Optimizing Your Antibiotic Prescribing in the ED in the Era of Resistance and Stewardship

Michael J. Burns, MD FACEP FACP FIDSA
Professor
Emergency Medicine & Infectious Diseases
UC Irvine Medical Center
University of California Irvine School of Medicine
Learning Objectives

• Recognize that improving antibiotic use is a public health imperative
• Demonstrate that using antibiotics wisely in the ED can minimize harm and optimize clinical outcomes
• Explain how listing of incorrect antibiotic allergies, especially penicillin, in the electronic health record, is dangerous
• Recognize the benefit of your ED having its own antibiotic protocols/guidelines for common infections
• Recognize the many adverse effects of antibiotics
• Explain why short course antibiotic therapy is the “new mantra”
Emergence of Antimicrobial-Resistant Bacteria
The Rise of Antimicrobial Resistance

- MRSA (methicillin-resistant *Staph aureus*)
- Fluoroquinolone-resistance
- Multi-drug resistant *Pseudomonas*
- ESBL (extended spectrum beta-lactamase)-producing organisms: resistant to all 3rd generation cephalosporins
- CRE (carbapenemase-producing *Enterobacteriaceae*)
- *Acinetobacter*
- Fluconazole-resistant *Candida* species
- Ceftriaxone-resistant gonorrhea
- Cipro-resistant *Salmonella, Shigella, & Campylobacter*
- Macrolide- and clindamycin-resistant streptococci
- The newest one: *E. coli* with the mcr-1 gene: resistant to colistin and polymyxin
Resistant bacteria spread rapidly throughout the world

Bacteria possessing the New Delhi metallo-beta-lactamase-1 gene, coding for carbapenem resistance, originally found in India in 2008, were recently detected in bacteria in the Svalbard Islands of Norway.
Adverse Effects of Antibiotics

*C. difficile* colitis
Adverse effects of antibiotics

Achilles tendon rupture from fluoroquinolone
Fluoroquinolone Adverse Effects

- Hypoglycemic coma and hyperglycemia, even in non-diabetics
- Psychiatric/CNS effects, including agitation, delirium, disorientation, seizures, memory impairment, tremor, dizziness, insomnia, hallucinations, suicidal ideation
- Ruptured aortic aneurysm; aortic dissection
- Tendinitis and tendon rupture: especially the Achilles tendon
- Peripheral neuropathy
- *C. difficile* and multiple drug resistant organisms
- Many others: retinal detachment, vasculitis, arthralgias and myalgias which can last for weeks after drug cessation, anemia, neutropenia, thrombocytopenia, QTc prolongation, severe allergic reactions including Stevens-Johnson syndrome.
Toxic Epidermal Necrolysis from a 2-week course of TMP-SMX prescribed for “sinusitis”
Erythema multiforme major (Stevens Johnson syndrome) from levofloxacin prescribed for “bronchitis” in an asthmatic.
Antimicrobials: It’s a Balancing Act
Antimicrobial Stewardship

• The goal is to **IMPROVE PATIENT CARE** by
  – Optimizing clinical outcomes associated with antimicrobial use (choosing the best antibiotic)
  – Minimizing harm associated with improper antimicrobial usage (adverse effects, *C. difficile* colitis, antibiotic resistance)
The Wrath of Burns

(happens in our ED when you prescribe a non-indicated antibiotic)
Antimicrobial Stewardship
Avoid Unnecessary Antibiotic Use

• Antibiotics are over-prescribed in the ED for
  – Bronchitis, URI’s, sinusitis
  – Asymptomatic pyuria/bacteriuria
  – Even when indicated, the duration of treatment is often too long

• ED-specific guidelines for antibiotic use should be adapted for your specific ED or your region, based on local antibiotic susceptibility patterns and your hospital’s formulary
Antimicrobial Stewardship

• Clinical decision support systems for ED antibiotic use can be integrated into an EMR antibiotic ordering system

• When an antibiotic is prescribed in the ED for a discharged patient, close telephone contact, or other method of contact, should be done to assure that patient is on the correct antibiotic when antimicrobial susceptibilities are available
The New Antibiotic Mantra
“Shorter Is Better”

