The Role of Surgeons in Antibiotic Stewardship

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• Surgical Infections (Journal): Editor-in-Chief (Independent Contractor)
Discovery of Penicillin

• Alexander Fleming discovered Penicillin in 1929.

• The introduction of antibiotics into clinical practice (early 1940s) raised great hopes in the treatment of bacterial infection.

• In surgery, the prospects of using antibiotics for prevention was immediately recognized as a possibility.
Discovery of Sulfanilamide

• Discovered Prontosil in 1931.
• Published results in 1935
• Treated patients with streptococcal and staphylococcal infections
• Received the Nobel Prize in 1939.

Gerhard Domagk (1895-1964)
Antimicrobial Resistance: Arrival of the Post-Antibiotic Era

**Why has resistance emerged?**

- Promiscuous use of antibiotics (e.g., preventive antibiotics)
- Failure to de-escalate combination therapy of empirical choices.
- Inappropriate antibiotic therapy
- Patient expectations and demands for antibiotic therapy
- Prolonged administration when infection does exist
- Poultry industry

**RESULT:** Pan-Resistance of Pathogens to all available antibiotics

Four Horsemen of the Microbial Apocalypse

- **S. aureus**
- **Enterococci**
- **P. aeruginosa**
- **Candida**
Other Potential Consequences of Antibiotics

• Asthma
• Allergies
• Obesity
• Type-2 Diabetes
• Reflux Esophagitis
• C. difficile Infection
• Oncogenesis
Antibiotic Stewardship Programs

**Antibiotic Stewardship Programs**

**ANTIBIOTIC STEWARDSHIP**

*In your facility will*

**DECREASE**

- Antibiotic resistance
- C. Difficile infections
- Costs

**INCREASE**

- Good patient outcomes

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**PROMOTE ANTIBIOTIC BEST PRACTICES—A FIRST STEP IN ANTIBIOTIC STEWARDSHIP**

- Ensure all orders have dose, duration, and indications
- Get cultures before starting antibiotics
- Take an "Antibiotic Timeout" reassessing antibiotics after 48-72 hours

**ANTIBIOTIC STEWARDSHIP PROGRAMS ARE A "WIN-WIN" FOR ALL INVOLVED**

A University of Maryland study showed one antibiotic stewardship program saved a total of $17 million over eight years.

Antibiotic stewardship helps improve patient care and shorten hospital stays, thus benefiting patients as well as hospitals.
Antibiotic Stewardship in Surgery

**Goals**

- Avoid Unnecessary Antibiotic Use
- Reduce Resistance Pressure
- Reduce Unnecessary Costs
- Reduce Antibiotic-Associated Morbidity

**Objectives**

- Appropriate Preventive Antibiotic Use
- Effective Source Control of the Infection
- Avoid delays in initiation
- Avoid Excessive duration
- Better use of non-antibiotic infection management strategies
Appropriate Antibiotic Use to Prevent Surgical Site Infection
Timing of Penicillin Administration with Respect to Bacterial Inoculation

Mean 24-Hour Lesion Diameter (mm)

- Staphylococcal lesions - no antibiotic
- Staphylococcal lesions - antibiotic
- Killed staphylococcal lesions

Lesion Age at Time of Penicillin Injection (hr)

Adapted from the American College of Surgeons. 1988-91.

Miles et al: Brit J Exp Pathol 1957
Prevention of Surgical Site Infection
Use of Preventive Antibiotics (cephaloridine): GI Surgery

<table>
<thead>
<tr>
<th></th>
<th>Cephaloridine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>101</td>
<td>98</td>
</tr>
<tr>
<td>Colon Pts</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Infections</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Colon Inf</td>
<td>7%</td>
<td>30%*</td>
</tr>
</tbody>
</table>

*(P < .05)*

### Preventive Systemic Antibiotics: Importance of Timing (Cefazolin)

<table>
<thead>
<tr>
<th></th>
<th>8-12Hrs Preop</th>
<th>1Hr Preop</th>
<th>1-4Hrs Postop</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric</strong></td>
<td>5%</td>
<td>4%</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Biliary</strong></td>
<td>3%</td>
<td>0%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Colon</strong></td>
<td>6%</td>
<td>6%</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4%</td>
<td>3%</td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>

