MANAGING ANTIBIOTIC THERAPY

ITS MORE THAN JUST ABOUT THE ‘S’ AND THE ‘R’

Larry M. Bush, MD, FACP
Affiliated Professor of Biomedical Science
Charles E. Schmidt College of Medicine
Florida Atlantic University

Affiliated Associate Professor of Medicine
University of Miami-Miller School of Medicine
“LETS FACE IT……
WE ARE OBSESSED WITH PRESCRIBING ANTIBIOTICS”

IN FACT, THE CDC SAYS THAT APPROXIMATELY 50% OF HOSPITALIZED PATIENTS RECEIVE ONE ANTIBIOTIC OR ANOTHER SOMETIME DURING THEIR STAY

AND.. EVEN THOUGH ABOUT 90% OF ALL RESPIRATORY OUTPATIENT INFECTIONS ARE CAUSED BY VIRUSES, ALMOST 70% OF PATIENTS ARE GIVEN AN ANTIBIOTIC, OFTEN BROAD SPECTRUM DRUGS i.e. fluoroquinolones
HOWEVER...THE CDC ALSO SAYS THAT ABOUT 50% OF THESE ANTIBIOTICS USED IN THE HOSPITAL ARE EITHER INCORRECTLY USED OR UNWARRANTED...

and FURTHERMORE...

The major instigating factors for the exponential rise in antimicrobial RESISTANCE is OUR OVER PRESCRIBING of this precious resource...along with their use in animal feeds...

To the point that approximately 2 Million persons become ill every year with antibiotic-resistant infections, and about 23,000 die!
The Unintended Deleterious Consequences of the ‘Routine’ Urinalysis

Larry M. Bush, MD\textsuperscript{a,b}
Maria T. Vazquez-Pertiejo, MD\textsuperscript{c}
\textsuperscript{a}Charles E. Schmidt College of Medicine
Florida Atlantic University
Boca Raton
\textsuperscript{b}University of Miami-Miller School of Medicine
Palm Beach County
Fla
\textsuperscript{c}Department of Pathology and Laboratory Medicine
Wellington Regional Medical Center
BlueHealth, LLC
Palm Beach County
Fla
SO THEN....
HOW DID WE GET TO THIS POINT....

AND WHAT ARE WE (YOU) GOING TO DO
to correct it?
KEEP IN MIND....

THE WORLD OF MEDICINE WAS CHANGED BY

SANITATION & IMMUNIZATION
FIRST OFF...LETS ALL BE TALKING ‘APPLES to APPLES’

..does it fascinate you as it does me that when one considers that the human body is comprised of approx. $10^{12}$ cells, and that located either within and/or on the surface of a human exists an estimated $10^{15}$ virions and $10^{13}$ bacteria (the indigenous microbiome).

..it is *astonishing* yet comforting to realize that Clinical Infectious Disease is actually an INFREQUENT EVENT!

..the question our patients should ask is..why have I not gotten more infections, rather than what we all hear..”HOW AND WHY did I get this”
LET'S KEEP THE ‘APPLE’ TERMS STRAIGHT

**INFECTION** *(COLONIZATION)* — A ‘BUG’ WITHIN OR ON A HOST, PERSISTENT OR TRANSIENT AND CAUSES NO HARM.

**INFECTIOUS DISEASE** — INTERACTION WITH THE ‘BUG’ CAUSES HARM TO THE HOST, ALTERS PHYSIOLOGY AND LEADS TO SIGNS AND SYMPTOMS.

**PATHOGEN** — A ‘BUG’ THAT HAS THE CAPACITY TO CAUSE DISEASE. ALMOST ALWAYS FROM THE ENDOGENOUS MICRO-FLORA ..so why the common question, how, why, and where did I get this infection from?

**VIRULENCE** — PROVIDES A QUANTITATIVE MEASURE OF A ‘BUG’S’ CAPACITY TO CAUSE DISEASE (i.e. Staph aureus, encapsulated Pneumococcus / Meningococcus, C dif toxins)
I CAN NOT STAND THE PHRASE... 
"PERCEPTION IS REALITY"...

REALITY IS REALITY... BUT WE ALL HAVE TO LIVE WITH OUR PATIENTS PERCEPTIONS EACH AND EVERY DAY

..."JUST TELL ME I DON’T HAVE MRSA, THEY TOLD ME YOU CAN NEVER GET RID OF IT”

..."OH NO, A POSITIVE TB SKIN TEST, I THOUGHT TUBERCULOSIS WAS ONLY IN THEM”

..."ZIKA, EBOLA... WERE ALL DOOMED”

..."GIVE ME (OR HERE, TAKE) THE ANTIBIOTIC, JUST TO BE SAFE.. IT CAN’T HURT”
BUT THIS IS THE ONE most misunderstood by patients, administrators, health-care agencies and regulatory bodies...AND FRANKLY... BY MANY OF OUR COLLEAGUES

‘SEPSIS’

…”THANK GOODNESS I DON’T HAVE ‘SEPSIS’, BUT JUST PNEUMONIA”
SEPSIS - WHAT REALLY IS THIS CONDITION ANYWAY?

EARLY 1980’S – SEPSIS IS ‘ENDOTOXEMIA’, HOW DO YOU REALLY MEASURE THAT

‘SEPTICEMIA’...THE ONGOING MISCONCEPTION OF BACTEREMIA

And then in 1991, and for 25 years thereafter..

The almost ‘religious’ adoption that ‘sepsis’ was...

‘THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

2 OR MORE OF: HR>90/MIN, RR>20/MIN, TEMP>100.4F or <96.8F, WBC>12,000 or <4,000 OR >10% Band forms
...BUT FINALLY IN FEBRUARY, 2016 (JAMA) WE GOT...

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

an actual **DEFINITION** of what ‘SEPSIS’ actually is...no longer clinical criteria alone

“**LIFE THREATENING ORGAN DYSFUNCTION** caused by a **DYSREGULATED HOST RESPONSE to INFECTION** (proven or suspected)...based on **PATHOBIOLOGY**

Leads to prolonged ICU stays and a significant risk of dying, 10% mortality
‘SEPSIS’ WHAT’S IN and WHAT’S OUT

OUT....SIRS and SEVERE SEPSIS... the reasons are

1- all based on clinical signs/symptoms, no definition
2- too sensitive, not specific enough
3- 50% have appropriate adaptive response, not dying
4- 1 in 8 missed organ failure and risk of death
5- all ‘sepsis’ is severe (10% mortality), why separate term

...but let’s remember that...

