Antibiotics in Hospital Medicine: Focus on Stewardship

Noah Wald-Dickler, MD
Clinical Instructor of Medicine
USC Keck School of Medicine
Outline

1. Intro:
   i. Background & Scenarios
   ii. Basic Stewardship principles
   iii. Diagnostics (procalcitonin etc)
   iv. Expected Practices

2. Common Infectious Syndromes

3. Practical References
   i. LAC+USC Stewardship “who to call”
   ii. Posted references
Antibiotic Stewardship

New Societal Approaches to Empowering Antibiotic Stewardship

Brad Spellberg, MD
Los Angeles County + University of Southern California Medical Center, Los Angeles; and Division of Infectious Diseases, Department of Medicine, Keck School of Medicine at University of Southern California, Los Angeles.

Substantial concern regarding the ever-worsening crisis of antibiotic resistance has been raised by the World Health Organization, US Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention.

Antibiotics are unique because they are the only pharmaceutical agents that have transmissible loss of efficacy over time. Other drug types should work as well as they do today. However, because of the expression of antibiotic resistance every patient, every patient must understand the ability of every antibiotic to become resistant. Antibiotics are expensive, and the public must protect these drugs. The traditional narrative not to tolerate unnecessary or inappropriate antibiotic use that is estimated more than 50% of antibiotic use that is unnecessary or inappropriate. The US government has recently emphasized the need for implementation of antibiotic stewardship programs at all hospitals.

To be effective, antibiotic stewardship programs must incorporate best practices, which include dedicating sufficient resources to the program, appointing a single leader to be accountable for performance, having appropriate antibiotic expertise, implementing active surveillance, and monitoring bacterial resistance, reporting an

JAMA March 22/29, 2016 Volume 315, Number 12 1229
Antibiotic Stewardship

• We need to recognize that antibiotics are unique among drugs
• Only they have transmissible resistance
• Those that work today won’t work in the future - they must be continually replaced
• Every person’s use affects everyone else’s
• Antibiotics are a shared societal trust—not true of any other type of drug
No one has a right to waste antibiotics - wasting them hurts everyone.
Common Scenarios

#1: The Surgical Patient on Medicine

• **You**: “Yeah I’ve got a patient with (perf’d appy, cholecystitis, cholangitis, etc). They’re spiking through ceftriaxone + metronidazole. I need Zosyn.”

• **Me**: “It was community onset, right? Why would *Pseudomonas* be in there?”

• **You**: “Probably not *Pseudomonas*. But they’re spiking through CTX/Flagyl.”
Common Scenarios

#2: The ED → Medicine Admit

- **Them:** “Yeah I’ve got a patient with GNB in the urine. ED started meropenem.”
- **Me:** “Do they have symptoms?”
- **Them:** “No. But they have GNR in urine.”
- **Me:** “Right. That’s asymptomatic bacteriuria. We don’t treat that.”
- **Them:** “I know. But there’s GNR in the urine, so I need the antibiotics ED started”
#3: The MICU Patient

- **Them**: “I need meropenem and vancomycin.”
- **Me**: “What are the indications?”
- **Them**: “I have a crashing patient.”
- **Me**: “Okay. I hear you. But looking at the chart, this is CAP, right?”
- **Them**: “Yeah, it’s CAP. But the patient’s really sick. I need broad coverage.”
Is This Really Education Deficit?

- Do we really believe physicians don’t know not to treat asymptomatic bacteriuria?

- Do we think that the medicine teams have logically thought through options and simply misunderstand how abx work?

- Do we think the MICU team believes *Pseudomonas* and MRSA are common CAP pathogens?
Or Is This About Fear?

- Abx are among the most potent psychoactive drugs in the pharmacopeia - they just act on prescribers rather than patients.

- When providers are afraid, they act instinctively, Abx sooth their fears.

- This is about fear—and fear cannot be overcome by rational education.

