   i. Highly utilized in orthopedic literature
   ii. First published in 1976 and categorized open fractures into one of three grades (I, II, and III)\(^6\)
      1. Severity increases from grade I through grade III
      2. Categorization based on laceration size, extent of soft tissue and osseous injury, and level of contamination
   iii. Identified four factors that predispose grade III fractures to complications
      1. Extensive soft tissue damage
      2. Severe wound contamination
      3. Compromised vascularity
      4. Fracture instability
   iv. Modified in 1984 to sub-classify grade III open fractures (III-A, III-B, and III-C) (See Table 1)\(^2,7\)
      1. Severity increases from grade III-A to grade III-C
      2. Sub-classification based on severity of soft tissue injury, soft tissue coverage, and need for vascular reconstruction
   v. Modification led to prognostic implications\(^2,8\)
      1. Rate of complications increase as Gustilo fracture grade increases
      2. Complications include infection, delayed union of bone, nonunion, or amputation
         a. Grade III open fractures are seven times more likely to develop an infection, although estimated rates vary widely between studies\(^4,8-9\)
         b. Amputation rates in grade III-C fractures range from 25% to 90%\(^9\)

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**Figure 2.** Distribution of 2386 open fractures by injury location.

*Locations other than the five most common, each occurring < 5% of the time (e.g. metacarpus 4.4%, proximal ulna 2.1%, metatarsus 2.1%, etc.)*\(^3\)
**Table 1. The Gustilo Classification System of Open Fractures**¹⁻⁸,¹⁰

<table>
<thead>
<tr>
<th>Feature</th>
<th>Fracture Grade</th>
<th>I</th>
<th>II</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IIIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound size, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 1</td>
<td>&gt; 1 and &lt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Energy</td>
<td></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Contamination</td>
<td></td>
<td>Minimal</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Deep soft tissue damage</td>
<td></td>
<td>Minimal</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Fracture comminution</td>
<td></td>
<td>Minimal</td>
<td>Moderate</td>
<td>Severe/segmental</td>
<td>Severe/segmental</td>
<td>Severe/segmental</td>
</tr>
<tr>
<td>Periosteal stripping</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Local coverage</td>
<td></td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Inadequate</td>
<td>--</td>
</tr>
<tr>
<td>Neurovascular injury</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Infection rate</td>
<td></td>
<td>0% - 2%</td>
<td>2% - 7%</td>
<td>7%</td>
<td>10% - 50%</td>
<td>25% - 50%</td>
</tr>
</tbody>
</table>

vi. Gustilo Classification limitations²

1. Does not take tissue viability or tissue necrosis into account
2. Moderate to poor inter-observer reliability¹¹,¹²
3. Wound size and outward appearance may not accurately reflect true extent of deep soft tissue injury
   a. Under-classification has occurred at Emergency Department admission
   b. Classification most accurately made by surgeon in the operating room

**Infection in Open Fractures**

I. Pathophysiology¹⁰

A. Wounds may contain bone fragments or soft tissue with minimal blood supply and inadequate soft tissue to cover exposed bone
   i. Exposed tissues serve as a rich culture medium with limited resistance to bacterial invasion
   ii. Potential exposure to nosocomial bacteria continues until membrane closure is achieved
B. Poor antibiotic penetration into devascularized tissues
C. Unfavorable environment for bactericidal function of phagocytes and host immune system

II. Risk for infection

A. Dependent on location, grade, mechanism, and surgical management
B. Tibia is most susceptible to open fractures and development of infection¹³
   i. Thin soft-tissue coverage along the shin
   ii. Commonly caused by high-energy injuries (See Figure 3)
   iii. Infection rates 10 to 20 times higher than open fractures in other areas¹⁴
Evaluation of fractures at lower risk for infection should not be used to predict effects of antibiotics in high risk injuries (e.g. open tibial fractures). Sites with rich vascularity and a lower infection risk include:

1. Skull and facial bones
2. Hands and upper extremities

Civilian gunshot fractures sustain little contamination or devascularization and rarely become infected.

**Management of Open Fractures**

I. **Treatment goals**
   A. Manage soft-tissue injury
   B. Minimize risk of infection
   C. Stabilize and repair skeletal injury
   D. Restore function to affected extremity

II. **Initial orthopedic evaluation and management** should begin as soon as concomitant life-threatening conditions have been stabilized.
   A. Determine mechanism of injury
   B. Perform systematic inspection of each limb
   C. Note dimensions, locations, and degree of soft-tissue involvement
   D. Perform complete neurovascular exam and vascular studies as necessary

III. **Surgical management**
   A. The most critical step in prevention of infection and promotion of wound healing is adequate surgical debridement.
   B. Irrigation is critical to removing foreign bodies and decreasing bacterial load.
C. Wound closure
   i. Delayed wound closure or coverage increases risk of infection with nosocomial pathogens\textsuperscript{1,15}
      1. Wound coverage recommended within 72 hours
      2. Flap coverage commonly utilized (e.g. tissue moved from donor site to recipient site with intact blood supply)
   ii. Closing the skin before removing devitalized tissue and allowing for granulation creates a contaminated dead space ideal for infection\textsuperscript{1,15}
      1. Multiple rounds of surgical debridement may be required
      2. Use of negative pressure wound therapy may allow for flap repair to occur beyond 72 hours without increased risk of infection