1- since the incorporation of SIRS, less sepsis mortality

??????? denominator increase
OUT……NO MORE, TOSSED UNDER THE BUS

Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:
- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or PaCO₂ <32 mm Hg (4.3 kPa)
- White blood cell count >12 000/mm³ or <4000/mm³
  or >10% immature bands

From Bone et al.⁹
‘SEPSIS’…WHAT’S IN and WHAT’S OUT

IN…NEW CLINICAL CRITERIA, INFECTION with ORGAN DYSFUNCTION

Identified as an ACUTE CHANGE in total ‘SOFA’ SCORE >2
CONSEQUENT TO INFECTION

‘SOFA’

SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT SCORE

RESPIRATION, COAGULATION, LIVER, CARDIOVASCULAR CNS, RENAL

ONLY validated for ICU PATIENTS and ALL BEGIN with SCORE = 0
unless known underlying abnormalities in parameters
<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td></td>
<td>Pao_{2}/FiO_{2} (mm Hg (kPa))</td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td>Platelets, ×10^{3}/μL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>Pao_{2}/FiO_{2} (mm Hg (kPa))</td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
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<tr>
<td>Coagulation</td>
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<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>Creatinine, mg/dL (μmol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>Urine output, mL/d</td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
QUICK ‘SOFA’…..qSOFA

EMERGENCY DEPARTMENT and GENERAL WARD
BEDSIDE EVALUATION

‘HAT’ ........

1- HYPOTENSION – SYSTOLIC BP ≤100 mm/hg
2- ALTERED MENTAL STATUS – GLASGOW COMA SCORE <15
3- TACHYPNEA – RESP RATE >22 / min

>2 OF THE PARAMETERS SERVE AS QUALIFIERS AND ELIMINATE THE NEED FOR LABORATORY TESTING
The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.
....and now ‘**SEPTIC SHOCK**’ is....

..a **SUBSET OF SEPSIS**, in which **UNDERLYING CIRCULATORY**

and **CELLULAR / METABOLIC ABNORMALITIES** are

PROFOUND enough to

**SUBSTANTIALLY INCREASE MORTALITY** (currently 42%)

....in other words...’**BAD SEPSIS’**
and for ‘SEPTIC SHOCK’

Having ‘SEPSIS” ……and 2 THINGS

The Need for Vasopressor medications to
Maintain a Mean Arterial Pressure(MAP) >65 mmHg

Serum LACTATE level >2 mmol/L
THE ISSUES WITH SEPSIS-3

1- **MAY BE TOO SENSITIVE AND LEAD TO UNWWARRANTED ANTIBIOTICS**
   (or, so what else is new !!)

2- **HOW TO MEASURE A DYSREGULATED HOST RESPONSE**
   (or, when does this transition from regulated and helpful to dysregulated and harmful ??)

3- **THE WHOLE CONCEPT IS PREDICATED ON INFECTION BEING THE TRIGGER**
   (they could not define infection, but relied on any patient having cultures sent and given antibiotics...how well has that worked out until now ??)

4- **REQUIRES CLINICAL PROMPTS FROM RNs, etc.**
   (here comes ‘code sepsis’ and more telephone random orders !)
AND IT IS STILL DEFINED AND CODED DIFFERENTLY BY:

CDC

JOINT COMMISION

CMS

HOSPITAL QUALITY MEASURES
Antibiotics

- We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock. (strong recommendation, moderate quality of evidence).
- We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens. (strong recommendation, moderate quality of evidence).
Antibiotics

- We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.
  - (Weak recommendation; low quality of evidence)
Antibiotics

- We suggest that combination therapy not be routinely used for on-going treatment of most other serious infections, including bacteremia and sepsis without shock.
  - (Weak recommendation; low quality of evidence).

- We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia.
  - (Strong recommendation; moderate quality of evidence).
..NOW TELL ME THIS IS NOT A COMMON EVERYDAY EVENT!

Systematic Review and Metaanalysis of Acute Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam

Drayton A. Hammond,¹ ¹² Melanie N. Smith,³ Chenghui Li,¹ Sarah M. Hayes,⁴ Katherine Lusardi,² and P. Brandon Bookstaver⁵

¹Department of Pharmacy Practice, University of Arkansas for Medical Sciences, College of Pharmacy, and ²Department of Pharmacy, University of Arkansas for Medical Sciences Medical Center, Little Rock; ³Department of Pharmacy, Medical University of South Carolina, Charleston; ⁴Department of Pharmacy, University of Minnesota Medical Center, Minneapolis; and ⁵Department of Clinical Pharmacy and Outcome Sciences, College of Pharmacy at the University of South Carolina, Columbia
THE FACT IS

- THE ADMINISTRATION OF ADEQUATE ANTIBIOTICS HAS BEEN THE ONLY CLEARLY PROVEN BENEFICIAL INTERVENTION IN LOWERING MORTALITY IN ‘SEPSIS’ AND ‘SEPTIC SHOCK’.
• SO THEN......

HOW DO WE GET IT RIGHT?
The Origins of Antimicrobial Drugs

- **Antibiotics**
  - *metabolic products* of aerobic bacteria and fungi
  - reduce competition for nutrients and space

  - **Bacteria**: *Streptomyces*, *Acromyces* and *Bacillus*
  - **Molds**: *Penicillium* and *Cephalosporium*

- **Antimicrobials**
  - Chemists have created new drugs by altering the structure of naturally occurring antibiotics
Flemming and Penicillin
Plate of *Staphylococcus aureus* inhibited by *Penicillium notatum*
Antibiotics Revolutionized Medicine

• Enable complicated surgery
• Enable cancer chemotherapy
• Enable critical care medicine
• Enable care for premature babies
• Enable organ transplantation
• Changed medicine from a diagnostic profession to a treatment profession
Early Optimism about Antimicrobials

William H. Stewart, U.S. Surgeon General 1965-1969, is purported to have said, “We have closed the book on infectious disease.”
Don’t Lose Forest Through the Trees

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years

All other medical technologies reduced deaths by ~20 per 100,000 over the next 45 years

## Power of Antibiotics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Antibiotic Death Rate</th>
<th>Death With Antibiotics</th>
<th>Change in Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Pneumonia¹</td>
<td>~35%</td>
<td>~10%</td>
<td>-25%</td>
</tr>
<tr>
<td>Hospital Pneumonia²</td>
<td>~60%</td>
<td>~30%</td>
<td>-30%</td>
</tr>
<tr>
<td>Heart Infection³</td>
<td>~100%</td>
<td>~25%</td>
<td>-75%</td>
</tr>
<tr>
<td>Brain Infection⁴</td>
<td>&gt;80%</td>
<td>&lt;20%</td>
<td>-60%</td>
</tr>
<tr>
<td>Skin Infection⁵</td>
<td>11%</td>
<td>&lt;0.5%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

*By comparison...treatment of heart attacks with aspirin or clot busting drugs⁶*  

Antibiotics Are UNIQUE

• They are the only drugs that:
  ➢ lose efficacy over time & must be continually replaced
  ➢ need to be used sparingly to prolong their efficacy
  ➢ we actively discourage use of when they are approved
Antibiotic brands

- 50 penicillin's
- 71 cephalosporins
- 12 tetracycline's
- 8 aminoglycosides
- 1 monobactam
- 5 Carbapenems
- 9 macrolides
- 2 streptogramins
- 3 dihydrofolate reductase inhibitors
- 1 oxazolidinone
- 5.5 quinolones
Figure 1. New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012. Modified from Spellberg 2004 [23].
**Figure 1. Time From Antibiotic Approval or Introduction to Detection of Resistance in Clinical Samples**