(Stone, Ann Surg 1976; 184:443)
Preventive Systemic Antibiotics
Postoperative Administration (Cefamandole)

<table>
<thead>
<tr>
<th></th>
<th>Preop Drug + 5 Days of Drug</th>
<th>Preop Drug + 5 Days of Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Biliary</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Colon</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Total</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Stone, Ann Surg 1979; 189:691)
Prevention of SSIs

**Surgical Infection Prevention Project**

- Administration of antibiotic within 60 min of skin incision.
- Antibiotic consistent with recommended choices.
- Antibiotic should not be continued beyond 24 hours after completion of the procedure.

# Surgical Infection Prevention

*Performance Stratified by Surgery*

<table>
<thead>
<tr>
<th>Surgery (N)</th>
<th>Antibiotic within 1 hour %</th>
<th>Correct Antibiotic %</th>
<th>Antibiotic Stopped within 24 hours %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (7,861)</td>
<td>45.3</td>
<td>95.8</td>
<td>34.3</td>
</tr>
<tr>
<td>Vascular (3,207)</td>
<td>40.0</td>
<td>91.9</td>
<td>44.8</td>
</tr>
<tr>
<td>Hip/knee (15,030)</td>
<td>52.0</td>
<td>97.4</td>
<td>36.3</td>
</tr>
<tr>
<td>Colon (5,279)</td>
<td>40.6</td>
<td>75.9</td>
<td>41.0</td>
</tr>
<tr>
<td>Hysterectomy (2,756)</td>
<td>52.4</td>
<td>90.8</td>
<td>79.1</td>
</tr>
<tr>
<td>All Surgeries (34,133)</td>
<td>47.6</td>
<td>92.9</td>
<td>40.7</td>
</tr>
</tbody>
</table>
Single vs Multiple Dose Surgical Prophylaxis: Systematic Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Antibiotic</th>
<th>Odds ratio (95% c.i.)</th>
<th>Proportion with surgical wound infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr et al.⁶⁸</td>
<td>1984</td>
<td>Metronidazole(1) versus (2-4)</td>
<td></td>
<td>7 of 22 versus 11 of 68</td>
</tr>
<tr>
<td>Aberg and Thore⁶⁹</td>
<td>1991</td>
<td>Cefuroxime + metronidazole(1) versus (3)</td>
<td></td>
<td>2 of 19 versus 1 of 29</td>
</tr>
<tr>
<td>Corman et al.²⁷</td>
<td>1993</td>
<td>Cefoxitin(1) versus (4)</td>
<td></td>
<td>2 of 31 versus 0 of 27</td>
</tr>
<tr>
<td>Kow et al.⁷⁰</td>
<td>1995</td>
<td>Cefoxitin(1) versus (3)</td>
<td></td>
<td>10 of 73 versus 8 of 81</td>
</tr>
<tr>
<td>Jensen et al.²⁵</td>
<td>1990</td>
<td>Ampicillin + metronidazole(1) versus (3)</td>
<td></td>
<td>14 of 100 versus 12 of 104</td>
</tr>
<tr>
<td>Juul et al.⁷¹</td>
<td>1987</td>
<td>Ampicillin + metronidazole(1) versus (4)</td>
<td></td>
<td>9 of 149 versus 8 of 145</td>
</tr>
<tr>
<td>Hall et al.³¹</td>
<td>1989</td>
<td>Latamoxef(1) versus (8)</td>
<td></td>
<td>12 of 119 versus 10 of 126</td>
</tr>
<tr>
<td>Bates et al.⁷²</td>
<td>1992</td>
<td>Co-amoxiclav(1) versus (3)</td>
<td></td>
<td>23 of 113 versus 17 of 111</td>
</tr>
<tr>
<td>Grundmann et al.⁷³</td>
<td>1987</td>
<td>Mezlocillin + metronidazole(1) versus (3)</td>
<td></td>
<td>4 of 77 versus 4 of 77</td>
</tr>
<tr>
<td>Mendel et al.⁷⁴</td>
<td>1987</td>
<td>Mezlocillin + metronidazole(1) versus (9)</td>
<td></td>
<td>2 of 54 versus 1 of 46</td>
</tr>
<tr>
<td>Bittner et al.⁷⁵</td>
<td>1989</td>
<td>Mezlocillin + metronidazole(1) versus (7)</td>
<td></td>
<td>6 of 46 versus 3 of 44</td>
</tr>
<tr>
<td>Cuthbertson et al.⁷⁶</td>
<td>1991</td>
<td>Ticarcillin/clavulanic acid(1) versus (2)</td>
<td></td>
<td>16 of 146 versus 17 of 132</td>
</tr>
<tr>
<td>Kow et al.⁷⁰</td>
<td>1995</td>
<td>Cefotaxime + metronidazole(1) versus (3)</td>
<td></td>
<td>7 of 84 versus 9 of 81</td>
</tr>
<tr>
<td>Goransson et al.⁷⁷</td>
<td>1984</td>
<td>Doxycycline(1) versus (4)</td>
<td></td>
<td>1 of 53 versus 2 of 49</td>
</tr>
<tr>
<td>Wenzel et al.⁷⁸</td>
<td>1985</td>
<td>Gentamicin + metronidazole(1) versus (3)</td>
<td></td>
<td>6 of 30 versus 10 of 30</td>
</tr>
<tr>
<td>Lohr et al.⁷⁹</td>
<td>1984</td>
<td>Cefotaxime(1) versus (3)</td>
<td></td>
<td>4 of 30 versus 3 of 30</td>
</tr>
<tr>
<td>Tuchmann et al.⁸⁰</td>
<td>1988</td>
<td>Piperacillin + metronidazole(1) versus (3)</td>
<td></td>
<td>4 of 61 versus 5 of 63</td>
</tr>
</tbody>
</table>