- It must be countered by psychology.
### The Psychology of Abx Prescription

**Heroin Withdrawal Sign/Symptom** | **Antibiotic Restriction Sign/Symptom**
--- | ---
Anger | Anger
Tachycardia | Tachycardia
Diaphoresis | Diaphoresis
Tremulousness | Tremulousness
Cursing | Cursing
Diarrhea | Diarrhea (of the mouth)
Potential Violence | Potential Violence

“Antibiotic stewardship is like prescribing methadone for antibiotic addicted providers”
Alleviating Fear through Stewardship

• Providers may push back on stewardship recs due to concerns of “liability” or “I’m in the hot seat, not you”

• Solutions:
  
  • Rapid diagnostics (↓ dx uncertainty)
  
  • Establishing an Expected Practice around stewardship, signed off on by MEC, re-distributes responsibility to the facility
  
  • EP can be around short-course therapy and around basic stewardship principles
Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

Lancet ID 2017 18:95-107


• Meta-analysis of 26 RCTs of RTIs in which procalcitonin results made available to providers or not, with Tx algorithm to support

• 6,708 patients from 12 countries

• Mortality lower with procalcitonin, >25% reduction in Abx days, >30% reduction in antibiotic AEs
Expected Practices

Specialty: Infectious Disease and Antibiotic Stewardship Workgroups
Subject: Duration of Antibiotic Therapy for Common Infections
Date: September 14, 2016

Expected Practices

Specialty: Infectious Disease and Antibiotic Stewardship Workgroups
Subject: Fundamental Principles of Antibiotic Stewardship
Date: January 4, 2018

*Reference/posting location @ end of presentation*
OVERRIDING PRINCIPLE #1:

MAKE SURE WHAT YOU’RE TREATING IS ACTUALLY AN INFECTION!
Basic Stewardship Principles

- Asymptomatic patients don’t require antibiotics irrespective of culture results.

- Skin, urine, respiratory (yes even BAL) results irrelevant if no symptoms!

- Don’t treat *Candida* in the urine or sputum.
OVER RIDING PRINCIPLE #2:

SHORTER = BETTER
WE ARE TREATING FOR TOO LONG
The New Antibiotic Mantra—“Shorter Is Better”

Brad Spellberg, MD

JAMA Internal Medicine

In AD 321, Roman Emperor Constantine the Great codified that there would be 7 days in a week. Even in the modern era of evidence-based-medicine, this 1695-year-old decree remains a primary reference for duration of antibiotic therapy: it leads physicians to treat infections in intervals of 7 days. Thus, it is gratifying when clinical trials challenge the standard antibiotic duration of 7 to 14 days.

Standard Abx durations: 1-2 Constantine units—based on 1695 year old decree
### Stewardship: Shorter = Better

- **Studies of numerous infection types**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Short (d)</th>
<th>Long (d)</th>
<th>Result</th>
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<tbody>
<tr>
<td>CAP</td>
<td>3 or 5</td>
<td>7, 8, or 10</td>
<td>Equal</td>
</tr>
<tr>
<td>HAP</td>
<td>7</td>
<td>10-15</td>
<td>Equal</td>
</tr>
<tr>
<td>VAP</td>
<td>8</td>
<td>15</td>
<td>Equal</td>
</tr>
<tr>
<td>Pyelo</td>
<td>7 or 5</td>
<td>14 or 10</td>
<td>Equal</td>
</tr>
<tr>
<td>Intra-abd</td>
<td>4</td>
<td>10</td>
<td>Equal</td>
</tr>
<tr>
<td>AECB</td>
<td>&lt;5</td>
<td>&gt;7</td>
<td>Equal</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5-6</td>
<td>10</td>
<td>Equal</td>
</tr>
<tr>
<td>Osteo</td>
<td>42</td>
<td>84</td>
<td>Equal</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>AF x 72 h</td>
<td>+ANC &gt; 500</td>
<td>Equal</td>
</tr>
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</table>

Studies of numerous infection types.
OVERRIDING PRINCIPLE #3:

DON’T USE

ANTI-PSEUDOMONAL

(OR ANTI-MRSA AGENTS)

WHEN THEY’RE NOT NEEDED
Basic Stewardship Principles

- Pseudomonal coverage not warranted for hospitalized patients with community infections (e.g., quinolones as outpt oral drugs, & no Zosyn for CAP or cellulitis!)