<table>
<thead>
<tr>
<th>Class</th>
<th>Antibiotic</th>
<th>Year of Approval or Introduction to Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Penicillin</td>
<td>1942</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>1960</td>
</tr>
<tr>
<td></td>
<td>Cephalothin</td>
<td>1964</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-clavulanic acid</td>
<td>1984</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Imipenem-cilastatin</td>
<td>1985</td>
</tr>
<tr>
<td>Amphenicols</td>
<td>Chloramphenicol</td>
<td>1950</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Tetracycline</td>
<td>1953</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Streptomycin</td>
<td>1946</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin</td>
<td>1952</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>1958</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Nalidixic acid</td>
<td>1964</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Quinupristin-dalfopristin</td>
<td>1999</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>2000</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>Daptomycin</td>
<td>2003</td>
</tr>
</tbody>
</table>

[Bar chart showing years from approval or introduction to market to first clinical report of resistance]
A Changing Landscape for Numbers of Approved Antibacterial Agents

Bars represent number of new antimicrobial agents approved by the FDA during the period listed.

Antibiotic Resistant Problems

Target the ESKAPE Bacteria

- *Enterococcus* (VRE)
- *S. aureus* (MRSA)

Primary Unmet Medical Needs

- *Klebsiella*
- *Acinetobacter*
- *Pseudomonas*
- ESBL (e.g., *E. coli*, *Enterobacter*)

#1) R to almost all agents

#2) R to all oral agents
10 × ’20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America

Helen W. Boucher,1 George H. Talbot,2 Daniel K. Benjamin Jr.,3,4 John Bradley,5,6 Robert J. Guidos,7 Ronald N. Jones,8,9 Barbara E. Murray,10 Robert A. Bonomo,11,12,13,14 and David Gilbert,15,16 for the Infectious Diseases Society of America8

1Division of Geographic Medicine and Infectious Diseases, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts; 2Talbot Advisors, Anna Maria, Florida; 3Duke University School of Medicine, and 4Duke Clinical Research Institute, Durham, North Carolina; 5Division of Infectious Diseases, Children’s Hospital San Diego, and 6Division of Infectious Diseases, Department of Pediatrics, University of California, San Diego; 7Infectious Diseases Society of America, Arlington, Virginia; 8JMI Laboratories, North Liberty, Iowa; 9Tufts University School of Medicine, Boston, Massachusetts; 10Division of Infectious Diseases, University of Texas Medical School at Houston; 11Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, and Departments of 12Medicine, 13Pharmacology, and 14Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio; and 15Division of Infectious Diseases, Providence Portland Medical Center, and 16Oregon Health & Science University, Portland, Oregon
NONINFERIORITY TRIALS

• How do we claim the need for new antibiotics is based on the lack of efficacy of older agents in diseases, because of resistant pathogens, and then design the trial such as to show “how much less effective” a new drug might be compared with the older drug whose effectiveness is in doubt?
<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>INDICATION</strong></th>
<th><strong>APPROVED</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbavancin (Dalvance)</td>
<td>Skin &amp; Soft Tissue (MRSA)</td>
<td>May 2014</td>
</tr>
<tr>
<td>Oritavancin (Orbactiv)</td>
<td>Skin &amp; Soft Tissue (MRSA)</td>
<td>August 2014</td>
</tr>
<tr>
<td>Tedizolid (Sivextro)</td>
<td>Skin &amp; soft Tissue (MRSA)</td>
<td>June 2014</td>
</tr>
<tr>
<td>Ceftaroloxine (Teflaro)</td>
<td>SSTI (MRSA), Pneumonia</td>
<td>October 2010</td>
</tr>
<tr>
<td>Ceftolozane-tazobactam (Zerbaxa)</td>
<td>Intra-Abdominal, UTI</td>
<td>December 2014</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam (Avycaz)</td>
<td>Intra-Abdominal, UTI</td>
<td>February 2015</td>
</tr>
<tr>
<td>Bedaquiline (Sirturo)</td>
<td>Drug-Resistant TB</td>
<td>December 2012</td>
</tr>
<tr>
<td>Obiltoxaximab (Anthim)</td>
<td>Inhalation Anthrax</td>
<td>March 2016</td>
</tr>
<tr>
<td>Bezlotoxumab (Zinplava)</td>
<td>Reduce C. Difficle Recurrence</td>
<td>October 2016</td>
</tr>
</tbody>
</table>
# Antibacterial Agents in Clinical Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solithromycin (Solithera)</td>
<td>Macrolide</td>
<td>Decision Pending</td>
<td>Community Pneumonia</td>
</tr>
<tr>
<td>Aztreonam-Avivactam</td>
<td>Monobactam-Novel Beta-lactamase Inhib</td>
<td>Phase 2</td>
<td>Intra-Abdominal Infections</td>
</tr>
<tr>
<td>Fosofmycin (IV)</td>
<td>Epoxide</td>
<td>Phase 2</td>
<td>Complicated UTIs</td>
</tr>
<tr>
<td>S-649266</td>
<td>Siderophore Cephalosporin</td>
<td>Phase 3</td>
<td>HAP / VAP, Bacteremia, UTIs</td>
</tr>
<tr>
<td>Imipenem-Relebactam</td>
<td>Carbapenem-Beta-lactamase Inhib</td>
<td>Phase 3</td>
<td>Intra-Abdominal Infections, UTIs, HAP / VAP</td>
</tr>
<tr>
<td>Meropenem-Vaborbactam</td>
<td>Carbapenem-novel boronic Beta-lactamase Inhib</td>
<td>Phase 3</td>
<td>Intra-Abdominal Infections, UTIs, HAP / VAP, Febrile Neutropenic</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Tetracycline</td>
<td>Phase 3</td>
<td>Intra-Abdominal Infections, UTIs</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Phase 3</td>
<td>UTIs, Bacteremia HAP / VAP (CREs)</td>
</tr>
</tbody>
</table>
SO WHY ALL THE RESISTANCE
Inappropriate Antimicrobial Use

- Prescription not taken correctly
- Antibiotics for viral infections
- Antibiotics sold without medical supervision
- Spread of resistant microbes in hospitals due to lack of hygiene

(Chart: Unnecessary Antibiotic Prescriptions)

More than 50 million unnecessary antibiotic prescriptions are written each year for patients outside of hospitals, according to estimates by the Centers for Disease Control and Prevention.
Cumulative clinical experience from over a decade of use of levofloxacin in urinary tract infections: critical appraisal and role in therapy

Larry M Bush¹,²
Fredy Chaparro-Rojas³
Victor Oke³
Joseph Etienne³

¹Charles E Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; ²University of Miami Miller School of Medicine, Miami, FL; ³Internal Medicine, University of Miami Miller School of Medicine Affiliated Program at JFK Medical Center, Atlantis, FL, USA

Abstract: The treatment of urinary tract infections (UTIs) continues to evolve as common uropathogens increasingly become resistant to previously active antimicrobial agents. In addition, bacterial isolates, which were once considered to be either colonizers or contaminants, have emerged as true pathogens, likely related to the more complex array of settings where health care is now delivered. Even though the reliability of many antimicrobial agents has become less predictable, the fluoroquinolone group of agents has remained a frequent, if not the most often prescribed, antimicrobial therapy for almost all types of UTIs. Levofloxacin has taken its position at the top of the list as one of the most regularly administered fluoroquinolone agents given to patients with a suspected or proven UTI. The authors review the clinical experience of the use of levofloxacin over the past decade and suggest that the use of levofloxacin for the treatment of UTIs, although still fairly dependable, is perhaps not the best use of this important antimicrobial agent.