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<tr>
<th>Disease</th>
<th>Treatment, Days</th>
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<td>Community-acquired pneumonia&lt;sup&gt;1-3&lt;/sup&gt;</td>
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<td>Nosocomial pneumonia&lt;sup&gt;6,7&lt;/sup&gt;</td>
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<td>Pyelonephritis&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Intraabdominal infection&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Acute exacerbation of chronic bronchitis and COPD&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>Acute bacterial sinusitis&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Cellulitis&lt;sup&gt;14&lt;/sup&gt;</td>
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<td>Chronic osteomyelitis&lt;sup&gt;15&lt;/sup&gt;</td>
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Abbreviation: COPD, chronic obstructive pulmonary disease.
Antibiotic use is harmful

- Approximately 40-50% of inpatients receive antimicrobial therapy
- Half of all antibiotic use is unnecessary
- It is falsely assumed that antibiotics do no harm
- Antibiotics can result in dangerous drug interactions, allergic reactions, kidney and liver toxicities, and cardiac arrhythmias
- According to the CDC, an estimated 150,000 cases per year present to U.S. emergency departments for antibiotic-related adverse events
- *Inappropriate antibiotic use leads to infections by antibiotic-resistant bacteria and Clostridium difficile*

Antibiotic-resistant bacteria

- Antimicrobial resistance is increasing worldwide.
- Gram negatives are a particular concern: ESBL, CRE, multi-drug resistant Acinetobacter, and multi-drug resistant Pseudomonas.
- Infection by antibiotic-resistant bacteria costs $23,800 per patient and increases length of hospital stay by 9.5 days\(^1\).
- Annual cost is estimated at more than $20 billion per year in the US\(^1\).
- Rise in antibiotic-resistant bacteria is a result of excessive antibiotic use\(^2\).

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Clostridioides difficile colitis

- *Clostridioides difficile* (C. difficile) has surpassed methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common hospital-acquired infection\(^1\)
- Inappropriate antibiotic use is the single most important risk factor for *C. difficile* colitis
- Up to 85% of patients with *C. difficile* colitis have antibiotic exposure in the 28 days before infection\(^3\)
- 77% of patients with *C. difficile* colitis received at least one unnecessary antibiotic\(^2\)
- 26% of patients with *C. difficile* colitis only received unnecessary antibiotics\(^2\)

Risk for *C. difficile* after Antibiotics

- Higher risk of *C. difficile* infection after:
  - Fluoroquinolones
  - Clindamycin
  - Broad-spectrum cephalosporins and penicillins

- Lower risk of *C. difficile* infection after:
  - Aminoglycosides
  - Doxycycline
  - Metronidazole
  - Vancomycin
  - TMP-SMX

- Tariq R et al: *Open Forum Infect Dis* 2017
Skin and Soft Tissue Infections
No need to add vancomycin for cellulitis if:
- No purulent drainage
- No evidence of abscess by exam and ultrasound
- Recent nasal MRSA swab negative, if available

Healthcare associated CAP
- Obtain induced sputum in the ED
- Serum procalcititin
- Viral respiratory panel by NP swab(s)
- Begin broad spectrum antimicrobials per our UCI algorithm
- If cultures negative for MRSA and resistant bacteria at 48 hrs, then de-escalate antimicrobial therapy
Outpatient Treatment of CAP—Adults—UCI ED Protocol

• Initial dose in the ED: ceftriaxone PLUS either azithromycin or doxycycline, or levofloxacin alone

• No co-morbidities and <60 years
  – Doxycycline

• Co-morbidities or recent (within 3 months) antibiotic use, or > 60 years
  – Amoxicillin or amox-clav or cefuroxime PLUS azithromycin or doxycycline
  – Or levofloxacin alone
Cellulitis/Abscess: UCI ED Protocol

- Non-purulent cellulitis/no abscess
  - ED bedside ultrasound if any suspicion for abscess
  - If IV treatment needed: ceftriaxone or clinda* 
  - PO cephalexin, amox-clav, or clinda*

