ANTIMICROBIAL UTILIZATION IN THE ICU

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Director, Clinical Pharmacy Services
HealthTrust
Objectives:

• Recall national consensus recommendations related to the proper utilization of antibiotics in critically-ill patients

• Discuss the evidence-based support for which the national consensus recommendations are based on

• Explain current challenges that ICU clinicians face with regards to appropriate antibiotics use

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Andrew Rhodes, MB BS; Djillali Annane, MD; Herwig Gerlach, MD, PhD; Steven M. Opal, MD; Jonathan E. Sevransky, MD; Charles L. Sprung, MD; Ivor S. Douglas, MD; Roman Jaeschke, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nunnally, MD; Sean R. Townsend, MD; Konrad Reinhart, MD; Ruth M. Kleinpell, PhD, RN-CS; Derek C. Angus, MD, MPH; Clifford S. Deutschman, MD, MS; Flavia R. Machado, MD, PhD; Gordon D. Rubenfeld, MD; Steven A. Webb, MB BS, PhD; Richard J. Beale, MB BS; Jean-Louis Vincent, MD, PhD; Rui Moreno, MD, PhD; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

**Objective:** To provide an update to the “Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock,” last published in 2008.

**Design:** A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings for those committee members who were unable to attend in person.

**Methods:** The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence...
Surviving Sepsis Campaign

Initial Approach to the Septic Patient

A. Initial Resuscitation
B. Screening for Sepsis and Performance Improvement
C. Diagnosis
D. Antimicrobial Therapy
E. Source Control
F. Infection Prevention
Surviving Sepsis Campaign

Sepsis Bundles

• Three Hour Bundle Goals:
  1. Measure lactate level
  2. **Obtain blood cultures prior to antibiotics**
  3. **Administer broad spectrum antibiotics**
  4. Administer 30 mL/kg crystalloid for hypotension or lactate (≥4 mmol/L)

• Six Hour Bundle Goals
  1. Vasopressors for fluid unresponsive hypotension
  2. Measure CVP & SCVO₂ in the event of persistant arterial hypotension
  3. Re-measure lactate if initial lactate was elevated
Surviving Sepsis Campaign

Antimicrobial Utilization

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).
Surviving Sepsis Campaign

Antimicrobial Utilization

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrugresistant bacterial pathogens such as Acinetobacter and Pseudomonas spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosa bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections (grade 2B).
Surviving Sepsis Campaign

Antimicrobial Utilization

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG)
Administration of Antibiotics within 1\textsuperscript{st} hour of Sepsis Recognition
Influence of timing of antibiotic therapy in septic shock

Retrospective cohort study of 2731 patients with septic shock (14 ICUs)
Timing of ABX administration after 1\textsuperscript{st} documented hypotension
In-hospital mortality: 1.119 [per hour delay], (95% CI 1.103–1.136)
Influence of timing of antibiotic therapy in septic shock

![Bar chart showing the influence of timing of antibiotic therapy in septic shock. The x-axis represents time from hypotension onset (hrs), and the y-axis represents the fraction of total patients. The chart includes two bars for each time interval: one for survival fraction and one for cumulative effective antimicrobial initiation.]
Timing of antibiotic therapy in infected critically ill surgical patients

- **335 surgical ICU patients with 1\textsuperscript{st} fever and infection identified**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95.0% C.I.</th>
<th>p value</th>
</tr>
</thead>
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<td>Age, years</td>
<td>1.028</td>
<td>1.001 - 1.055</td>
<td>0.04</td>
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<td>APACHE III</td>
<td>1.025</td>
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<td>0.62 - 1.978</td>
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<td>Days of antibiotics</td>
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<td>0.997 - 1.292</td>
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<td>Time to Abx administration</td>
<td><strong>1.021</strong></td>
<td><strong>1.003 - 1.038</strong></td>
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<td>Time to Abx confirmation</td>
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<td>Male gender</td>
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<tr>
<td>Appropriateness Abx 2</td>
<td>0.923</td>
<td>0.824 - 1.033</td>
<td>0.162</td>
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</table>

Abx, antibiotic.