Keywords: fluoroquinolone, antimicrobial agent, UTI, resistance
Skin and Soft-Tissue Infections Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

Timothy C. Jenkins,14 Allison L. Sabel,35 Ellen E. Sarcone,24 Connie S. Price,14 Philip S. Mehler,234 and William J. Burman14

1Department of Medicine and Division of Infectious Diseases, 2Department of Medicine, and 3Department of Patient Safety and Quality, Denver Health Medical Center, and Departments of 4Medicine and 5Preventive Medicine and Biometry, University of Colorado Denver, Denver

(See the editorial commentary by Spellberg, on pages 904–906.)

Background. Although complicated skin and soft-tissue infections (SSTIs) are among the most common infections requiring hospitalization, their clinical spectrum, management, and outcomes have not been well described.

Methods. We report a cohort of consecutive adult patients hospitalized for SSTI from 1 January through 31 December 2007 at an academic medical center. Cases meeting inclusion criteria were reviewed and classified as cellulitis, cutaneous abscess, or SSTI with additional complicating factors.

Results. In total, 322 patients were included; 66 (20%) had cellulitis, 103 (32%) had cutaneous abscess, and 153 (48%) had SSTI with additional complicating factors. Injection drug use, diabetes mellitus, and alcohol abuse were common comorbidities. Serum inflammatory markers were routinely measured and blood cultures and imaging studies were routinely performed in each group. Of 150 patients with a positive culture result for an abscess, deep tissue, or blood, Staphylococcus aureus or streptococci were identified in 145 (97%). Use of antibiotics with broad aerobic gram-negative activity (61%–80% of patients) or anaerobic activity (73%–83% of patients) was frequent in each group. The median duration of therapy for cellulitis, cutaneous abscess, and SSTI with additional complicating factors was 13 (interquartile range [IQR], 10–14), 13 (IQR, 10–16), and 14 (IQR, 11–17) days, respectively. Treatment failure, recurrence, or rehospitalization due to SSTI within 30 days occurred in 12.1%, 4.9%, and 9.2% of patients, respectively.

Conclusions. Hospitalizations for SSTI were common; more than half were due to cellulitis or cutaneous abscess. Frequent use of potentially unnecessary diagnostic studies, broad-spectrum antibiotic therapy, and prolonged treatment courses in these patients suggest targets for antimicrobial stewardship programs.
Clinical Trial: Comparative Effectiveness of Cephalexin Plus Trimethoprim-Sulfamethoxazole Versus Cephalexin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial

Daniel J. Pallin,1,2 William D. Binder,3 Matthew B. Allen,1,4 Molly Lederman,1,5 Siddharth Parmar,1 Michael R. Filbin,3 David C. Hooper,6 and Carlos A. Camargo Jr3

1Department of Emergency Medicine, Brigham and Women’s Hospital, 2Division of Emergency Medicine, Boston Children’s Hospital, and 3Department of Emergency Medicine, Massachusetts General Hospital, Boston; 4Perelman School of Medicine at the University of Pennsylvania, Philadelphia; 5Department of Pediatrics, and 6Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston

(See the Editorial Commentary by Chambers on pages 1763–4.)

Background. Community-associated methicillin-resistant S. aureus (CA-MRSA) is the most common organism isolated from purulent skin infections. Antibiotics are usually not beneficial for skin abscess, and national guidelines do not recommend CA-MRSA coverage for cellulitis, except purulent cellulitis, which is uncommon. Despite this, antibiotics targeting CA-MRSA are prescribed commonly and increasingly for skin infections, perhaps due, in part, to lack of experimental evidence among cellulitis patients. We test the hypothesis that antibiotics targeting CA-MRSA are beneficial in the treatment of cellulitis.
Drugs for Human Treatment are Excreted into Sewage

- Some drugs excreted in metabolized amounts via the urine and feces
- Some yield bioactive metabolites.
- Some excreted as conjugates
STRATEGIES TO REDUCE RESISTANCE (R)

“BLAST THEM”
antibiotic combinations never been shown to reduce emergence of ‘R’ in routine bacteria

“FOOL THEM”
cycling drugs only temporarily changes ‘R’ selection pressure

“STOP IRRITATING THEM”
Best Idea - 3 points

Before Rx begins – only treat true infection

During – avoid combos where single agents suffice

Tail end – only treat as long as needed to cure the infection
Modern Day “Buzz Words”

Evidence Based Medicine

Recommendations graded (strong-very weak) on Quality of Evidence (high-low) from studies

Consensus of Expert Opinions

Published Guidelines

Experience, Anecdotal, Random

What would seem to make Rational Scientific Sense
“APPROPRIATE” ANTIBIOTIC THERAPY

THE USE OF ANTIBIOTICS WITH GOOD OR SUSCEPTIBLE IN-VITRO ACTIVITY AGAINST THE BACTERIA AT THE TISSUE SITE OF INFECTION

i.e. just look for the ‘S, I or R’ on the micro sheet
“ADEQUATE” ANTIMICROBIAL THERAPY

INCLUDES APPROPRIATE PLUS

DESCRIBES THE OPTIMAL THERAPY

BASED UPON DOSAGE, PENETRATION

TO THE SITE OF INFECTION, ROUTE OF

ADMINISTRATION, COMBINATION THERAPY

AND DURATION

i.e. you need to really understand the drug and the infection
APPROPRIATE DOES NOT EQUAL ADEQUATE
Higher Mortality With Inadequate Antibiotic Therapy in Infections Requiring ICU Admission\textsuperscript{1,\textasciitilde}.

Prospective, single-center, cohort study (1997-1998)

\begin{itemize}
  \item Inadequate antimicrobial treatment
  \item Adequate antimicrobial treatment
\end{itemize}

\textbf{Hospital Mortality (%)}

\begin{itemize}
  \item All Cause: 52% (\textit{P}<.001)
  \item Infection Related: 42% (\textit{P}<.001)
\end{itemize}

\textbf{Mortality Type}

ICU=intensive care unit.

\textsuperscript{1}Site of infection includes bloodstream, lung, wound, gastrointestinal tract, urinary tract, and miscellaneous (includes peritoneal infection, meningitis, endocarditis, and infections of the skin and fascia).

Higher Mortality Associated With Inadequate Empirical Antibiotic Therapy in Patients With Pneumonia

Retrospective\(^1\) and prospective,\(^2\) single-center, cohort analyses

![Mortality Graph]

Among patients with healthcare-associated pneumonia, subsequent escalation\(^a\) of antibiotic therapy among patients who received inadequate initial therapy did not result in reduced risk of mortality\(^1\).