D. Fracture stabilization\textsuperscript{1,15}
   i. Early stabilization prevents further soft tissue injury and promotes healing
   ii. Choice of stabilization method is dependent upon
      1. Hemodynamic status
      2. Fracture location and injury pattern
      3. Extent of soft tissue injury

IV. Wound cultures\textsuperscript{1,18-21}
   A. Routine wound cultures are not recommended
      i. Pre-debridement, during-debridement, and post-debridement cultures have been shown to have little utility
      ii. Pathogens causing infections are not routinely present in previous cultures
   B. Cultures should be obtained if signs of infection present or strong suspicion of infection

V. Tetanus prophylaxis is routine practice\textsuperscript{1}

VI. Antibiotic prophylaxis in open fractures
   A. Antibiotic prophylaxis to reduce morbidity associated with deep fracture site infections is standard of care\textsuperscript{10}
   B. Optimal timing and duration of prophylaxis are not well defined in clinical practice\textsuperscript{1,22}
   C. Choice of antibiotics remains controversial, especially with regards to Gustilo grade III fractures

Conflicting Recommendations for Prophylaxis

I. Patzakis, et al. 1974\textsuperscript{23}
   A. One of the first randomized controlled trials to demonstrate benefit of prophylactic antibiotics
      i. Evaluated 333 open fractures prior to the establishment of Gustilo classification system
      ii. Tibia and femur fractures accounted for 34% to 48% of open fractures in each group
   B. Established efficacy of first-generation cephalosporins in reducing infection rate
      i. Cephalothin (n = 107) $\rightarrow$ 2.3% developed infections
      ii. Penicillin + streptomycin (n = 120)$\rightarrow$ 9.7% developed infections
      iii. No antibiotics (n = 106) $\rightarrow$ 13.9% developed infections
   C. Proposed addition of aminoglycoside to first-generation cephalosporin to provide additional benefit
      i. Quickly adopted in practice despite lack of data for combination
      ii. Practice became known as extended or expanded Gram-negative (EGN) coverage
      iii. Despite a large amount of literature surrounding antibiotic prophylaxis in open fractures, well-designed clinical trials comparing different antibiotic agents are limited (See Appendix A for an evidence table summarizing several influential studies)
II. Two prominent professional societies have published guidelines for prophylactic antibiotic use in open fractures (See Table 2)
   A. The Eastern Association for the Surgery of Trauma (EAST)\textsuperscript{24,25}
   B. The Surgical Infection Society (SIS)\textsuperscript{10}

Table 2. Comparison of EAST and SIS recommendations for antibiotic prophylaxis based on Gustilo grade\textsuperscript{10,24-26}

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0% - 9%</td>
<td>Gram-positive coverage (e.g., cefazolin)</td>
<td>Gram-positive coverage (e.g., cefazolin)</td>
</tr>
<tr>
<td>II</td>
<td>1% - 12%</td>
<td>Gram-positive coverage (e.g., cefazolin)</td>
<td>Gram-positive coverage (e.g., cefazolin)</td>
</tr>
<tr>
<td>III</td>
<td>9% - 55%</td>
<td>Gram-positive coverage (e.g., cefazolin) + Gram-negative coverage (e.g., gentamicin)</td>
<td>Gram-positive coverage (e.g., cefazolin)</td>
</tr>
</tbody>
</table>

III. EAST and SIS ultimately came to different conclusions regarding antibiotic recommendations for prophylaxis of grade III open fractures
   A. Scientific evidence exists to support use of systemic antibiotics with Gram-positive coverage initiated as soon as possible after injury\textsuperscript{10,24-25}
   B. Antibiotics are adjunctive to proper surgical management of these injuries
   C. EAST concluded scientific evidence supports addition of EGN coverage in grade III open fractures and recommend use of an aminoglycoside and a first-generation cephalosporin\textsuperscript{24-25}
   D. SIS concluded scientific evidence was insufficient to support addition of EGN coverage in grade III open fractures\textsuperscript{10}
      i. Determined EGN practice was based on a small number of antiquated, poorly designed studies that no longer accurately reflect current management of open fractures
      ii. Determined the risks of local fracture-related infections must be balanced with the risks associated with unnecessary use of broad-spectrum antibiotic regimens

IV. Lack of high-quality evidence to support one regimen over another combined with inconsistent recommendations from EAST and SIS has generated wide variability in clinical practice (See Table 3).