- MRSA coverage not required for most CAP, cellulitis, IAI, UTI
Syndromes

- Skin and soft tissue infections (SSTI)
- Community acquired pneumonia (CAP)
- Healthcare-Associated Pneumonia (HCAP)
- Urinary tract infections (UTI)
- Intra-abdominal infections (IAI)
- Meningitis
SSTI

• Cellulitis: caused mostly by strep species

• Guidelines: **don’t** use MRSA agent if no abscess/pus—data now support

• Purulent abscess w/ cellulitis: tx for MRSA

• Stable admits from ED: cefazolin or clindamycin iv (not ceftriaxone please!)

• Necrotizing SSTI/unstable: stat ACS consult & vanc/clinda/ceftriaxone*
Do Gram Negatives Cause Cellulitis?

- Devitalized tissue, puncture wound, IVDA, or soil/vegetation exposure that triggered the cellulitis, think about Gram negatives—ceftiraxone a good option

- Rare other syndromes, e.g., *Vibrio vulnificus* in cirrhotics eating oysters

- Diabetic cellulitis is still strep, not Gram negatives
Cellulitis—Beware Mimickers!

- Cellulitis is commonly misdiagnosed
- Most common cause is chronic venous stasis, but also dermatitis, necrobiosis lipoidicum, etc.
- Look for alternative cause if:
  - bilateral—cellulitis is very rarely bilateral
  - it’s not warm and tender
  - it’s itchy
Wounds

• Not all wounds are infected!

• Infection indicated by inflammation and purulence—look for erythema, warmth, fluctuance, purulent exudates

• If you give antibiotics for an uninfected open wound, you are guaranteeing when the wound does get infected it will be resistant
Wounds – Decubitus Ulcers

- Not all decubitus ulcers are infected!
- Even with underlying osteomyelitis, role of antibiotics is only to bridge through peri-operative surgical flap closure by Plastic Surgery
- If no plans for surgery: wound care and no antibiotics (antibiotics don’t cure holes)
SSTI: Duration

- Numerous trials of SSTI, including cellulitis, major abscess, wound infections, found 5-7 days as effective as 10-14 days.

Hepburn 2004 Arch Int Med 164:1669-74;
Prokocimer 2013 JAMA 309:559-69;
Syndromes

- Skin and soft tissue infections (SSTI)
- Community acquired pneumonia (CAP)
- Healthcare-Associated Pneumonia
- Urinary tract infections (UTI)
- Intra-abdominal infections (IAI)
- Meningitis
CAP Microbiology

- *Streptococcus pneumoniae* used to be the most common cause
- Recent studies: viral or no identifiable organism considerably more common
- Others include *H. influenzae, Moraxella, Chlamydophila, Mycoplasma, Legionella*
- **NOT** MRSA and NOT Pseudomonas!
National Guidelines for CAP

• **Hospitalized ward pts (PORT III):**
  \(\beta\)-lactam (CTX) + macrolide or doxy - guidelines say quinolone ok, but don’t waste them!

• **PCU/ICU:** must use a \(\beta\)-lactam plus a macrolide - doxy not ok bc *Legionella* risk (don’t waste quinolone)

• **ICU patients** quinolone monotherapy not acceptable per guidelines due to risk of bacteremia—must use combination (\(\beta\)-lactam + macrolide or quinolone)
CAP: Short Course

- Multiple randomized trials showing 5 (or even 3) days NI to 7-10 days of Abx
- Now includes a study of pts with PORT IV and V (Uranga et al. JAMA IM)
- Reduced emergence of resistance with shorter course therapy

Is It CAP?