\(^a\)Escalation was defined as the switch to or addition of antibiotics with a broader spectrum.

Inadequate Therapy Increases Mortality Among Patients With Bloodstream Infections

Mortality in ICU Patients (%)

<table>
<thead>
<tr>
<th>Adequate Therapy (n=345)</th>
<th>Inadequate Therapy (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>62</td>
</tr>
</tbody>
</table>

$P < .001$

ICU=intensive care unit.

Major isolates: coagulase-negative staphylococci, *Staphylococcus aureus*, and *Candida* species.

SO THEN HOW DOES ONE CHOOSE AN ADEQUATE ANTIBIOTIC?
Many infections are self limited and lead to minimal morbidity and mortality in hosts with normal defense mechanisms.

I.E. They get better in spite of our correct or incorrect antibiotic choice and usage.
In seriously ill patients, because of compromised immune function, anatomic abnormalities or infection with more virulent organisms, the outcome of the infection depends on early institution and correct use of APPROPRAITE AND ADEQUATE antimicrobial therapy.
Empiric Antimicrobial Regimens are based on:

- History and Physical
- Likely site of infection
- Knowledge of pathogens commonly causing infection at that site
- Gram stain of appropriate specimen, modify regimen when pathogen(s) known
The role of antibacterials is to eradicate the causative organisms from the site of infection.
The “New Science”: Pharmacokinetics and Pharmacodynamics

**Concept in Summary:**

- Is there an antibiotic level in blood that predicts bacterial eradication and clinical success?
- If so, what is the optimal profile to maximize bacterial kill?
  - ↑Peak level of Abx = ↑ bacterial kill ?
  - ↑ Length of Time that Abx level exceeds the MIC = ↑ bacterial kill ?
- Once PK/PD requirements are known, one can:
  - √ Calculate appropriate doses of new or existing agents
  - √ Compare antimicrobial activity of existing agents and utilize data in the development of guidelines
  - √ Determine susceptibility of isolated pathogens
**MIC: MINIMAL INHIBITORY CONCENTRATION**

Drug potency is measured by determining lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism after overnight exposure.

Known bacterial inoculum placed into each tube.

- **MIC (MINIMAL INHIBITORY CONCENTRATION):** 4.0 µg/mL

<table>
<thead>
<tr>
<th>Increasing Antibiotic Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 µg/mL</td>
</tr>
<tr>
<td>0.5 µg/mL</td>
</tr>
<tr>
<td>1.0 µg/mL</td>
</tr>
<tr>
<td>2.0 µg/mL</td>
</tr>
</tbody>
</table>
| 4.0 µg/mL                          | **MIC**
| 8.0 µg/mL                          |
| 16 µg/mL                           |
Minimum Inhibitory Concentration

The minimum inhibitory concentration (MIC) is the lowest concentration of a particular drug that inhibits the growth of an organism.

Breakpoints for the interpretation of MIC values are defined independently by the FDA and the CLSI.

- Susceptible
- Intermediate
- Resistant

Nonsusceptible: classification for organisms for which only a susceptible interpretive criterion has been designated because resistant strains are absent or rarely occur.

FDA = Food and Drug Administration; CLSI = Clinical and Laboratory Standards Institute.

PROCEDURE/OTHER SITE CALL TEST: Final
Notification of 1+ WBC, 2+ GRAM POSITIVE COCCI PAIRS AND
CLUSTERS and 1+ GRAM VARIABLE RODS
was taken and read back by: ALICIA PELLO
on 03/29/17 at 0113.
The call was made by BURKE, MARTHA (CL)

WOUND/OTHER CALL TEST: Final
Notification of 1+ WBC, 2+ GRAM-POSITIVE COCCI IN PAIRS AND
CLUSTERS, 1+ GRAM-VARIABLE RODS
was taken and read back by: JNUREW4
on 03/29/17 at 0115.
The call was made by PELLO, ALICIA S

GRAM STAIN: Final
1+ (5-10/slide) WBC(s)
2+ (1-5/0.1 F) Gram Positive Cocci in Pairs in Clusters
1+ (5-10/slide) Gram Variable Rods
Wound call test ordered

SURGICAL CULTURE AER/ANAER: Final
Organism 1
*Enterococcus species
Moderate
Mixed Anaerobic Flora Present

RILLING INFORMATION
No Sensitivity Charge

*MIC mcg/ml INTERPRETATION
AMPICILLIN <=2 S
VANCOMYCIN 2 S
LEVOFLOXACIN 1 S
I suppose it was in part my undergraduate studies in microbiology or perhaps my fortunate encounters during medical school clinical rotations with physicians who possessed a unique command of medical knowledge and an understanding of disease processes that kindled within me a special fascination and interest,

Available evidence indicates that acquired resistance was absent from bacteria collected prior to the antibiotic era [3], thus strongly implying that past and current antimicrobial prescribing patterns serve as the driving force behind the progressive increase in bacterial resistance we are now experiencing. Historically, resistance has been most prevalent in health care settings, particularly in intensive care units, where heavy antibiotic use has had a substantial influence on selective resistance pressures. On the other hand, the more contemporary problems of drug-resistant *Streptococcus pneumoniae*, community-acquired methicillin-resistant *Staphylococcus aureus*, and extended-spectrum β-lactamase–producing Enterobacteriaceae are directly linked to the community, the setting for 80% of current human antimicrobial use [4].
‘TIME DEPENDENT ANTIBIOTICS’

TIME > MIC CORRELATES WITH CLINICAL ADEQUACY

HOW MUCH TIME IS THAT?

MORE IS NOT BETTER, JUST MORE
Pharmacokinetics and Pharmacodynamics: Required information

**Step 1: Determine MIC:**
How much antibiotic is required to inhibit further growth (stasis) *in a test tube?*

- Pathogen broth
- Antibiotic conc. (ug/mL)
- 0.12 0.25 0.5 1.0 2.0 4.0 4.0

**Step 2: Determine Dose:**
How much antibiotic is required *in the blood* to kill the pathogen at its site?
(i.e. What is the correlation between the required serum level in the body and the MIC found in the lab?)

- ABX Conc. (ug/ml)
- MIC
- Time

• How high? (peak level vs MIC)
• How long? (time above MIC)
• How high for how long? (AUC vs MIC)
Predictors of Bacterial Eradication:
Pharmacokinetic/Pharmacodynamic Profiles


- **Quinolones**
- **Aminoglycosides**
- **Azithromycin**

**Time >MIC**
(time-dependent activity)

- Penicillins
- Cephalosporins
- Erythromycin
- Clarithromycin

- **AUC\(_{24}/MIC**
(concentration-dependent activity)

- Quinolones
- Aminoglycosides
- Azithromycin

Optimal profile:
Antibiotic level exceeds MIC for at least 40% of dosing interval

Optimal profile:
AUC/MIC ratio at least:
25-30 (Strep., other gram-positive)
125 (gram-negative bacilli)
The relationship between ‘time above MIC \( \text{MIC}_{90} \)’ and bacteriological cure in *S. pneumoniae* (red) and *H. influenzae* (blue) in otitis media and sinusitis.