Table 3. ACCP Emergency Medicine PRN Open Fracture Antibiotic Prophylaxis Survey, April 2017

<table>
<thead>
<tr>
<th>Facility</th>
<th>ABX by Fracture Grade</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT - San Antonio</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>Anonymous</td>
<td>CFZ</td>
<td>PIP-TZP</td>
</tr>
<tr>
<td>Baylor - Dallas</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>Santa Clara Valley MC</td>
<td>CFZ; if gross contamination, give clindamycin. Gent may be added post operatively</td>
<td></td>
</tr>
<tr>
<td>Sparrow Hospital</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>UF Health - Shands</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>UAMS</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>UMass MC</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>Univ Vermont MC</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>Denver Health MC</td>
<td>CFZ</td>
<td>CFZ</td>
</tr>
<tr>
<td>Vidant MC</td>
<td>Follows EAST Guidelines</td>
<td></td>
</tr>
</tbody>
</table>

Legend: ABX = antibiotic, CFZ = cefazolin, Gent = gentamicin, PIP-TZP = piperacillin-tazobactam, CTX = ceftriaxone, AG = aminoglycoside, PCN = penicillin
Additional Considerations

I. Pathogenic considerations
   A. A prospective study found that primary wound cultures in open lower extremity fractures do not add value to the management of these injuries18
      i. 76% (89/117) of initial cultures were negative, remaining 24% (28/117) only grew skin flora
         1. 26.5% (9/34) grade III open fractures had growth on primary culture (only skin flora)
         2. 11.8% (4/34) grade III open fractures went on to develop infections
            a. Three Pseudomonas aeruginosa
            b. One Enterobacter cloaceae
      ii. Supports targeting normal skin flora with prophylactic antibiotics immediately post-injury
      iii. Infections most often occur secondary to nosocomial pathogens10,21
           1. Suggests contamination after hospital admission plays larger role than contamination at time of injury
           2. Highlights the importance of institutional infection prevention strategies
   B. Using broader spectrum antibiotics for prophylaxis has not been shown to guarantee absence of infection development
      i. Univariate analysis of 310 Gustilo grade III open fractures failed to show a protective effect when adding additional antibiotics to cephalosporins to expand coverage28
      ii. Alternative strategies might be the key to reducing infection rates
          1. Time to wound coverage and time to antibiotic administration are independently associated with deep infection development in grade III open tibia fractures29
             a. Wound coverage at > 5 days (OR 7.39, 95% CI 2.33-23.45)
             b. Antibiotics administered > 66 minutes (OR 3.78, 95% CI 1.16-12.31)
             c. Only 2.8% (1/36) infection rate in patients receiving antibiotics within 60 minutes and wound coverage within 5 days
             d. 93% (128/137) of these patients given cefazolin as sole prophylactic agent
          2. More aggressive early soft-tissue coverage decreases exposure time and reduces opportunity for contamination by nosocomial pathogens20

II. Risks associated with broad-spectrum prophylactic antibiotics
   A. The microbiologic ecosystem of a hospital is influenced by antibiotics used within that system
      i. Reducing the unnecessary use of broad-spectrum antibiotics slows resistance development10
      ii. Critical to weigh benefits of broad-spectrum prophylaxis against risks of predisposing patients to later infection with resistant nosocomial pathogens10,26
   B. Compared to < 24 hours, prophylactic cefazolin and tobramycin use > 48 hours in trauma patients (n = 2417, 36% with open fracture as an indication for prophylaxis) was associated with statistically significant increased incidence of31
      i. Nosocomial pneumonia secondary to resistant and/or Gram-negative bacteria
      ii. Clostridium difficile colitis
      iii. Central line infections
C. Prolonged prophylaxis with multiple agents in trauma patients admitted to a surgical ICU is an independent risk factor for development of resistant infections (>1 antibiotic for > 24 hours compared to 1 antibiotic for 24 hours; OR 2.13, 95% CI 1.22-3.74, p = 0.008)\textsuperscript{32}
   i. No difference in sepsis, organ failure, or death between groups
   ii. Patients with resistant infections had statistically significant increases in hospital length of stay and higher mortality rates compared to those without resistant infections

III. Risk of acute kidney injury (AKI)\textsuperscript{33-35}
   A. Estimated frequency of nephrotoxicity with aminoglycoside use ranges from 5% - 15%
   B. Even low dose, short-duration gentamicin, 1 mg/kg every 8 hours for ≤ 2 days, has previously been associated with increased nephrotoxicity
   C. Trauma patients are at high risk for AKI development
      i. Incidence as high as 50%, with 9-26% reported as severe AKI per KDIGO classification
      ii. Severe AKI independently associated with increased mortality and length of stay
      iii. Factors contributing to increased AKI susceptibility
         1. Renal hypoperfusion
         2. Rhabdomyolysis
         3. Intraoperative hypotension
         4. Administration of IV contrast agents

Clinical Question

Should an aminoglycoside be added to expand Gram-negative coverage in prophylaxis of Gustilo grade III open lower extremity fractures?
Evidence-based protocol for prophylactic antibiotics in open fractures: Improved antibiotic stewardship with no increase in infection rates

Objective To examine infection rates before and after implementation of an evidence-based protocol

Methods

Design
- Single-center, retrospective cohort study

Population
- Patients with open extremity fractures admitted to Level I trauma center in Michigan