**Song and Glenny: Brit J Surg 1998; 85:1232**

Fig. 5 Effect of single versus multiple doses of antibiotic in preventing surgical wound infection in colorectal surgery. Values in parentheses are number of doses. c.i., Confidence interval
Preventive Antibiotics
Why Postoperative administration does not work

Figure 4.3  The fibrin layer on the wound interface and the presence of the fibrin matrix in the closed wound. Note the “halo” of edema about the closed wound and the potential consequences of increased tissue hydrostatic pressure and ischemia of the interface.
Systemic Preventive Antibiotics
Elimination Half-life Counts!

- Cephalothin is gone from the wound in 90 min from time of administration.
- Cefazolin in therapeutic concentrations beyond 2½ hours.

(Fry, Arch Surg 1990; 125:1490)
Preventive Antibiotics in Trauma
Effect of dosing

Ericsson et al: J Trauma 1989; 29:1356
Preventive Antibiotics in Surgery Coverage of MRSA?

Randomized trial in cardiovascular procedures.
An environment with high rates of MRSA infection
Randomization of vancomycin vs. cefazolin
Overall SSI rates were the same. Cefazolin-associated infections had high frequency of MRSA
Vancomycin-associated infections had high frequency of MSSA

Finkelstein et al: JTCVS, 2002;123:326

| TABLE 2. Outcomes of 885 patients receiving vancomycin or cefazolin prophylaxis for cardiovascular operations |
|-------------------------------------------------|-----------------|-----------------|
| Superficial incisional SSI (No.)                | Vancomycin (n = 452) | Cefazolin (n = 433) |
| All                                             | 25 (5.5%)         | 20 (4.6%)        |
| Donor site                                      | 7 (1.5%)          | 10 (2.3%)        |
| Chest                                           | 18 (4%)           | 10 (2.3%)        |
| Deep incisional SSI (No.)                       | ----------------- | ----------------- |
| All                                             | 12 (2.6%)         | 7 (1.6%)         |
| Donor site                                      | 2 (0.4%)          | 2 (0.4%)         |
| Chest                                           | 10 (2.2%)         | 5 (1.2%)         |
| Organ-space SSI (No.)                           | ----------------- | ----------------- |
| All                                             | 6 (1.3%)          | 12 (2.7%)        |
| Mediastinitis                                   | 5 (1.1%)          | 7 (1.6%)         |
| Osteomyelitis                                   | 0                 | 3 (0.7%)         |
| Endocarditis                                    | 1 (0.2%)          | 2 (0.4%)         |
| Pericarditis                                    | 0                 | 0                |
| Any SSI (No.)                                   | 43 (9.5%)         | 39 (9.0%)        |
| Duration of postoperative hospitalization (d, mean ± SD) | 8.7 ± 8 | 9.3 ± 11 |
| Deaths (No.)                                    | 13 (2.9%)         | 14 (3.2%)        |