Model $\chi^2$ 8.038 (good discrimination), Hosmer-Lemeshow goodness of fit $p = 0.441$ (good calibration).

- **2.1% increase in risk of death for every 30 minute delay in AB**
Combination Empiric Antibiotic Therapy
To Double Cover or Not???

• Meta-analysis of 64 randomized trials
  – N = 7,586 patients

• βLactam monotherapy versus βlactam + aminoglycoside

• Tx of severe infections/sepsis

BMJ. 2004 Mar 20;328(7441):668
To Double Cover or Not???

• βLactam Monotherapy
  – Clinical Failure RR – 0.87 (0.78 to 0.97)
  – Mortality RR – 0.90 (0.77 to 1.06)
  – Bacteriological Failure RR – 0.86 (0.72 to 1.02)
  – Resistance RR – 0.83 (0.50 to 1.39)
To Double Cover or Not???

• 28-day Mortality (propensity score adjusted)
  – HR 0.77 (0.67-0.88)

• Ventilation Free-Days 17 vs. 10, p 0.008

• Vasoactive Free-Days 25 vs. 23, p 0.007

• Benefit observed in G+ and G- pathogens
  – β-lactams + aminoglycosides, fluoroquinolones, or macrolides/clindamycin
Inadequate Empiric Antibiotics → Excess Mortality

P < 0.001

52.1% 12.2%

42.0% 17.7%

Inadequate antimicrobial treatment

Adequate antimicrobial treatment

All-Cause Mortality

Infection-Related Mortality

12.2% 17.7%

Established Duration of Antibiotic Therapy
How Long Should an Antibiotic Course Be?

• Prospective, randomized, double-blind trial
  – 51 French ICUs

• 401 patients with VAP (quantitative culture of BAL specimens)

• Intervention:
  – 8 days vs. 15 days of AB therapy

Chastre, J. et al. JAMA 2003;290:2588-2598
How Long Should an Antibiotic Course Be?

• Death from all causes: 1.6% (-3.7 to 6.9)

• MV-free days: -0.4% (-1.9 to 1.1)

• Organ failure-free days: -0.5% (-1.9 to 1.0)

• Pulmonary infection reoccurrence
  – All patients 2.9% (-3.2 to 9.1)
  – Nonfermenting GNB 15.2% (3.9 to 26.6)
Kaplan-Meier Estimates of the Probability of Survival

![Graph showing Kaplan-Meier Estimates of the Probability of Survival with comparison of 8-Day and 15-Day Antibiotic Regimens. Log-Rank P = .65.](image)
Challenges related to Antimicrobial Use: ANTIMICROBIAL RESISTANCE
ANTIBIOTIC RESISTANCE THREATS in the United States, 2019

Urgent Threats
- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae

Serious Threats
- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococcus (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant Non-typhoidal Salmonella
- Drug-resistant Salmonella Typhi
- Drug-resistant Shigella
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Drug-resistant Streptococcus pneumoniae
- Drug-resistant tuberculosis

Concerning Threats
- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group A Streptococcus
Resistance Organisms → National Threat

- Impact of drug-resistant bacteria yearly in the US
  - 2,049,442 illnesses
  - 23,000 deaths
  - $20 billion in excess healthcare dollars
Carbapenem Resistant Enterbacteriaceae (CRE)

Urine culture (clean catch)

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<th>Target</th>
<th>Route</th>
<th>Dose</th>
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<th>AB</th>
<th>Cost</th>
<th>M.I.C.</th>
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CRE “Threat”
CRE “Threat”

• National Annual Impact:
  – 9,000 infections per year
  – 600 Deaths

• Carbapenem-resistant *Klebsiella spp.*
  – 11% resistant isolates – 520 deaths

• Carbapenem-resistant *E.Coli spp*.
  – 2% resistant isolates – 90 deaths
AB Misuse → Resistance

• Trauma Pts: Infection w/resistant pathogen
  – Prolonged Broad-Spectrum AB (≥24 hours) – OR 2.13, P=0.008