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>Moribund patients</td>
</tr>
<tr>
<td>Femur, tibia and/or fibula open fracture</td>
<td>Managed at another institution for &gt; 24 hours</td>
</tr>
<tr>
<td>Admitted to University of Michigan Level I trauma center between January 2006 and July 2010</td>
<td></td>
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</table>

Intervention

<table>
<thead>
<tr>
<th>Pre-Protocol Recommendation</th>
<th>Post-Protocol Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustilo grade I or II</td>
<td>Gustilo grade I or II</td>
</tr>
<tr>
<td>Cefazolin 1-2 g IV load then 1 g IV q8h for 48 h</td>
<td>Cefazolin 1-2 g IV load then 1 g IV q8h for 48 h</td>
</tr>
<tr>
<td>Gustilo grade III</td>
<td>Gustilo grade III</td>
</tr>
<tr>
<td>Cefazolin 1-2 g IV load then 1 g q8h + gentamicin 1-2 mg/kg (IBW) IV q8h ± penicillin G 4 million units q4h for 48 h</td>
<td>Ceftriaxone 1 g IV q24h for 48 h</td>
</tr>
</tbody>
</table>

Outcomes

- Difference in SSI rate pre- and post-protocol implementation
- Difference in SSI rates with stratification of injuries by (1) Gustilo grade, (2) NHSN risk index (See Appendix B), (3) fracture site, and (4) resistant organisms
- Changes in MDR, XDR, PDR organisms, defined using CDC criteria (See Appendix C)

Statistics

- Continuous data analyzed using Wilcoxon nonparametric rank-sum test
- Categorical data analyzed by Chi-square or Fisher’s exact test where appropriate
- Normality assessed by Kolmogorov-Smirnov test
- p < 0.05 used to assess for statistical significance between groups

Results

Baseline Characteristics
- n = 176, majority male, mean age 37.2 vs. 40 y

<table>
<thead>
<tr>
<th>Mechanism of injury, n (%)</th>
<th>Pre-protocol (n = 101)</th>
<th>Post-protocol (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor vehicle crash</td>
<td>68 (67.3)</td>
<td>47 (64.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Other blunt trauma</td>
<td>29 (28.7)</td>
<td>24 (32.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>4 (4.0)</td>
<td>2 (2.7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of Injury, n (%)</th>
<th>Pre-protocol (n = 101)</th>
<th>Post-protocol (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia/fibula</td>
<td>76 (75.2)</td>
<td>48 (65.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fibula only</td>
<td>7 (5.9)</td>
<td>4 (5.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Femur</td>
<td>19 (18.8)</td>
<td>21 (29)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gustilo grade, n (%)</th>
<th>Pre-protocol (n = 101)</th>
<th>Post-protocol (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>37 (36.6)</td>
<td>20 (27.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>IIIA</td>
<td>13 (35.1)</td>
<td>5 (25.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>IIIB</td>
<td>11 (29.7)</td>
<td>6 (30.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>IIIC</td>
<td>9 (24.3)</td>
<td>6 (30.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>III-unspecified</td>
<td>4 (10.8)</td>
<td>3 (15.0)</td>
<td>0.69</td>
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Outcomes

<table>
<thead>
<tr>
<th>Aminoglycoside/glycopeptide use</th>
<th>Pre-protocol rate (per fracture event)</th>
<th>Post-protocol rate (per fracture event)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.5% (54/101)</td>
<td>16.4% (12/73)</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

| SSI rate                       | Pre-protocol (20.8% (21/101))          | Post-protocol (24.7% (18/73))          | 0.58    |
### SSI rate by Gustilo grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>29.4% (5/17)</td>
<td>6.7% (1/15)</td>
<td>29.7% (11/37)</td>
<td>13.6% (3/22)</td>
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</tbody>
</table>

### SSI rate by fracture site

<table>
<thead>
<tr>
<th>Site</th>
<th>Rate</th>
<th>Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia/fibula</td>
<td>22.0% (18/82)</td>
<td>25% (13/52)</td>
<td>0.68</td>
</tr>
<tr>
<td>Femur</td>
<td>15.8% (3/19)</td>
<td>23.8% (5/21)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

### SSI rate by NHSN risk index

<table>
<thead>
<tr>
<th>Index</th>
<th>Rate</th>
<th>Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHSN risk index 2</td>
<td>13.3% (8/60)</td>
<td>28.2% (11/29)</td>
<td>0.07</td>
</tr>
<tr>
<td>NHSN risk index 3</td>
<td>21.7% (5/23)</td>
<td>11.8% (2/15)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