No differences were significant at P ≤ .05.
Preventive Antibiotic Stewardship Summary

- No Antibiotics administered after wound closure
- Use longer half-life antibiotics and re-dose at two half-life intervals for longer operation.
- Administer the drugs within < 60 minutes before incision.
- Increase the administration dose for emergency/trauma cases
- Monitor home antibiotic following Outpatient/Ambulatory Surgery

Antibiotic Choice

- SCJP choices are appropriate for uncomplicated patients.
- Beware of the Patient with adverse colonization!
  - 90-day prior hospitalization
  - 90-day prior antibiotic therapy
  - Hemodialysis Patient
  - Nursing Home Patients
  - History of Prior Surgical Site Infections
  - Known MRSA carrier

The Best Antibiotic Stewardship in Surgery in avoiding preventable Infections!
Effective Source Control of Infection
Inadequate Source Control
Fix the hole; Debride dead tissue; Drain the Pus!

**Gross Contamination/Pus**

- Very large bacterial inoculum (> \(10^7\) bacteria/ml)
- Inoculum Effect neutralizes anticipated antimicrobial activity
- Environment is anaerobic, acidic, protein-rich.
- Fibrin-entrapped bacteria not affected by systemic drugs
- Polymicrobial and Synergistic
Inadequate Source Control

• Tellor (Mazuski), Surg Infect 2015
  • N = 108 patients
  • All with positive blood cultures from an intraabdominal infection
  • Median APACHE II = 20
  • 72% Mechanically ventilated
  • Overall Mortality = 28%

• Significant Clinical Outcome Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR, 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate source control</td>
<td>7.46, 2.08–26.32</td>
<td>0.002</td>
</tr>
<tr>
<td>Inappropriate antibiotics</td>
<td>3.86, 1.28–11.64</td>
<td>0.016</td>
</tr>
<tr>
<td>APACHE II score (1 point increments)</td>
<td>0.93, 0.87–1.01</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Table 9. Multivariate Logistic Regression Analysis

Hosmer-Lemeshow p = 0.943, AUROC = 0.776.
AOR = adjusted odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation.
Inadequate Source Control Promotes Multidrug Resistant (MDR) Pathogens

- 220 ICU Patients: Initial operation for IAI
- Reoperated and non-reoperated patients had similar Pathogens at initial cultures.
- Initial antibiotic profiles were similar between no reoperation and reoperation groups.

**Conclusion:** Failed source control promotes resistant pathogens.


- Danish Clinical Registry of Emergency Surgery (N=2,668)
- 30-day mortality measured by number of hours from admission to OR.
- Mean age = 70 years
- ASA ≥ 3 in 45.6%
- Alcohol Abuse = 18.9%
- Tobacco Abuse = 61.3%
- 30 Day Morality = 26.5%
- Death rate increase 2% per hour of delay.
Delay in Source Control: IAI

Table 1 Primary diseases of all patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients, number (%)</th>
<th>Deaths, number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon/rectal diverticulitis</td>
<td>35 (22.7)</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Mechanical small bowel obstruction</td>
<td>27 (17.5)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Mesenteric ischemia and necrotic bowel</td>
<td>21 (13.6)</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Idiopathic lower digestive tract perforation</td>
<td>16 (10.4)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Colon/rectal cancer</td>
<td>15 (9.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gastric/duodenal peptic ulcer</td>
<td>9 (5.8)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Non-occlusive mesenteric ischemia</td>
<td>9 (5.8)</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>Gastric canes</td>
<td>5 (3.2)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>5 (3.2)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Sigmoid volvulus</td>
<td>3 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Strangulated inguinal/femur hernia</td>
<td>3 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Toxic mega-colon</td>
<td>2 (1.3)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.6)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>154</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

60-day survival rate

- 0.98 for 0-2 hr.
- 0.78 for 2-4 hr.
- 0.55 for 4-6 hr.