Craig & Andes, Pediatr Infect Dis J 15;255,1996
Outcomes of Bacteremia due to *Pseudomonas aeruginosa* with Reduced Susceptibility to Piperacillin-Tazobactam: Implications on the Appropriateness of the Resistance Breakpoint

Vincent H. Tam, Eric A. Gamez, Jaye S. Weston, Laura N. Gerard, Mark T. LaRocco, Juan Pablo Caeiro, Layne O. Gentry, and Kevin W. Garey

1University of Houston College of Pharmacy and 2St Luke’s Episcopal Hospital, Houston, Texas

**Background.** Bacteremia due to *Pseudomonas aeruginosa* is associated with grave clinical outcomes. Recent studies have emphasized the importance of appropriate empirical therapy, but controversy arises when piperacillin-tazobactam is used against isolates with reduced susceptibility.

**Methods.** We performed a retrospective cohort study of pseudomonal bacteremia from 2002 to 2006. Patients were identified by the microbiology laboratory database, and pertinent clinical data (demographic characteristics, baseline Acute Physiology and Chronic Health Evaluation [APACHE] II scores, source of bacteremia, and therapy) were retrieved from the electronic medical records. All patients received appropriate empirical therapy within 24 h of positive culture results. Patients receiving piperacillin-tazobactam were compared with those receiving other agents (control subjects). The primary outcome was 30-day mortality from the first day of bacteremia.

**Results.** A total of 34 bacteremia episodes were identified involving isolates with reduced susceptibility to piperacillin-tazobactam (minimum inhibitory concentration, 32 or 64 mg/L, reported as susceptible). Piperacillin-tazobactam was empirically given in 7 episodes. There was no significant difference in baseline characteristics between the 2 groups. Thirty-day mortality was found to be 85.7% in the piperacillin-tazobactam group and 22.2% in the control group ($P = .004$). Time to hospital mortality was also found to be shorter in the piperacillin-tazobactam group ($P < .001$). In the multivariate analysis, 30-day mortality was found to be associated with empirical piperacillin-tazobactam therapy (odds ratio, 220.5; 95% confidence interval, 3.8–12707.4; $P = .009$), after adjustment for differences in age and APACHE II score.

**Conclusions.** In *P. aeruginosa* bacteremia due to isolates with reduced piperacillin-tazobactam susceptibility, empirical piperacillin-tazobactam therapy was associated with increased mortality. Additional studies are warranted to examine the appropriateness of the current Clinical Laboratory Standards Institute resistance breakpoint of piperacillin-tazobactam.
Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and Aztreonam

Michael N. Dudley, Paul G. Ambrose, Sujata M. Bhavnani, William A. Craig, Mary Jane Ferraro, and Ronald N. Jones for the Antimicrobial Susceptibility Testing Subcommittee of the Clinical and Laboratory Standards Institute

1Rempex Pharmaceuticals, San Diego, California; 2Institute for Clinical Pharmacodynamics, Inc., Latham, New York; 3Department of Medicine, University of Wisconsin School of Medicine, Madison; 4Massachusetts General Hospital and Harvard Medical School, Boston; 5JMI Laboratories, North Liberty, Iowa

Widespread resistance in Enterobacteriaceae and *Pseudomonas aeruginosa* to cephalosporin and monobactam antibiotics due to extended-spectrum β-lactamases (ESBLs) has resulted in the need for reassessment of the interpretative criteria (breakpoints) established for these agents more than 2 decades ago. Following extensive evaluation, the Clinical and Laboratory Standards Institute recently adopted and published new breakpoints for these agents for use in clinical laboratories and provided updated recommendations for use of the ESBL screening test. This paper summarizes the background and supportive rationale for new interpretative criteria for cephalosporins and aztreonam for testing Enterobacteriaceae.
Table 1. Clinical Outcome by Minimum Inhibitory Concentration in 42 Patients With Bacteremia Due to *Escherichia coli* and *Klebsiella pneumoniae* Producing Various β-Lactamases Treated With Cephalosporin Monotherapy

<table>
<thead>
<tr>
<th>MIC, mg/L</th>
<th>% Response</th>
<th>% Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>73</td>
</tr>
<tr>
<td>≥8</td>
<td>11</td>
<td>89</td>
</tr>
</tbody>
</table>
Table 3. Revised and Pre-2010 Clinical and Laboratory Standards Institute Breakpoints for Cephalosporins and Aztreonam for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Drug (Dosage)</th>
<th>Revised MIC (µg/mL)</th>
<th>Pre-2010 MIC (µg/mL)</th>
<th>Revised Disk (mm)</th>
<th>Pre-2010 Disk (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Aztreonam (1 g q8h)</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
<td>≤8</td>
</tr>
<tr>
<td>Cefotaxime (1 g q8h)</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td>≤8</td>
</tr>
<tr>
<td>Ceftazidime (1 g q8h)</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
<td>≤8</td>
</tr>
<tr>
<td>Ceftizoxime (1 g q12h)</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td>≤8</td>
</tr>
<tr>
<td>Ceftriaxone (1 g q24h)</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td>≤8</td>
</tr>
</tbody>
</table>
‘CONCENTRATION DEPENDENT ANTIBIOTICS’

• AUC / MIC CORRELATES WITH CLINICAL ADEQUACY

MORE IS BETTER!
Pharmacokinetic/Pharmacodynamic Predictors of Efficacy

Parameters of Interest:

- AUC/MIC ratio
  - 25: S. pneumoniae, Gram (+)
  - 125: Gram (-) bacilli

C<sub>max</sub> (Peak)

Area = “length x width”

MIC = “how much abx is required to inhibit growth in a test tube”

**AUC:MIC ratio** (area under the curve:MIC ratio): Quinolones, Aminoglycosides and Azithromycin

Concentration-dependent killing

\[
\text{AUC}_{24}: \text{MIC ratio} \\
25-30 = \text{gm (+)} \\
125 = \text{gm (-)}
\]
Relationship between Antibiotic concentration (24-Hr AUC/MIC) and Mortality in Immunocompetent Animals infected with S. pneumoniae using Fluoroquinolones

Mortality (%)

24-hr AUC/MIC

Craig WA. Presented at ICAAC. 2000.
Effect of Differences in MIC Values on Clinical Outcomes in Patients with Bloodstream Infections Caused by Gram-Negative Organisms Treated with Levofloxacin

Robyn DeFife,¹ Marc H. Scheetz,¹,²* Joc M. Feinglass,³ Michael J. Postelnick,¹ and Kimberly K. Scarsi⁴

Department of Pharmacy, Northwestern Memorial Hospital, Chicago, Illinois¹; Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, Downers Grove, Illinois²; Division of Internal Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois³; and Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, Illinois⁴

Received 2 May 2008/Returned for modification 30 August 2008/Accepted 8 December 2008