### Resistant organisms

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Rate</th>
<th>Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas species</td>
<td>3</td>
<td>5 (2 resistant non-MDR)</td>
<td>1.0</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>2 (1 resistant non-MDR)</td>
<td>3 (1 resistant non-MDR)</td>
<td>1.0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>2 (1 MDR)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Serratia species</td>
<td>1 (resistant non-MDR)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcaligenes faecalis</td>
<td>0</td>
<td>2 (1 MDR, 1 resistant non-MDR)</td>
<td>1.0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Providencia stuartii</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>0</td>
<td>1 (MDR)</td>
<td>1.0</td>
</tr>
<tr>
<td>Achromobacter xylosidans</td>
<td>0</td>
<td>1 (MDR)</td>
<td>1.0</td>
</tr>
<tr>
<td>Unspecified Gram-negative</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Total Positive Cultures by Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Rate</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas species</td>
<td>3</td>
<td>5 (2 resistant non-MDR)</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>2 (1 resistant non-MDR)</td>
<td>3 (1 resistant non-MDR)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>2 (1 MDR)</td>
<td>0</td>
</tr>
<tr>
<td>Serratia species</td>
<td>1 (resistant non-MDR)</td>
<td>0</td>
</tr>
<tr>
<td>Alcaligenes faecalis</td>
<td>0</td>
<td>2 (1 MDR, 1 resistant non-MDR)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Providencia stuartii</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Achromobacter xylosidans</td>
<td>0</td>
<td>1 (MDR)</td>
</tr>
<tr>
<td>Unspecified Gram-negative</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Author’s Conclusions

- Implementation of evidence-based protocol utilizing short course, narrow spectrum antibiotics significantly decreased aminoglycoside and glycopeptide use
- This protocol was not associated with an increase in skin and soft tissue infection rates even after risk stratification for Gustilo grade, fracture site, and NHSN risk index

### Reviewer’s Critique

#### Strengths
- Limited to open fractures of the lower extremity
- Majority caused by high-energy trauma
- Stratification of fractures by grade and location
- Evaluated culture data pre- and post-protocol

#### Limitations
- Single-center, retrospective study design
- Small sample size
- Did not separate aminoglycoside and glycopeptide usage in pre- and post- protocol
- Occasional use of antibiotic beads unaccounted for
- Compliance with components of the protocol unrelated to antibiotics not evaluated
- Low dose gentamicin is not optimal for Gram-negative pathogens

### Overall Conclusion

- Protocolizing the management of open fractures significantly reduced the use of broad-spectrum antibiotics
- Removing aminoglycosides from the protocol did not lead to significant increases in SSI rates, regardless of fracture grade or site of injury
- Rate of infections caused by resistant pathogens did not increase with narrow-spectrum regimen and ≤ 40% of SSI isolates were Gram-negative in either group

**Legend:** SSI = surgical site infection, NHSN = National Healthcare Safety Network, MDR = multidrug resistant, XDR = extensively drug resistant, PDR = pandrug resistant, CDC = Centers for Disease Control and Prevention
Impact of Body Mass Index and Bacterial Resistance in Osteomyelitis after Antibiotic Prophylaxis of Open Lower-Extremity Fractures

Objective
To assess the effectiveness of EAST guideline-based antimicrobial prophylaxis in preventing OM in patients with lower extremity open fractures

Methods

Design
- Single-center, observational, retrospective chart review
- Data collected over 35-month period

Population
- Patients with open fractures admitted to Palmetto Health Richland Level I trauma center
  
  Inclusion Criteria
  - Age ≥ 18 years
  - Open lower extremity fractures of any grade
  
  Exclusion Criteria
  - Received antibiotic therapy for purposes other than open fracture prophylaxis
  - Concomitant upper extremity open fractures

Groups
- Did not receive additional EGN coverage
  - Cefazolin 1 g or 2 g IV q8h
- Did receive additional EGN coverage
  - Cefazolin 1 g or 2 g IV q8h plus additional Gram-negative coverage with either gentamicin (n=23), tobramycin (n=1), aztreonam (n=3), ceftriaxone (n=1), or piperacillin/tazobactam (n=1)

Endpoints

  Primary Endpoint
  - Occurrence of OM within 12 months of open fracture event stratified by Gustilo grade

  Secondary Endpoints
  - Time to initiation of prophylactic therapy
  - Impact of specific factors on rate of OM (antimicrobial agents received, mechanism of injury, age, weight, and ethnicity)
  - Rate of CDI and AKI during hospital stay

Statistics
- Fisher’s exact and Chi-square tests used for categorical data
- Mann-Whitney test for continuous data
- Small number of OM cases prevented use of multivariable predictor logistic regression, and secondary outcomes addressed by cross-tabulating the risk factor with the outcome

Results

Primary Endpoint
n = 90, majority male

Incidence of Osteomyelitis

<table>
<thead>
<tr>
<th></th>
<th>All (n = 90)</th>
<th>Grade I (n = 12)</th>
<th>Grade II (n = 47)</th>
<th>Grade III (n = 27)</th>
<th>Undetermined (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent OM</td>
<td>8.9</td>
<td>0</td>
<td>10.6</td>
<td>11.1</td>
<td>0</td>
</tr>
</tbody>
</table>

Median time to development of OM was 72 days (range 7 to 239 days)