- For patients who failed outpatient therapy for CAP, do **NOT** think resistant pathogen and just change antibiotics—rather:
  - Viral
  - TB (more reason not to use quinolone monotherapy)
  - Cocci
  - Undrained effusion/empyema
- Check procalcitonin if dx uncertainty!
Syndromes

- Skin and soft tissue infections (SSTI)
- Community acquired pneumonia (CAP)
- Healthcare-Associated Pneumonia
- Urinary tract infections (UTI)
- Intra-abdominal infections (IAI)
- Meningitis
- Sepsis without source
HAP Options

• For HAP with no recent antibiotic exposure, cefepime +/- anaerobic coverage (clindamycin or metronidazole)
  • Aspiration pneumonitis: **no** abx!

• MRSA coverage not routinely necessary, add if sicker or necrotizing pneumonia

• If shock, recent abx, or from a problem SNF/ward: pip-tazo or meropenem
HAP/VAP: Short Course

• Several randomized trials showing that 7-8 days as effective as 10-15 days

• Reduced emergence of resistance with shorter course therapy

• Original concerns re non-fermenting GNB have not panned out; new guidelines recommend 7 days for all, irrespective of pathogen

Syndromes

- Skin and soft tissue infections (SSTI)
- Community acquired pneumonia (CAP)
- Healthcare-Associated Pneumonia
- Urinary tract infections (UTI)
- Intra-abdominal infections (IAI)
- Meningitis
- Sepsis without source
Don’t Treat aSx Bacteriuria!

• Patients who have no urinary symptoms but have bacteria in the urine SHOULD NOT BE TREATED, irrespective of pyuria.

• The only definitive exception is a patient who neurologically can’t feel dysuria.

• Consider in limited situations (e.g., renal transplant, urinary surgery, pregnant, unrelieved urinary obstruction) — immune suppression not a reason to treat.
• For cystitis, guidelines now recommend nitrofurantoin 100 mg bid x 5 d or fosfomycin 3 g x1 (TMP-SMX x3 d if resistance rates <20% in community)

• For pyelonephritis and other complicated UTIs, we don’t have anything oral to replace quinolones - we’re stuck
Pyelonephritis: Short Course

• Numerous randomized trials showing that 5-7 days as effective as 10-14 days

• Short course equally effective despite diabetes & even *despite GNR bacteremia*

Sandberg et al. 2012 Lancet 380:484-90;
Peterson et al. 2008 Urology 71:17-22;
 Syndromes

- Skin and soft tissue infections (SSTI)
- Community acquired pneumonia (CAP)
- Healthcare-Associated Pneumonia
- Urinary tract infections (UTI)
- Intra-abdominal infections (IAI)
- Meningitis
IAI What to Do?: Ward vs ICU

- For community infections *not* in shock, ceftriaxone + metronidazole (cephalo-sporins alone inadequate for anaerobes)

- For healthcare associated, cefepime + metronidazole—reserve pip-tazo for more complex cases

- If patient in shock, or with risks for ESBL, use meropenem
Intra-abdominal: Short Course

- 4 days as effective as 10 for cIAI
- Assumes source control obtained

Syndromes

• Skin and soft tissue infections (SSTI)
• Community acquired pneumonia (CAP)
• Healthcare-Associated Pneumonia
• Urinary tract infections (UTI)
• Intra-abdominal infections (IAI)
• **Meningitis**
• Sepsis without source
Vancomycin & Ampicillin

• For community meningitis, the reason to use vancomycin is the risk of ceftriaxone-resistant *S. pneumoniae*

• CFTRX-resistance rare in LA (esp. adults)
  • almost always in children with recurrent otitis

• Do NOT give empiric vancomycin prior to LP—wait for the LP results

• Empiric ampicillin only for: elderly >50 y/o, alcoholic, pregnant, immunocompromised
Acyclovir

• Acyclovir is to treat HSV encephalitis—there are minimal data that it matters for pure meningitis

• Do not give empirically

• Await LP results, and consider if you are treating encephalitis
Antimicrobial Stewardship at LAC+USC