- Purulent cellulitis/abscess (obtain culture)
  - PO TMP-SMX or doxycycline
  - If IV treatment needed: vancomycin

- “Double coverage” rarely indicated

- 5-7 days total duration

*if penicillin allergy
UCI Antimicrobial Stewardship Initiatives

Urine cultures

• Do not obtain urine for UA or culture from an indwelling Foley catheter
  – if need urine, remove the Foley, insert new catheter, then obtain urine for UA and culture
• Do not order urine cultures in the absence of symptoms or signs of urinary tract infection
• Do not treat asymptomatic pyuria and bacteriuria
  – Don’t treat urine cultures + for Lactobacillus, Strep viridans, or Group B streptococci: are contaminants
• Strict use criteria for insertion and removal of Foley catheters
START HERE!

DOES PATIENT HAVE SYMPTOMS OF UTI?

- Y: Do NOT PREScribe EMPIRIC ANTIMOBiotics (females, pregnant or elderly, lower urinary tract problems)
- N: STOP Consider STD, vaginitis or non-infectious cause of symptoms

IS UA GOOD QUALITY?
- Y: WBC <9, or moderate positive LE
- N: STRAIGHT CATH

DOES UA SHOW...

- Y: S/S Upper UTI + Kidney pain, fever or leukocytospermia
- N: Subclinical Pyelonephritis
  - Y: Nitrofurantoin (Macrolid) 100mg PO BID x5 days
  - N: Nitrofurantoin (Macrodantin) 50-100mg PO QID x3-7 days
  - Note: This is a problem due to increased compliance with BID dosing

IS CREATININE CLEARANCE < 40?

- Y: ALLERGIC TO NITROFURANTOIN?
  - Y: AGENTS
    1. Cefuroxime 250mg BID x7 days
    2. Cefdinir 300mg PO BID x7 days
    3. Sulfamethoxazole/Trimethoprim DS 1 Tab PO BID x3-7 days
    4. Amoxicillin-Clavulanate 500mg PO BID x3-10 days
  - N: ALTERNATIVE AGENT (if unable to tolerate all other agents)
    Fosfomycin 3gm PO x1 dose
  - Y: LAST RESORT (if unable to tolerate or afford Fosfomycin)
    Ciprofloxacin 250mg PO BID x3 days
    Levofloxacin 250mg PO BID x3 days

CAN PATIENT GO HOME?
- Y: LOW CHANCE OF RESISTANT ORGANISM
  - CHOOSE EITHER:
    1. EDO Pyelonephritis Protocol
    2. Consult ID or Text Dr. Burns
  - DISCHARGE with:
    - Cefdinir* 300mg PO BID x6 days to start the day AFTER the ED visit
      *Confirm susceptibility prior to empiric broad-spectrum treatment

- N: OUTPATIENT: EDO for PICC line + ID consult Admission

UCI ED
UTI
Algorithm/Guideline
Antibiotic Resistance

- **Azithromycin**: 40-50% of *Streptococcus pneumoniae* and *Haemophilus influenzae*, and 10-15% of Group A strep, are now resistant to azithromycin
  - Avoid azithro alone for otitis media, sinusitis, COPD, pneumonia

- If antibiotic treatment is needed for suspected infectious diarrhea not caused by *C. diff*, use azithromycin as resistance to cipro is high (but antibiotic treatment rarely required for this condition)
Penicillin Allergy

• The penicillins and cephalosporins are the treatment of choice for most bacterial infections

• Use of alternative antibiotics often results in suboptimal treatment, more adverse effects, contribute to antimicrobial resistance, and are associated with increase costs, more adverse effects and more drug reactions

• Patients who are labeled as allergic to penicillin may be given broad-spectrum antimicrobial agents that increase the risk of developing *C. difficile* infection, MRSA, VRE, and multiple drug resistant organisms
Penicillin allergy