Secondary Endpoints

Characteristics of patients who developed OM compared to those who did not develop OM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Developed OM (n = 8)</th>
<th>Did not develop OM (n = 82)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) (y)</td>
<td>53.5 (48.0-56.0)</td>
<td>41.5 (26.0-55.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>Median BMI (kg/m²) (IQR)</td>
<td>33.4 (32.3-36.5)</td>
<td>27.8 (23.7-31.8)</td>
<td>0.021</td>
</tr>
<tr>
<td>Median time to antibiotics (h) (IQR)</td>
<td>5.8 (3.2-17.8)</td>
<td>4.0 (0.8-9.3)</td>
<td>0.301</td>
</tr>
<tr>
<td>Median antibiotic stop post-op (h) (IQR)</td>
<td>23.0 (19.9-61.7)</td>
<td>22.9 (19.6-36.7)</td>
<td>0.715</td>
</tr>
<tr>
<td>Gustilo fracture grade (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
<td>12 (14.6)</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>5 (67.5)</td>
<td>42 (51.2)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>3 (37.5)</td>
<td>24 (29.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>0 (0)</td>
<td>4 (4.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>
• No statistically significant difference in fracture site or mechanism of injury between those who developed or did not develop OM
• No difference in OM rates with regard to additional EGN coverage (p = 0.25)
  o Cefazolin alone: 0% (0/11)
  o Cefazolin + EGN coverage: 18.8% (3/16) \( \rightarrow \) all 3 cases caused by GNRs
• 98% (88/90) of patients received cefazolin for prophylaxis
  o Dosed 2 g IV q8h for 47.9% of patients and 1 g IV q8h for remaining patients
  o Author’s stated that cefazolin was appropriately dosed in 74% of patients according to recent guideline recommendations
• One patient developed an AKI
• No patients developed a CDI

**Author’s Conclusions**

• Patients receiving EGN coverage still developed OM caused by Gram-negative organisms
  o Attributed this to increasing rates of multi-drug resistant Gram-negative pathogens and variability in the ability of gentamicin to penetrate bone
• Host factors such as age and BMI may play an important role in the development of osteomyelitis
  o May be inadequately dosing antibiotics in obese patients
  o Both factors are associated with decreased vascularity and prolonged healing time

**Reviewer’s Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Focused on lower extremity open fractures</td>
<td>• Single-center, retrospective design</td>
</tr>
<tr>
<td>• Majority of injuries caused by high-energy trauma</td>
<td>• Small sample size (only 27 grade III fractures)</td>
</tr>
<tr>
<td>• Classified fractures by grade and location</td>
<td>• Antibiotics after discharge not accounted for</td>
</tr>
<tr>
<td>• Aimed to determine risk factors for OM</td>
<td>• Multiple different agents with unspecified dosing were used to provide EGN coverage</td>
</tr>
<tr>
<td>• Evaluated OM rates based on addition of EGN activity</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Conclusions**

• Rates of OM were not statistically different in patients not receiving EGN coverage
• The three cases of OM observed in grade III fractures were all due to Gram-negative pathogens
  o Each pathogen remained susceptible to the prophylactic agents used, which generates questions about appropriate dosing and ability of these agents to reach the site of action
• Provides low-level support that EGN coverage is not warranted
• Utilization of first-generation cephalosporin monotherapy appears sufficient to reduce incidence of infectious complications

Legend: OM = osteomyelitis, AKI = acute kidney injury, CDI = *Clostridium difficile* infection, BMI = body mass index, GNR = Gram-negative rod
# Antibiotics and open fractures of the lower extremity: less is more

## Objective
To investigate the necessity of aminoglycoside usage for patients with open grade III lower extremity fractures

## Methods

### Design
- Single-center, retrospective chart review

### Population
- Patients with grade III lower extremity open fractures admitted to Level I trauma center between 2010 – 2015

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gustilo grade III fracture of lower extremity</td>
<td>• Age &lt; 18 years</td>
</tr>
</tbody>
</table>

### Groups*
- CEPH only: cefazolin (65/126, 52%)
- CEPH + AG: cefazolin + gentamicin (61/126, 48%)

### Outcomes
- Differences in clinical course events (acute kidney injury, surgical site infection, hardware removal, and hospital length of stay) and disposition between groups
- Differences in injury characteristics (Gustilo grade and presence of multiple orthopedic injuries) or surgical intervention between groups

### Statistics
- Student’s t-test or Chi-square as appropriate
- *p ≤ 0.05 considered statistically significant for all analysis

## Results

### Baseline Characteristics
- n = 126, majority male, mean age 47, mean ISS 12

<table>
<thead>
<tr>
<th>Mechanism of Injury (%)</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>Penetrating</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of Injury (%)</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Fall</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Gunshot</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dL)</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.12</td>
<td></td>
<td>0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV contrast use (%)</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td></td>
<td>91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of prophylaxis (h)</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td></td>
<td>72</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Clinical course events</th>
<th>CEPH only (n = 65)</th>
<th>CEPH + AG (n = 61)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury (%)</td>
<td>4</td>
<td>10</td>
<td>0.05*</td>
</tr>
<tr>
<td>Surgical site infection (%)</td>
<td>7</td>
<td>5</td>
<td>0.99</td>
</tr>
<tr>
<td>Hardware removal (%)</td>
<td>4</td>
<td>13</td>
<td>0.50</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>8 ± 9</td>
<td>13 ± 15</td>
<td>0.11</td>
</tr>
</tbody>
</table>

