Antimicrobial Stewardship: Prima non Nocere!

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Conflict of Interest Disclosure

I have no conflicts and nothing to disclose

Objectives

• Describe antimicrobial stewardship and it’s core elements

• Recognize the importance of antimicrobial stewardship and identify the consequences of improper antibiotic use

• Identify key ways in which clinicians can optimize antimicrobial use
What is Antimicrobial Stewardship?

- Multidisciplinary approach optimizing appropriate antimicrobial selection (drug), dosing, and duration
- Minimize unintended consequences

Multidisciplinary Approach

- Primary Medical Providers
- ID Pharmacists
- ID Physicians
- Microbiology
- Infection Control
- Hospital Epidemiologists
- Information System Specialist
- Antimicrobial Stewardship Program
- Hospital Administration

Need for timely, appropriate antimicrobial initiation in serious infections

Need to avoid unnecessary antimicrobial use to prevent resistance and adverse effects
ASP - National Priority

- 2014 – CDC recommended that all acute care hospitals implement an Antimicrobial Stewardship Program (ASP).
- June 2016 – Centers for Medicare and Medicaid Services (CMS) released a proposed rule change to require hospitals to implement ASPs, enhancements to infection control programs, and greater surveillance activities with ASP in order to participate in Medicare and Medicaid.
- July 2016 – The Joint Commission (TJC) approves new antimicrobial stewardship standards for all hospitals, critical care hospitals and nursing facilities.
Antibiotics
A Double Edged Sword

PROS

• Antibiotics appropriately selected and *dosed, given early, may be life saving*
  
  • IF host defenses are adequate
  
  • IF infection unrelated to an abscess or obstruction
  
  • IF infection not device associated

CONS

• Antibiotic side effects
  
  • Phlebitis
  
  • Hepatotoxicity
  
  • Nephrotoxicity
  
  • Diarrhea (non-C. difficile & C. difficile)

• Antibiotic drug-drug interactions

• Acquired antibiotic resistance (MDROs)

*C. difficile* Infection (CDI)

• Antibiotic exposure is the single most important risk factor for the development of CDI

• Patients who receive broad-spectrum antibiotics during hospitalization are 2.9 times more likely to develop CDI
Antibiotics May be Misused

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection
  - Inappropriate for site, nonsusceptible at site, tissue penetration problem

Development of Antibiotics in Response to Resistance Due to β-Lactamases

Percentage of ESBLs among Enterobacteriaceae Isolates Across 9 US Census Regions (2012)

*KPC-producing K. pneumoniae, E. coli, and K. oxytoca.
Data are from The Tower Laboratories, LLC.
KPC-Producing Isolates as a Percentage of ESBL Strains in 9 US Census Regions (2012)

Pacific
ESBL rate: 9.1%
ESBL = KPC 5.4%

Mountain
ESBL rate: 12.8%
ESBL = KPC 14.3%

West South Central
ESBL rate: 16.2%
ESBL = KPC 12.8%

West North Central
ESBL rate: 4.4%
ESBL = KPC 4.2%

East North Central
ESBL rate: 8.8%
ESBL = KPC 13.1%

New England
ESBL rate: 9.7%
ESBL = KPC 2.1%

South Atlantic
ESBL rate: 19.9%
ESBL = KPC 16.4%

East South Central
ESBL rate: 8.2%
ESBL = KPC 2.6%

Mid-Atlantic
ESBL rate: 23.2%
ESBL = KPC 40.6%

National
ESBL rate: 12.2%
ESBL = KPC 16.8%

Note: Percent KPC-producing isolates represent a percentage of ESBL-producing strains for that region.
KPC = Klebsiella pneumoniae carbapenemase.
Data on file. Forest Laboratories, LLC.

Examples of How Antibiotic Resistance Spreads

Alexander Fleming - 1945

“The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out... In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

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**Antibiotic "Misuse"**

- **Outpatient settings**
  - 30% Appropriate Use
  - 70% Inappropriate Use

- **Acute Care Setting**
  - 50% Appropriate Use
  - 50% Inappropriate Use

- **Long Term Care Settings**
  - 30% Appropriate Use
  - 70% Inappropriate Use

**What Does An Effective ASP Do?**

- Assist in selection, dosing, and duration of antibiotic therapy
- Reduce broad-spectrum antibiotic use when appropriate
- Ultimately, improve patient outcomes and reduce hospital length of stay

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**Antibiotic Development Is Dwindling**

- 1983-1987
- 1988-1992
- 1993-1997
- 1998-2002
- 2003-2007
- 2008-2012

CDC Core Elements of ASP

- **Leadership Commitment**: Dedicating necessary human, financial and information technology resources
- **Accountability**: Appointing a single leader responsible for program outcomes
- **Drug Expertise**: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- **Action**: Implementing at least one recommended action, i.e. “antibiotic time out” after 48 hours

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Essential Resources and Strategies for Antibiotic Stewardship Programs in the Acute Care Setting

Table 1. Minimal full-time equivalent support recommended by bed size

<table>
<thead>
<tr>
<th>Variable</th>
<th>500–1,000</th>
<th>1,000–5,000</th>
<th>&gt;5,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>0.4</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Nurse</td>
<td>1.8</td>
<td>2.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

For hospitals with <500 beds, there were limited data to make recommendations.