Time from admission to initiation of surgery (hr.)
Prompt Initiation of Antibiotics for Established Infection
Delay in Initiation of Antibiotic Therapy
Barie et al: Surg Infect, 2005

Patient Population:
- 334 ICU Surgical Patients
- 40% Pneumonia
- 30% IAI
- 10% Soft Tissue
- 30.8% Deaths

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.028</td>
<td>1.001</td>
<td>1.055</td>
<td>0.04</td>
</tr>
<tr>
<td>APACHE III</td>
<td>1.025</td>
<td>1.01</td>
<td>1.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak temperature</td>
<td>1.108</td>
<td>0.62</td>
<td>1.978</td>
<td>0.729</td>
</tr>
<tr>
<td>ICU day peak temperature</td>
<td>1.088</td>
<td>0.979</td>
<td>1.208</td>
<td>0.116</td>
</tr>
<tr>
<td>Days of antibiotics</td>
<td>1.135</td>
<td>0.997</td>
<td>1.292</td>
<td>0.056</td>
</tr>
<tr>
<td>Time to Abx administration</td>
<td>1.021</td>
<td>1.003</td>
<td>1.038</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to Abx confirmation</td>
<td>0.996</td>
<td>0.99</td>
<td>1.003</td>
<td>0.266</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.482</td>
<td>0.228</td>
<td>1.019</td>
<td>0.056</td>
</tr>
<tr>
<td>Appropriateness Abx 1</td>
<td>1.623</td>
<td>0.776</td>
<td>3.391</td>
<td>0.198</td>
</tr>
<tr>
<td>Appropriateness Abx 2</td>
<td>0.923</td>
<td>0.824</td>
<td>1.033</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Abx, antibiotic.
Model \( \chi^2 = 8.038 \) (good discrimination), Hosmer-Lemeshow goodness of fit \( p = 0.441 \) (good calibration).
### Delay in Initiation of Antibiotics

Surviving Sepsis Campaign Database: **Ferrer et al, Crit Care Med, 2015**

<table>
<thead>
<tr>
<th>Patient Characteristic, n (%)</th>
<th>0.0–1.0</th>
<th>1.0–2.0</th>
<th>2.0–3.0</th>
<th>3.0–4.0</th>
<th>4.0–5.0</th>
<th>5.0–6.0</th>
<th>&gt; 6.0</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2,388 (50.5)</td>
<td>2,308 (50.2)</td>
<td>1,398 (46.3)</td>
<td>729 (42.0)</td>
<td>430 (41.5)</td>
<td>252 (39.4)</td>
<td>982 (43.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1,076 (22.8)</td>
<td>1,332 (29.0)</td>
<td>950 (31.5)</td>
<td>518 (29.9)</td>
<td>273 (26.3)</td>
<td>164 (25.6)</td>
<td>444 (19.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal</td>
<td>914 (19.3)</td>
<td>738 (16.1)</td>
<td>545 (18.1)</td>
<td>387 (22.3)</td>
<td>225 (21.7)</td>
<td>146 (22.8)</td>
<td>550 (24.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Meningitis</td>
<td>101 (2.1)</td>
<td>57 (1.2)</td>
<td>39 (1.3)</td>
<td>23 (1.3)</td>
<td>16 (1.5)</td>
<td>5 (0.8)</td>
<td>36 (1.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Skin</td>
<td>294 (6.2)</td>
<td>294 (6.4)</td>
<td>212 (7.0)</td>
<td>119 (6.9)</td>
<td>66 (6.4)</td>
<td>35 (5.5)</td>
<td>113 (5.1)</td>
<td>0.040</td>
</tr>
<tr>
<td>Bone</td>
<td>46 (1.0)</td>
<td>57 (1.2)</td>
<td>48 (1.6)</td>
<td>28 (1.6)</td>
<td>7 (0.7)</td>
<td>9 (1.4)</td>
<td>37 (1.7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Wound</td>
<td>206 (4.4)</td>
<td>242 (5.3)</td>
<td>124 (4.1)</td>
<td>78 (4.5)</td>
<td>50 (4.8)</td>
<td>20 (3.1)</td>
<td>95 (4.3)</td>
<td>0.080</td>
</tr>
<tr>
<td>Catheter</td>
<td>169 (3.6)</td>
<td>157 (3.4)</td>
<td>106 (3.5)</td>
<td>75 (4.3)</td>
<td>37 (3.6)</td>
<td>29 (4.5)</td>
<td>88 (3.9)</td>
<td>0.596</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>46 (1.0)</td>
<td>42 (0.9)</td>
<td>33 (1.1)</td>
<td>15 (0.9)</td>
<td>14 (1.4)</td>
<td>11 (1.7)</td>
<td>26 (1.2)</td>
<td>0.548</td>
</tr>
<tr>
<td>Device</td>
<td>54 (1.1)</td>
<td>51 (1.1)</td>
<td>43 (1.4)</td>
<td>24 (1.4)</td>
<td>16 (1.5)</td>
<td>9 (1.4)</td>
<td>22 (1.0)</td>
<td>0.704</td>
</tr>
<tr>
<td>Other infection</td>
<td>260 (9.7)</td>
<td>528 (11.5)</td>
<td>399 (13.2)</td>
<td>216 (12.5)</td>
<td>145 (14.0)</td>
<td>95 (14.8)</td>
<td>337 (15.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Delay in Initiation of Antibiotics
Surviving Sepsis Campaign Database: *Ferrer et al, Crit Care Med, 2015*