- *NNH = 16
- AKI defined using RIFLE criteria, a 50% decrease in GFR or a twofold increase in Scr
- No statistically significant differences observed between groups regarding disposition, injury characteristics or surgical interventions

### Author’s Conclusions
- Addition of an aminoglycoside for prophylaxis in lower extremity grade III open fractures is associated with a significant increase in AKI with no observed differences in surgical site infections, hardware removal, or hospital length of stay
- Addition of aminoglycosides may not only be unnecessary, but also detrimental
Reviewer’s Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Broad inclusion criteria</td>
<td>• Single-center, retrospective design</td>
</tr>
<tr>
<td>• Study population limited to grade III open fractures of the lower extremity</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>• Compared surgical management between groups</td>
<td>• Creatine kinase levels not reported</td>
</tr>
<tr>
<td>• Evaluated clinically relevant outcomes</td>
<td>• Antibiotic dosing not addressed</td>
</tr>
<tr>
<td></td>
<td>• Did not identify causative pathogens</td>
</tr>
</tbody>
</table>

Overall Conclusion

- Additional support to the idea that aminoglycosides are unnecessary in the prophylaxis of grade III open fractures
- Aminoglycoside use led to a statistically significant increase in incidence of AKIs
- Provides additional evidence that cefazolin alone appears sufficient to prevent infectious complications in grade III fractures of the lower extremity

Legend: Abbreviations: CEPH = cephalosporin, AG = aminoglycoside, ISS = injury severity score, MVC = motor vehicle crash

*Specific antibiotic agents utilized in this study were not described in the publication itself, but were confirmed via email correspondence with the authors (B. Bankhead-Kendall, personal communication, August 21, 2018)

Conclusions

I. While it remains common in clinical practice, the addition of aminoglycosides for prophylaxis of Gustilo grade III open fractures is not supported by available evidence
   A. Recommendation based on expert opinion, now more than 40 years old
   B. No clear benefits for addition of an aminoglycoside
   C. Potential risks associated with addition of an aminoglycoside include
      i. Increased risk of
         1. Nosocomial infections such as pneumonia
         2. Acute kidney injury
         3. Clostridium difficile colitis
         4. Central line infections
      ii. Contribution to resistance development among nosocomial pathogens

II. Administration of first-generation cephalosporins is an evidence-based practice

III. Several retrospective studies provide evidence that first-generation cephalosporins without additional Gram-negative coverage are as effective as the cephalosporin-aminoglycoside combination for reducing infective complications

IV. Prophylactic antibiotics are not a substitute for adequate surgical management of these injuries
   A. Surgical debridement and irrigation are critical to preventing infection and decreasing bacterial load
   B. Soft-tissue coverage should be achieved as soon as possible, ideally within 72 hours

Recommendations

I. Patients admitted with Gustilo grade III open fractures of the lower extremity should receive cefazolin
   A. Administration within one hour of injury is ideal
   B. Cefazolin 1 to 2 g q8 for a duration of 24-48 hours perioperatively

II. Cefazolin is administered as an adjunct to, not in place of, appropriate surgical management
   A. Adequate irrigation and debridement are necessary to prevent infection and complications
   B. Soft-tissue coverage should be achieved as soon as possible, ideally within 72 hours
**Future Directions**

I. Large, randomized controlled trials are necessary to establish an optimal antibiotic regimen for prophylaxis of grade III open fractures