- Here to **help** you
- Staffed daily (Mon-Sun) with an ID attending
- Blood culture & restricted antimicrobial use reviews
LAC+USC Antimicrobial Stewardship

- Here to **help** you!
- Staffed daily with an ID attending
- Most common interaction: approval/review of a restricted antibiotic
<table>
<thead>
<tr>
<th>Daytime (8am-5pm)</th>
<th>Nights (5pm-8am)</th>
</tr>
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<tbody>
<tr>
<td><strong>Mon</strong></td>
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<tr>
<td>ID Pharmacy</td>
<td>Listed ID fellow</td>
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<tr>
<td><strong>Tues</strong></td>
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<td><strong>Wed</strong></td>
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<td><strong>Thurs</strong></td>
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<td><strong>Fri</strong></td>
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<td>Weekend ID resident</td>
<td>Keck on-call ID fellow</td>
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<tr>
<td><strong>Sun</strong></td>
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<td>Weekend ID resident</td>
<td>Keck on-call ID fellow</td>
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<tr>
<td><strong>Holidays</strong></td>
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</tr>
<tr>
<td>Weekend ID resident</td>
<td>Keck on-call ID fellow</td>
</tr>
</tbody>
</table>

**ID Antibiotic Stewardship**

- **Mon - Fri 8am - 5pm (except holidays)**
  - ID Pharmacy
  - Dizon, Erin

- **Weekends & Nights 5pm - 8am**
  - ID Pharmacy
  - Dizon, Erin
  - ID Antibiotic Approval
  - FPGY2
  - 213-717-0039
  - 323-260-0112
## Restricted Antibiotics at LAC+USC

<table>
<thead>
<tr>
<th>AmBisome</th>
<th>Itraconazole</th>
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<tbody>
<tr>
<td>Aztreonam</td>
<td>Linezolid (IV or PO)</td>
</tr>
<tr>
<td><strong>Cefepime</strong></td>
<td><strong>Meropenem</strong></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Micafungin</td>
</tr>
<tr>
<td>Colistin (IV and inhaled)</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Piperacillin-tazobactam <em>(Zosyn)</em></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Posaconazole (PO or IV)</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Isavuconazole (PO or IV)</td>
<td>Voriconazole* (IV or PO)</td>
</tr>
</tbody>
</table>

If you haven’t heard of it, it’s probably restricted: Avycaz, Zerbaxa, Vabomere, Synercid…

*Heme ward exceptions
Welcome to LAC+USC Intranet

ADMINISTRATIVE SERVICES
- Decedent Affairs
- Emergency Management / Hospital Command Center
- Facilities Management
- Human Resources
- Information Services
- Nursing Information Systems
- Patient Financial Services (PFS)
- Quality Improvement
- Radiation Safety
- Risk Management
- Utilization Review (UR)

DIAGNOSTIC SERVICES
- CHC Homepage
- Labs and Pathology
- Pharmacy
- Radiology IT
Pharmacy Services Homepage

Resources

- Antibiogram
- Adult Anti-infective Agents Dosing Guide
- Basic Prescription Writing (video)
- Black Box Warnings - DHS High Priority List
- Contact Info
- ESA Authorized Prescribers
- Expected Practice of Antibiotic Durations for Common Infections in Adults
- Fundamental Principles of Antimicrobial Stewardship and Antimicrobial Selection
- Guidelines for Restricted Antimicrobials Approval
- Initial Management of Neutropenic Fever in Patients with Cancer
- Inpatient Adult Empiric Antibiotic Recommendations for Common Infectious Diseases
- MSDS Info
- PADI Online
- Prevention of Opportunistic Infections in Patients with Cancer while Neutropenic
- Procalcitonin algorithm for Respiratory Tract Infections
- Procalcitonin algorithm for Sepsis in the ICU
- Re-assessment of Empiric Antibiotic Therapy in Neutropenic Fever in Patients with Cancer
- Standard-Dose Vancomycin Nomogram for Adult Patients
Thank you! Any comments or discussion points?