<table>
<thead>
<tr>
<th>Time to Antibiotics (Hr)</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>$p$</th>
<th>Probability of Mortality (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00</td>
<td></td>
<td></td>
<td>24.6</td>
<td>23.2–26.0</td>
</tr>
<tr>
<td>1–2</td>
<td>1.07</td>
<td>0.97–1.18</td>
<td>0.165</td>
<td>25.9</td>
<td>24.5–27.2</td>
</tr>
<tr>
<td>2–3</td>
<td>1.14</td>
<td>1.02–1.26</td>
<td>0.021</td>
<td>27.0</td>
<td>25.3–28.7</td>
</tr>
<tr>
<td>3–4</td>
<td>1.19</td>
<td>1.04–1.35</td>
<td>0.009</td>
<td>27.9</td>
<td>25.6–30.1</td>
</tr>
<tr>
<td>4–5</td>
<td>1.24</td>
<td>1.06–1.45</td>
<td>0.006</td>
<td>28.8</td>
<td>25.9–31.7</td>
</tr>
<tr>
<td>5–6</td>
<td>1.47</td>
<td>1.22–1.76</td>
<td>&lt;0.001</td>
<td>32.3</td>
<td>28.5–36.2</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1.52</td>
<td>1.36–1.70</td>
<td>&lt;0.001</td>
<td>33.1</td>
<td>30.9–35.3</td>
</tr>
</tbody>
</table>
De-escalate Antibiotic Therapy with Culture Results
De-escalation of Antibiotic Therapy: Post-operative Intraabdominal Infection (IAI)

- 13-year study of 311 consecutive ICU patients with post-operative IAI
- Antibiotics were a clinical choice
- De-escalation was also a clinical decision
- De-escalation was evaluated on Median day 3 of treatment.
- No evaluation of adequacy of Source Control

De-escalation of Antibiotic Therapy: Post-operative Intraabdominal Infection (IAI)

Determinants of De-escalation:
- Adequate Empirical Choice
- Use of Vancomycin
- Use of Carbapenem
- Use of Aminoglycoside

Risk Factors for No De-escalation:
- Multidrug Resistant Bacteria
- Non-fermenting Gram Negatives
- Enterococcus

Risk Factors for 28-day Deaths:
- Positive fungal Culture
- Elevated SOFA score
- Age > 69 years