Emerging evidence suggests that current fluoroquinolone dosing strategies may be inadequate to treat bloodstream infections caused by organisms classified as sensitive. This study sought to determine if differences in MICs for levofloxacin-susceptible gram-negative organisms correlate with differences in patient outcomes. A retrospective cohort study evaluated patients treated with levofloxacin for bloodstream infections caused by susceptible gram-negative organisms. Patients infected with gram-negative organisms for which MICs indicated susceptibility were categorized into three groups: those with organisms for which MICs were low (≤0.25 mg/liter), intermediate (0.5 mg/liter), and high (1 or 2 mg/liter). Patients were evaluated for baseline similarity, all-cause mortality, and measurements of morbidity. A total of 404 patients with bloodstream infections caused by gram-negative organisms were identified. Of these patients, 312 were treated with levofloxacin and included in the analysis. No significant difference in all-cause mortality among the three groups was observed. The high-MIC group had a significantly longer average hospital stay postculture than the low- and intermediate-MIC groups (16.4 days versus 7.3 and 7.9 days; $P < 0.01$) and a significantly longer duration of infection (2.1 days versus 1.0 and 1.2 days; $P < 0.001$). Multivariate analysis adjusting for covariates revealed that a high MIC was associated with an increase of 5.67 days (95% confidence interval, 0.77 to 10.62 days; $P = 0.02$) in the mean length of stay postculture compared to the mean length of stay for the low-MIC group. Patients treated with levofloxacin for bloodstream infections caused by gram-negative organisms for which MICs were elevated, yet still in the susceptible category, had worse outcomes than similar patients infected with organisms for which MICs were lower. In vitro susceptibility classifications of fluoroquinolones for the treatment of bloodstream infections caused by gram-negative organisms require further study.
Vancomycin Utilization Over 20 Years

Time-Kill Curves* for Nafcillin and Vancomycin at 4 Times the MIC

*10 clinical isolates of S. aureus.

Rapid *In Vitro*\(^a\) Bactericidal Activity Against MRSA

Daptomycin vs Vancomycin

![Graph showing the bactericidal activity of Daptomycin and Vancomycin against MRSA over time.](graph)

- **Daptomycin (4×MIC)**
- **Vancomycin (8×MIC)**
- **Control**

**CFU/mL** vs **Time (h)**

- Limit of detection

---

Daptomycin MIC=0.5 µg/mL; vancomycin MIC=1.0 µg/mL.

MRSA=methicillin-resistant *Staphylococcus aureus*; CFU=colony forming unit; MIC=minimum inhibitory concentration.

\(^a\)The clinical significance of *in vitro* data has not been established.

Consequences of Increasing Vancomycin Utilization

- Susceptible but higher vancomycin MICs
- Heterogeneous (heteroresistant) vancomycin-intermediate *Staphylococcus aureus* (hVISA)
- Vancomycin-intermediate *S. aureus* (VISA)
- Vancomycin-resistant *S. aureus* (VRSA)

MICs=minimum inhibitory concentrations.

Increasing Prevalence of Vancomycin MIC of 1 µg/mL Among Staphylococcus aureus Isolates

Retrospective Single Center Study (n=6003)

MIC=minimum inhibitory concentration; MRSA=methicillin-resistant S. aureus; MSSA=methicillin-susceptible S. aureus.

Relationship of MIC to Vancomycin Treatment Failures in MRSA Infections

Probability of Achieving an AUC/MIC >400 With High- and Low-Dose Vancomycin\textsuperscript{1,2}

Vancomycin pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Mean Trough</th>
<th>Mean AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (troughs &lt;15 µg/mL) (n=68)</td>
<td>9.4±3.2\textsuperscript{a}</td>
<td>318±111\textsuperscript{a}</td>
</tr>
<tr>
<td>High dose (troughs ≥15 µg/mL) (n=34)</td>
<td>20.4±3.2\textsuperscript{a}</td>
<td>418±152\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}P<.001; \textsuperscript{b}By Monte Carlo simulation; \textsuperscript{c}Determined by Clinical and Laboratory Standards Institute Kirby-Bauer disk diffusion methods. AUC=area under the curve; MIC=minimum inhibitory concentration.

Therapeutic Efficacy of Vancomycin in Relation to MIC and Bactericidal Activity

Vancomycin in MRSA Bacteremia

**Vancomycin MIC (μg/mL)**
- \( \leq 0.5 \) (n=9): 56, \( P = .01 \)
- 1.0-2.0 (n=21): 10

**Log\(_{10}\) of Killing (CFU/mL)**
- <4.71 (n=9): 0
- 4.71-6.26 (n=13): 23, \( P = .05 \)
- ≥6.27 (n=8): 50, \( P = .029 \)

MIC = minimum inhibitory concentration; MRSA = methicillin-resistant Staphylococcus aureus; CFU = colony forming units.

Vancomycin Treatment Response by Vancomycin MIC

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin MIC (µg/mL)</td>
<td>≤0.5ᵃ</td>
<td>52.4</td>
<td>62</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>0.5ᵇ</td>
<td>29.4</td>
<td>62</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>&gt;1ᶜ</td>
<td>2.0</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Vancomycin Treatment Success Rates (%)

- ¹Determined by agar dilution; ᵇDetermined by broth dilution; ᶜDetermined by Etest.
- MRSA = methicillin-resistant Staphylococcus aureus; MIC = minimum inhibitory concentration.

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

S. J. van Hal, T. P. Lodise, and D. L. Peterson

Background. Emerging data suggest that vancomycin may be less effective against serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections with minimum inhibitory concentration (MIC) values at the higher end of the susceptibility range. The purpose of this review is to examine the strength of these associations.

Methods. All relevant studies pertaining to treatment outcomes or mortality associated with vancomycin MIC were retrieved from the medical literature from January 1996 through August 2011 and analyzed according to Cochrane guidelines.

Results. Of the 270 studies identified, 48 studies were reviewed, with 22 studies included in the final meta-analysis. Vancomycin MIC was significantly associated with mortality for MRSA infection irrespective of the source of infection or MIC methodology (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.14–2.32; \( P < .01 \)). This mortality association was predominantly driven by bloodstream infections (BSIs; OR, 1.58; 95% CI, 1.06–2.37; \( P = .03 \)) and isolates with a vancomycin MIC of 2 \( \mu \)g/mL by Etest (OR, 1.72; 95% CI, 1.34–2.21; \( P < .01 \)).

Vancomycin MIC was significantly associated with treatment failure irrespective of source of infection or MIC methodology (OR, 2.69; 95% CI, 1.60–4.43; \( P < .01 \)).

Conclusion. High vancomycin MIC was associated with a higher mortality rate in MRSA BSI. Thus, institutions should consider conducting Etest MIC on all MRSA BSI isolates. Although these data highlight concerns about vancomycin, currently, there are no data to support better survival rates with alternative antibiotics. Data are sorely needed to determine whether other agents can remedy these outcomes observed with vancomycin for MRSA infections with elevated vancomycin MIC values.