II. Updated, comprehensive clinical practice guidelines are needed to standardize management of these patients

**Appendices**

**Appendix A.** An abbreviated summary of evidence surrounding antibiotic prophylaxis in grade III open fractures

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design/Population</th>
<th>Results/Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patzakis (1974)</td>
<td>Randomized, placebo-controlled</td>
<td>• Infection rates: 13.9% for no antibiotics, 9.7% for PCN + streptomycin, and 2.3% for cephalothin</td>
<td>- First study proving the benefit of prophylactic antibiotics in open fractures&lt;br&gt;- Provides strong evidence for efficacy of first-generation cephalosporins&lt;br&gt;- Patients received 10-14 days of antibiotics, which is really treatment not prophylaxis&lt;br&gt;- Did not stratify open fractures, published before classification scheme developed&lt;br&gt;- Suggestion of combination therapy with a first-generation cephalosporin and an aminoglycoside was not supported by the data, but still became incredibly influential</td>
</tr>
<tr>
<td>Benson (1983)</td>
<td>Randomized, prospective study</td>
<td>• No statistically significant difference in infection rate found between cefazolin and clindamycin (7.1% vs. 5.9%)&lt;br&gt;• 46% of wounds were contaminated, but observed overall infection rate was 6.5%</td>
<td>- Four out of 82 fractures became infected with Gram-negative pathogens (4.9%)&lt;br&gt;- Antibiotics were not administered until after tissue sample collected for culture at time of debridement, averaging 5.38 to 5.53 hours&lt;br&gt;- Did not stratify open fractures</td>
</tr>
<tr>
<td>Braun (1987)</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>• Infection rate significantly lower in cloxacillin group (2%) compared to placebo group (12%)&lt;br&gt;• Six superficial and six deep infections in placebo grp&lt;br&gt;• One superficial and one deep infection in cloxacillin grp&lt;br&gt;• All infections occurred in lower extremities&lt;br&gt;• Prophylaxis with narrow-spectrum antibiotics with activity against staphylococci reduced infection frequency</td>
<td>- Supports use of single antibiotic active against staphylococcal species&lt;br&gt;- Chose cloxacillin because 80% of infections following open fractures historically caused by Staphylococcus aureus at their institution&lt;br&gt;- Single deep infection in cloxacillin grp was due to Pseudomonas aeruginosa and enterococci&lt;br&gt;- Included all grades of open fractures, but only ~20% were grade III</td>
</tr>
<tr>
<td>Johnson (1988)</td>
<td>Randomized, prospective study</td>
<td>• No statistically significant difference in infection rate between groups&lt;br&gt;• 10/46 (20.8%) overall infection rate</td>
<td>- Results do not support author’s conclusions&lt;br&gt;- No statistically significant difference observed between first-generation and</td>
</tr>
</tbody>
</table>
Excluded those with vascular injury
- Grp 1: cefazolin x 48 hours (N = 25)
- Grp 2: cefotaxime x 48 hours (N = 21)
- Wounds cultured when drainage or other signs of infection present

- 6/25 (24%) cefazolin infection rate
  - 0/9 (0%) grade II
  - 6/16 (37%) grade III
- 4/21 (19%) cefotaxime infection rate
  - 2/10 (20%) grade II
  - 2/11 (18%) grade III

Authors claimed a "trend toward decreased infection rate using cefotaxime"; recommended against first-generation cephalosporins alone in prophylaxis of grade II or grade III open tibial fractures

Vasenius (1998)46
- Randomized, prospective study
- N = 227 patients (240 open fractures), majority were long bone; 62 grade I, 109 grade II, 56 grade III
- Grp 1: clindamycin x 72 hours
- Grp 2: cloxacillin x 72 hours

- Statistically significantly more infections occurred in the cloxacillin grp (20%) compared to the clindamycin grp (9.3%)
- For grade III-B fractures infection rates were high in both groups:
  - 8/11 (73%) in cloxacillin grp
  - 3/4 (75%) in clindamycin grp
- Among pathogens in grade III fractures, 56% were Gram-positive and 43% were Gram-negative
- Authors conclude additional Gram-negative coverage is necessary in prophylaxis of grade III open fractures

- The majority of infections were still due to Gram-positive pathogens and neither group had Gram-negative coverage, so the author’s conclusion remains untested
- 76% of pathogens cultured from infection not present on admission, indicating inoculation during hospitalization

Abbreviations: Avg = average, Grp = Group, PCN = penicillin

**Appendix B. National Healthcare Safety Network (NHSN) Risk Index**47

The NHSN risk index is used to provide risk adjustment of surgical site infection rates. There are four identified levels of risk, with increasing infection risk from level 0 to level 3. Stratification points are added together to determine an individual’s NHSN risk level.

<table>
<thead>
<tr>
<th>Variables for Stratification</th>
<th>NHSN Risk Index</th>
<th>Stratification Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound classification</td>
<td>Class &gt; 2</td>
<td>1</td>
</tr>
</tbody>
</table>
  - Class 1: Clean – uninfected operative wound and respiratory, alimentary, genital, or urinary tract not entered
  - Class 2: Clean-contaminated – respiratory, alimentary, genital, or urinary tract entered, under controlled condition and without unusual contamination
  - Class 3: Contaminated – open, fresh, accidental wound; operations with major breaks in sterile technique; incisions in which acute, non-purulent inflammation is encountered
  - Class 4: Dirty or infected – old traumatic wound with retained devitalized tissue and wound that involves existing clinical infection or perforated viscera
| American Society of Anesthesiologist (ASA) score | > 2 | 1 |
  - Score 1: Normally healthy patient
  - Score 2: Mild systemic disease
  - Score 3: Severe systemic disease that is not incapacitating
  - Score 4: Incapacitating disease that is a constant threat to life
  - Score 5: Moribund patient not expected to live 24 hours with or without surgery
Appendix C. European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention (CDC) standard definitions for acquired resistance

<table>
<thead>
<tr>
<th>Multidrug-resistant (MDR)</th>
<th>The isolate is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensively drug-resistant (XDR)</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories</td>
</tr>
<tr>
<td>Pandrug-resistant (PDR)</td>
<td>Non-susceptibility to all agents in all antimicrobial categories</td>
</tr>
</tbody>
</table>

References

27. Antibiotic prophylaxis for open fractures, personal communication, Gavin Jones, PhD, PharmD, University of Arkansas for Medical Sciences.