De-escalation did not adversely affect 28-day outcomes

Escalation was of NO SURVIVAL BENEFIT
Avoid Excessive Duration of Antibiotic Therapy
Excessive Duration of Antibiotic Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N=260)</th>
<th>Experimental Group (N=257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)</td>
<td>58 (22.3)</td>
<td>56 (21.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>23 (8.8)</td>
<td>17 (6.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intraabdominal infection</td>
<td>36 (13.8)</td>
<td>40 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Time to event — no. of days after index source-control procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of surgical-site infection</td>
<td>15.1±0.6</td>
<td>8.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis of recurrent intraabdominal infection</td>
<td>15.1±0.5</td>
<td>10.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>19.0±1.0</td>
<td>18.5±0.5</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Sawyer RG: NEJM, 2015
Excessive Duration of Antibiotic Therapy

Potential Weapons of Mass Destruction
Alternatives to Antibiotics in Surgery: The Post Antibiotic Era
Surgical Infection in the Post-Antibiotic Era

- Bacteriophage Treatment
- Antimicrobial Peptides
- Passive Immune Enhancement
- Immunization of the Host
- Ionic Modulation of Microbial Virulence
- Manipulation of the Host Microbiome
- Revisiting Topical Antiseptics/Irrigation
Bacteriophage

- Viruses that infect Bacteria
- Commonly identified in feces
- Estimated to be $>10^{30}$ phage types
- Virus injects phage DNA into the bacterial cell
- Two Effects upon Infected Bacterial Cell
  - Lysis due to viral replication, or
  - Lysogenic effects: phage DNA is incorporated into the bacterial cell genome
Bacteriophage Therapy

Advantages

• **Phage have bacterial specificity**; will not affect or promote resistance in the normal microflora.
• Phage do not attach human cells
• We ingest and are exposed to phage constantly with no identified effects.
• Phage multiply at the site of an active infection and are then eliminated when susceptible pathogens are gone.
• New phage are constantly evolving.
• Phage components (lysins) can be developed as targeted antibiotic treatments

Disadvantages

• No clinical trials have proven human efficacy
• High degree of specificity is problematic when the pathogen is unknown.
• Resistance can develop to specific phage strains.
• Phage are large particles compared to antibiotics; pharmacokinetics?
• Antibodies to phage may pose an issue with sustained or repeated therapy.
• Can lysogenic phage transduce resistance genes from lysed bacteria to sensitive organisms?
Ionic Modulation of Bacterial Virulence

**Managing the Pathobiome**

- **Probiotics**: Restore normal bacteria (e.g., gut anaerobes) from exogenous sources
- **Selective Gut Decontamination**: Oral antibiotics to eliminate all potential pathogens
- **Phosphate Replacement**:
  - Phosphate is depleted in the stress response
  - Low phosphate is a quorum signal for microbes
  - Low phosphate increases the virulent microbial phenotype
Ionic Modulation of Bacterial Virulence

C. Elegans (nematode)

Ionic Modulation of Bacterial Virulence
Mechanical Bowel Preparation

<table>
<thead>
<tr>
<th></th>
<th>Polyethylene Glycol</th>
<th>Sodium Phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>303</td>
<td>367</td>
</tr>
<tr>
<td>SSIs</td>
<td>103 (34%)</td>
<td>87 (24%)</td>
</tr>
</tbody>
</table>

P = 0.03 (Univariate analysis)
P = 0.065 (Multi-variate analysis)

Probiotics: A Commercial “Orgy”
Restoration of the Gut Microbiome: Fecal Transplants

Artificial Poop, RePOOPulate, May Lead To Synthetic Fecal Transplants

By Christie Wilcox
Pressure Lavage of the Surgical Wound
Pressure Lavage: Unanswered Questions

- Optimum Pressure
- Addition of Antiseptics to Irritants
- Angle of Irrigation
- Treatment or Preventive applications

Fry DE: Surgical Infections, 2017
Chlorhexidine: A potential open wound application?