• MICU: VAP w/resistant pathogen
  – Prior AB – OR 13.5, p=0.0003; Broad-spectrum AB – OR 4.1, p=0.03

• CABG surgery: Acquired *Enterobacteriaceae* resistance
  – Surgical AB Prophylaxis >48 hours – OR 1.6, P=0.027

• MICU & SICU: Inadequate AB Coverage
  – Prior ABs – OR 3.39, p<0.001

Velmahos *Arch Surg.* 2002; 137:537-542
Trouillet *Am J Respir Crit Care Med.* 1998;157:531-539
Unnecessary ABXs Endemic in US ICUs

- Prospective observational cohort
  - 68 ICUs, 27 Centers, 998 patient cases

- Prolonged Empiric Antibiotic Therapy (PEAT)
  - Defined as ABX ≥ 72 hrs in absence of adjudicated infection

- Of 649 empiric courses:
  - 58% (n=377) considered PEAT
  - Suspected pneumonia accounted for 60% of PEAT

SCCM 2011 submitted abstract
Unnecessary Use of Antimicrobials in Hospitalized Patients

- Prospective observational study in ICU
- 576 (30%) of 1941 antimicrobial days of therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy

- Duration of Therapy Longer than Necessary: 192 days
- Noninfectious or Nonbacterial Syndrome: 187 days
- Treatment of Colonization or Contamination: 94 days

Hecker MT. Arch Intern Med. 2003;163:972-978
Risk Factors for Unnecessary Antibiotic Use

• 128 patients with suspected pneumonia + negative BAL cx
  – 57 received >4 days empiric abx (mean 9 days)
  – 71 received ≤4 days empiric abx (mean 3 days)

• No differences in baseline characteristics/demographics & clinical outcomes (ICU days, vent-free days, mortality)

• Independent risk factors for prolonged empiric abx:
  – Non-BAL site culture positive [OR 4.7 (1.8-12.7)]
  – *Positive Gram-Stain [OR 3.1 (1.1-9.2)]*
How Common are SIRS, Sepsis and Severe Sepsis in the ICU?

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

Rangel-Frausto *JAMA* 273: 117, 1995
Challenges related to Antimicrobial Use: ANTIBIOTIC AVAILABILITY
A PERFECT STORM
As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant Staphylococcus aureus. VRE, vancomycin-resistant Enterococcus. FQR, fluoroquinolone-resistant Pseudomonas aeruginosa.
• Meropenem
• Imipenem
• Cefepime
• Piperacillin-Tazobactam
• Vancomycin

Nationwide Shortage
(As of September 2015)
Why the Shortages?

• Manufacturing Quality Issues

• Manufacturing Cessation

• Company Mergers

• Product Divestures
Antimicrobial Market Shortages

Root Cause

• Meropenem
  – Supplier A
    • Produces 70% of the US supply of meropenem
    • Experiences Water Quality Issue from API source in India
  – Suppliers B & C
    • Cannot keep pace with national demand
  – Suppliers A,B,C
    • Inability to ramp immediately up production
      – FDA Approval
      – Difficult process to produce lyophilized power
      – 3-6 month quarantine of new product

Meropenem Shortage

Mitigation Strategy

• Reserve for documented/confirmed infections due to multi-drug resistant *Pseudomonas* resistant to other beta-lactam antibiotics

• Restrict ALL carbapenem use to *targeted/definitive* indications where culture & susceptibility data is available and the presence of multi-drug resistant (MDR) pathogens has been confirmed
  – Avoid use of carbapenems if the identified pathogen is susceptible to other non-carbapenem agents.
  – Use susceptibility data to deescalate to the most appropriate narrow spectrum alternative when possible
Meropenem Shortage

Mitigation Strategy

• Avoid the empiric use of meropenem for suspected sepsis
  – Exceptions:
    • Existing high rate of MDR gram-negative pathogens within a given geographical patient care unit
    • History of colonization or high-risk of resistant infection

• Enforce defined courses of therapy for diagnosed infections with MDR pathogens
Challenges related to Antimicrobial Use: HIGH ACQUISITION COSTS
New Antimicrobials → Cost Prohibitive?