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a major public concern. Hospital-acquired MRSA infection rates have steadily increased over the past 25 years, and the bacterial strain is making inroads to the community [1–6]. Vancomycin is currently the cornerstone of therapy for serious infections caused by this pathogen. Although vancomycin has been widely used in the treatment of MRSA infection for the past 2 decades [7], the majority of MRSA strains have remained susceptible to vancomycin at the current minimum inhibitory concentration (MIC) susceptibility breakpoint designated by the Clinical Laboratory Standards Institute (CLSI) [2]. It has taken approximately 40 years for the first isolates with reduced susceptibility to glycopeptides to emerge.
The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in Staphylococcus aureus Infections: A Systematic Review and Meta-analysis

S. J. van Hal, T. P. Lodise, and D. L. Peterson

Background. Emerging data suggest that vancomycin may be less effective against serious methicillin-resistant Staphylococcus aureus (MRSA) infections with minimum inhibitory concentration (MIC) values at the higher end of the susceptibility range. The purpose of this review is to examine the strength of these associations.

Methods. All relevant studies pertaining to treatment outcomes or mortality associated with vancomycin MIC were retrieved from the medical literature from January 1996 through August 2011 and analyzed according to Cochrane guidelines.

Results. Of the 271 studies identified, 48 studies were reviewed, with 22 studies included in the final meta-analysis. Vancomycin MIC was significantly associated with mortality for MRSA infection irrespective of the source of infection or MIC methodoloy (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.14–2.32; P < .01). This mortality association was predominantly driven by bloodstream infections (BSIs; OR, 1.58; 95% CI, 1.06–2.37; P = .03) and isolates with a vancomycin MIC of 2 μg/mL by Etest (OR, 1.72; 95% CI, 1.34–2.21; P < .01). Vancomycin MIC was significantly associated with treatment failure irrespective of source of infection or MIC methodology (OR, 2.69; 95% CI, 1.60–4.51; P < .01).

Conclusion. High vancomycin MIC was associated with a higher mortality rate in MRSA BSI. Thus, institutions should consider conducting Etest MICs on all MRSA BSI isolates. Although these data highlight concerns about vancomycin, currently, there are no data to support better survival rates with alternative antibiotics. Data are sorely needed to determine whether other agents can remedy these outcomes observed with vancomycin for MRSA infections with deviated vancomycin MIC values.

Infections caused by methicillin-resistant Staphylococcus aureus (MRSA) are a major public concern. Hospital-acquired MRSA infection rates have steadily increased over the past 25 years, and the bacterial strain is making inroads to the community [1–6]. Vancomycin is currently the cornerstone of therapy for serious infections caused by this pathogen. Although vancomycin has been widely used in the treatment of MRSA infection for the past 2 decades [7], the majority of MRSA strains have remained susceptible to vancomycin at the current minimum inhibitory concentration (MIC) susceptibility breakpoint designated by the Clinical Laboratory Standards Institute (CLSI) [8]. It has taken approximately 40 years for the first isolates with reduced susceptibility to glycopeptides to emerge.
Is It Time to Replace Vancomycin in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections?

Sebastiaan J. van Hal\textsuperscript{1,2} and Vance G. Fowler Jr\textsuperscript{3,4}

\textsuperscript{1}Department of Microbiology and Infectious Diseases, Royal Prince Alfred Hospital, Camperdown, Sydney, and \textsuperscript{2}Antibiotic Resistance and Mobile Elements Group, Microbiology and Infectious Diseases Unit, School of Medicine, University of Western Sydney, Australia; \textsuperscript{3}Duke University Medical Center, and \textsuperscript{4}Duke Clinical Research Institute, Durham, North Carolina

For more than 4 decades, vancomycin has been the antibiotic of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Recently, infections due to isolates with high but susceptible vancomycin minimum inhibitory concentrations have been associated with additional treatment failures and patient mortality. These poorer outcomes may in part be explained by the inability of attaining appropriate vancomycin levels in these patients. However, assumptions that these poor outcomes are solely due to failure to achieve optimal serum levels of vancomycin are premature. The availability of effective alternatives further erodes the position of vancomycin as first-line therapy. The emergence of resistance and cost considerations, however, favor a more measured approach when using alternative antimicrobials. Collectively, the current available data suggest that the optimal therapy for MRSA infections remains unclear. In the absence of further data, the Infectious Diseases Society of America guidelines remain relevant and inform clinicians of best practice for treating patients with MRSA infections.
Drug Acquisition vs Total Costs

Drug acquisition costs are <5% of overall treatment costs for hospitalized MRSA patients\(^1,2\)

LOS=length of stay; MRSA=methicillin-resistant *S. aureus.*
Best Alternative to Vancomycin for Serious Methicillin-Resistant Staphylococcus aureus Infections: Let’s Just Say It

To the Editor—The recently published articles by Patel et al [1], Kullar et al [2], and Lubin et al [3] persuasively bolster the growing consensus opinion that the gold-standard antimicrobial agent for treatment opinion as to what actually is, or likely would be, the best alternative anti-MRSA agent.

Acknowledging the absence of evidence from any head-to-head clinical trials among the relatively new antimicrobial agents with approved MRSA treatment indications (eg, quinupristin–dalfopristin, linezolid, daptomycin, tigecycline, telavancin, and ceftaroline),
Goals of Antimicrobial Stewardship

1. Combat the Emergence of Resistance
2. Control Costs
3. Improve Clinical Outcomes

Antimicrobial Stewardship—A Balancing Act

- Appropriate initial antibiotic treatment
- Avoid unnecessary antibiotics

De-Escalation—A Balancing Act¹

Appropriate initial antibiotic treatment
- Select correct antibiotics
- Consider combination therapy
- Use proper dosing and interval
- Monitor cultures/labs

Avoid unnecessary antibiotics
- Evaluate micro data to narrow scope
- Shorten therapy duration
- Monitor clinical endpoints
- Conduct diagnostic evaluation

¹ Kollef MH. Drugs. 2003;63(20):2157-2168.
...this HAS BEEN TAKING PLACE FOR YEARS

Eight Habits of Highly Effective Antimicrobial Stewardship Programs to Meet the Joint Commission Standards for Hospitals

Debra A. Goff,1 Ravina Kullar,2 Karri A. Bauer,2 and Thomas M. File Jr3

1The Ohio State University Wexner Medical Center, The Ohio State University College of Pharmacy, Columbus, Ohio; 2MRL, Merck & Co., Inc., Kenilworth, New Jersey; and 3Division of Infectious Disease, Northeast Ohio Medical University, and Summa Health, Akron, Ohio

“asking physicians to do a better job at prescribing antibiotics has and does not work and will require a behavior change.”

AREN’T WE REALLY TALKING KNOWLEDGE AND UNDERSTANDING?
ASPs: Job of a steward, or time for a pilot?

Infectious Disease News, May 2016
Larry M. Bush, MD, FACP; Donald Kaye, MD, MACP
ANTIBIOTICS
THE END OF MIRACLE DRUGS?

WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS
"...the risks of action are far less serious than those posed by comfortable status quo and inaction"

JFK..circa 1962
NOW, PERHAPS MORE THAN EVER...

TIME TO GET IT RIGHT!

THANK YOU