Table 1
Log reduction of selective gram-positive and gram-negative surgical isolates following timed exposure to 0.05% chlorhexidine gluconate solution*

<table>
<thead>
<tr>
<th>Organism</th>
<th>CFU</th>
<th>60 Seconds</th>
<th>5 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>8.7</td>
<td>3.4 (&gt;5 logs)</td>
<td>2.6 (&gt;6 logs)</td>
</tr>
<tr>
<td>MSSA</td>
<td>8.4</td>
<td>3.5 (&gt;5 logs)</td>
<td>2.6 (&gt;6 logs)</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>8.3</td>
<td>2.9 (&gt;5 logs)</td>
<td>2.5 (&gt;5 logs)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>8.8</td>
<td>2.7 (&gt;6 logs)</td>
<td>2.1 (&gt;6 logs)</td>
</tr>
<tr>
<td><em>Escherichia aerogenes</em></td>
<td>8.9</td>
<td>3.1 (&gt;5 logs)</td>
<td>2.8 (&gt;6 logs)</td>
</tr>
</tbody>
</table>

CFU, Colony-forming units; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

*0.05% Chlorhexidine gluconate (IRRISEPT; IrriMax Corp, Lawrenceville, GA).
†Postexposure: log_{10} CFU/milliliter.
‡Baseline: initial log_{10} CFU/milliliter.
§Biofilm-producing strain from vascular graft infection.

Antibacterial Suture

Control Polyglactin 910 Suture without Triclosan

Polyglactin 910 Suture with Triclosan
Triclosan-coated Sutures

- 34 Clinical Trials in the Analysis
- A Heterogeneous populations of surgical cases and surgical patients
- Triclosan-coated sutures associated with a significant reduction in SSI rates (P<0.001)
- Cost savings per case = 91.25 £

Other Proposed Methods for Reducing SSIs

• Antimicrobial Wound Barrier Devices
• Chlorhexidine + pressure irrigation devices
• Chlorhexidine/Silver plastic adhesive skin devices
• Implantable drug delivery systems
• Negative Pressure Wound Therapy
• Many Others
CDC Antibiotic Awareness Week
November 13-19, 2017

- Stop needless antibiotic administration
- Use Preventive Antibiotics for only the perioperative period
- Reduce the length of antibiotic administration with active infections; remember, failed antibiotics may mean failed source control!
- De-escalate combination empirical therapy when culture results are available.
- **Significant reductions in total antibiotic utilization can reverse resistance trends (e.g. aminoglycosides)**

**Annual Burden of Antibiotic Resistance in the United States**

Estimated minimum number of illnesses and deaths caused annually by antibiotic resistance*:

- At least 2,049,442 illnesses,
- 23,000 deaths

* bacteria and fungus included in this report
BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

U.S. ANTIBIOTIC AWARENESS WEEK
November 18–24, 2019
www.cdc.gov/antibiotic-use

1. **Antibiotics save lives.** When a patient needs antibiotics, the benefits outweigh the risks of side effects or antibiotic resistance.

2. **Antibiotics aren’t always the answer.** Everyone can help improve antibiotic prescribing and use.

3. **Antibiotics do not work on viruses,** such as those that cause colds, flu, bronchitis, or runny noses, even if the mucus is thick, yellow, or green.

4. **Antibiotics are only needed for treating infections caused by bacteria,** but even some bacterial infections get better without antibiotics, including many sinus infections and some ear infections.

5. **Antibiotics will not make you feel better if you have a virus.** Respiratory viruses usually go away in a week or two without treatment. Ask your healthcare professional about the best way to feel better while your body fights off the virus.

6. **If you need antibiotics, take them exactly as prescribed.** Talk with your doctor if you have any questions about your antibiotics, or if you develop any side effects, especially diarrhea, since that could be a *Clostridioides difficile* infection (also called C. difficile or C. diff), which needs to be treated.

7. **Antibiotics are critical tools for treating life-threatening conditions** such as pneumonia and sepsis.
Antibiotic Stewardship in Surgical Care

- Select the correct drug specific to the patient for prophylaxis
- Discontinue needless post-operative antibiotic administration
  - Inpatient procedures
  - Outpatient/Ambulatory procedures
- Effective Source Control
- Reduce inappropriate/unnecessary antibiotic therapy in established infections
- Cover all likely pathogens with empirical antibiotic choices
- Engage in de-escalation when culture results are available
- Consider alternatives to Antibiotics as future data for prevention and treatment evolve.