- Avycaz (ceftazidime/avibactam) → $1,000 per day
- Zerbaxa (ceftolozane/tazobactam) → $250 per day
- Dalvance (dalbavancin) → Two dose - $4,400 per course
- Orbactiv (oritavancin) → Single dose - $3,000 per course
High Costs NOT Limited to New Antibiotics

• Generic minocycline injection
  – Originally Approved October 1972
  – December 2012 - $60 per 100 mg vial

• Medicines Co.
  – SNDA approved March 2015 for “reformulation”
  – Today - $150 per 100 mg vial
• CMS can require adoption of an antibiotic stewardship program as a Condition of Participation (CoP)

• Federal agencies should require implementation of antibiotic stewardship programs as a condition for receiving Federal funding for health care delivery
1.C. 9 The hospital has written policies and procedures whose purpose is to improve antibiotic use (antibiotic stewardship).

1.C. 1 1 The hospital’s antibiotic stewardship policy and procedures requires practitioners to document in the medical record or during order entry an indication for all antibiotics, in addition to other required elements such as dose and duration.

1.C. 1 2 The hospital has a formal procedure for all practitioners to review the appropriateness of any antibiotics prescribed after 48 hours from the initial orders (e.g., antibiotic time out).

1.C. 1 3 The hospital monitors antibiotic use (consumption) at the unit and/or hospital level.
Infection Reduction Strategies Including Antibiotic Stewardship Protocols in Surgical and Trauma Intensive Care Units Are Associated with Reduced Resistant Gram-Negative Healthcare-Associated Infections

Marcus J. Dortch, Sloan B. Fleming, Rondi M. Kauffmann, Lesly A. Dossett, Thomas R. Talbot, and Addison K. May
SICU/TICU Protocols

- **AB Stewardship Protocols**
  - **AB Rotation**
  - AB De-escalation
  - AB Prophylaxis
    - Peri-operative prophylaxis
    - ICP Monitor
    - Traumatic Orthopedic Fractures
    - Penetrating Abdominal Trauma
    - Craniofacial Trauma
  - Dx/Rx of pneumonia
    - Bronchoscopy/Quantitative BAL
  - Dx/Rx of sepsis
  - Rx fungal infections
  - Hand Hygiene Program
  - Transfusion guidelines
  - Intensive Insulin Protocol
  - Skin breakdown risk assessment protocol
  - Critical Care Nutrition Guidelines
  - VAP Bundle
    - Head of bed elevation
    - Oral hygiene
    - Daily spontaneous breathing screening and trials
    - ICU Sedation/Analgesia – RASS Scale
    - Stress Ulcer/DVT Prevention
  - Central line insertion & management
  - Lung protective ventilator protocol
Percentage of Pan-Sensitive and Multidrug resistant pathogens in the VUMC - SICU between 2001 - 2008

Combined broad spectrum AB usage in the SICU 2001 to 2008

**Significant reduction in broad spectrum use over time**

Linear Coefficient -0.09 (95% confidence interval -0.11 to -0.08, p<0.001)

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Quarter</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Quarter</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Quarter</th>
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<td><strong>TICU</strong></td>
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<td>PNEU (Day 1-3)</td>
<td>Ceftriaxone</td>
<td>Ampicillin/Sulbactam</td>
<td>Levofloxacin</td>
<td>Ertapenem</td>
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<td>PNEU (Day ≥4)</td>
<td>Tobramycin/Levofloxacin</td>
<td>Tobramycin/Impinenem</td>
<td>Tobramycin/Cefepime</td>
<td>Tobramycin/Piperacillin/Tazobactam</td>
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<tr>
<td>Excluded AB Class</td>
<td>CARB</td>
<td>FQ</td>
<td>BLIC</td>
<td>CEPH</td>
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<td><strong>SICU</strong></td>
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<td>Levofloxacin</td>
<td>Piperacillin/Tazobactam</td>
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<tr>
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<td>BLIC</td>
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<td>CEPH</td>
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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>
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</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