- Only 2% of patients labeled as having penicillin allergy actually have a true allergy.
- The most commonly reported penicillin hypersensitivity reaction is a delayed benign maculopapular rash, usually caused by a type IV hypersensitivity reaction. **This type of reaction is not associated with anaphylaxis and may not recur with reexposure to penicillins.**
- IgE mediated penicillin allergy wanes over time with 80% of patients becoming tolerant after 10 years.
Figure 1. Symptoms Distinguishing Groups of Cutaneous Drug Reactions

IgE-mediated reactions
- Onset minutes to hours into treatment course
- Raised off of the skin
- Pruritic
- Each lesion lasts <24 h
- Fades without scarring

Benign T-cell-mediated reactions
- Onset days into treatment course
- Typically less pruritic than IgE-mediated reactions
- Each lesion lasts >24 h
- Fine desquamation with resolution over days to weeks

Severe T-cell-mediated reactions or severe cutaneous adverse reactions
- Onset days to weeks into treatment course
- Blistering and/or skin desquamation
- Mucosal and/or organ involvement
- Usually requires hospitalization
Cross Reactivity Among Penicillins

- Cross-reactivity between penicillin and a cephalosporin occurs in about 2% of cases, but may be as high as 40% in patients with history of anaphylaxis to penicillin who are treated with an aminoccephalosporin that have shared chemical side chains (R1 groups).
- Extremely low cross-reactivity between cefazolin and penicillins/other cephalosporins due to the unique side chain of cefazolin.
- Cross-reactivity between penicillins and carbapenems is less than 1%. There is no cross-reactivity between penicillins and monobactams (aztreonam).
Cephalosporin cross-reactivity, by R1 groups

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<th>Common amino R1 group</th>
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*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices may be used if avoiding identical and similar structures at both side chain locations is desired.*
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Penicillin Allergy

- Patients reporting penicillin allergy should be referred to an allergist for penicillin skin testing, but RN’s, NP’s, PA’s, pharmacists, and non-allergist physicians can be trained to safely perform penicillin skin testing using protocols developed by allergists.
Amoxicillin Challenge Test

- Amoxicillin challenge test: 250 mg PO and observe for one hour. Do not use another penicillin for the test.
- If no reaction one hour after amoxicillin, then all beta-lactams can be administered without any risk of an allergic reaction.
Penicillin Allergy

- If an amoxicillin challenge is tolerated (with or without penicillin skin testing), the medical record notation that a patient is allergic to penicillin should be deleted, as the chance of an IgE-mediated reaction is zero.

- EHR allergy modules: When penicillin is tolerated in a patient with a history of penicillin allergy, the active penicillin allergy should be deleted from the EHR. If there has been a reaction and the allergy cannot be deleted, then qualifying comments should be added. Examples: “penicillin skin test positive,” or “tolerates cephalexin” or “tolerates ceftriaxone.”
EDSevereSepsis Smart Phrase
Meets CMS Requirements

• "At @NOW@ the patient was diagnosed with severe sepsis: **2 SIRS criteria + suspected infection + one of more of the following evidence of acute end-organ damage** (creatinine > 2.0 that is new, or urine output <0.5 mL/kg/hour for 2 consecutive hrs that is new; bilirubin > 2.0 that is new; platelet count <100,000 that is new; INR > 1.5 unless on anticoagulation or chronic; lactate > 2.0; MAP < 65 or SBP < 90; or acute respiratory failure with new need for invasive or non-invasive mechanical ventilation)"
Summar y

• Inappropriate antimicrobial use is harmful
• Antimicrobial stewardship programs can improve patient care by improving clinical cure rates and potentially decreasing the incidence of *C. difficile* colitis and antibiotic-resistant bacteria and decreasing adverse effects of antibiotics
• Your ED should have its own antibiotic treatment protocols/guidelines, and improved penicillin allergy labeling
• Funding and accrediting agencies (CMS, Joint Commission) will likely emphasize antimicrobial stewardship programs in the near future
• ACGME is committed to antimicrobial stewardship
Selected References


• Spellberg B: The new antibiotic mantra – “Shorter is Better”. *JAMA Internal Medicine* 2016;76:1254
Selected References

- Weiskopf: Teachable moment: Asymptomatic bacteriuria, what are you treating? *JAMA Internal Medicine* 2015;175:344