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Predictive margins with 95% CIs
**CDC Core Elements of ASP**

- **Tracking:** Monitoring antibiotic prescribing and resistance patterns
- **Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff
- **Education:** Educating clinicians about resistance and optimal prescribing

**ASP – Not Just an Inpatient Issue**

- Inpatient is important and is typically the most developed / has most resources
- Long term-care facilities
- Dialysis facilities

**ASP – Not Just an Inpatient Issue**

- Outpatient settings:
  - Emergency departments
  - Walk-in clinics/Urgent care centers
  - Ambulatory Surgery Centers (ASCs)
  - Physician offices
  - Outpatient pharmacies
- Non-human antibiotic use (livestock, etc)
Antibiotic Prescription Rates Declining

Antibiotic prescription fill rates in the U.S. have been declining among the commercially insured population since 2010. Exhibit 1. There has been a 9 percent decline in fill rates from 2010 to 2016.

EXHIBIT 1: TOTAL ANTIBIOTIC PRESCRIPTION FILL RATES (PER 100 MEMBERS)

EXHIBIT 2: ANTIBIOTIC PRESCRIPTION FILL RATES BY TYPE OF ANTIBIOTIC (PER 100 MEMBERS)

EXHIBIT 3: TYPE OF ANTIBIOTIC PRESCRIPTION FILL BY SITE OF CARE IN 2016
How Can You be Good Stewards?

Avoid Antibiotics for Inappropriate Indications

- Upper respiratory tract infections (URTIs)
  - Colds, acute bronchitis, non-streptococcal pharyngitis
- Early or mild sinusitis
- Asymptomatic bacteriuria (ASB)
- Colonization of wounds

Educate Your Patients on When Antibiotics are and are Not Effective

- One of the most difficult obstacles practitioners face, especially in outpatient setting
- Discuss indications, appropriate use and risks of antibiotic use
- Recommend specific symptomatic relief and a back-up plan
- Constructively correct false popular beliefs
Optimize Dose and Route of Antibiotic Administration

- IV-to-PO Switch
  - Antibiotics with adequate oral bioavailability
    - Doxycycline / minocycline, azithromycin, fluoroquinolones, fluconazole, linezolid, metronidazole, clindamycin

IV vs PO

- When using highly bioavailable agents, use PO if GI absorption intact
- Do not forget different class IV to PO switch
- Consider only PO therapy from the start
Effective PO Options for MDR UTIs

- Treatment options for multi-drug resistant (MDR) Gram negative bacilli (GNB) are increasingly limited.

- Most urinary tract infections (excluding urosepsis / complicated UTIs) in adults are due to acute uncomplicated cystitis (AUC) / catheter associated bacteriuria (CAB).

- The usual therapy for MDR GNB AUC is often IV and expensive.

Interpretational Problems with UA & UC

Urine Specimens must be transported rapidly to microbiology lab and processed rapidly.

UA:
- Use uncentrifuged urine to avoid clumping of WBCs.
- WBCs in clumps underestimates degree of pyuria.

Ucx:
- Low initial bacterial counts → increase over time to high counts.
- Bacterial colony counts ~ urinary pH and urinary osmolarity dependent.
Factors in Antibiotic Selection

Key Factors

- **Appropriate Spectrum** *(based coverage of usual body site flora)*

- **Tissue Penetration** *(must achieve therapeutic concentration at site of infection)*

- **“Low Resistance Potential”** *(first do no harm!)*

- **Side Effect Profile** *(avoid antibiotics with high C. difficile potential)*

Factors in Antibiotic Selection

Unimportant Antibiotic Selection Factors

- **Bactericidal vs. bacteriostatic**

- **Synergy** *(rarely important and applicable to very few organisms)*
**Primer on Antibiotic Resistance**

### High Level/Absolute Resistance

- MIC beyond achievable serum concentrations
- Not site or concentration dependent
  
  Example: gentamicin resistant *P. aeruginosa*

### Intermediate/Relative Resistance

- Susceptibility is, in part, concentration dependent
- Achievable concentrations > MIC at site of infection (urine/GU tract)

Relative resistance is site & concentration dependent

Example: meropenem "resistant" *P. aeruginosa*

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**Antibiotic Resistance Potential**

"High resistance potential" antibiotics: *antibiotics to avoid if possible*

- Ciprofloxacin
  (S. pneumoniae, *P. aeruginosa*, ↑ MRSA)
- TMP-SMX
  (S. pneumoniae, *E. coli*)
- Imipenem
  (*P. aeruginosa*, ↑ MRSA)
Antibiotic Resistance Potential

“High resistance potential” antibiotics:
*antibiotics to avoid if possible*

- Gentamicin/tobramycin
  (P. aeruginosa)
- Ceftazidime
  (P. aeruginosa, ↑ MRSA)
- Macrolide
  (S. pneumoniae)

“Low resistance potential” antibiotics

IV
- Meropenem
- Ceftriaxone
- Piperacillin/tazobactam
- Aztreonam
- Cefepime
- Colistin/Polymyxin B
- Tigecycline

PO
- Doxycycline
- Minocycline
- Levofloxacin/Moxifloxacin
- Fosfomycin
- Methenamine salts
- Nitrofurantoin

Interpretation of Urine Susceptibility

<table>
<thead>
<tr>
<th>Urinary Susceptibility</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S (susceptible)</td>
<td>Clinical effectiveness likely †</td>
</tr>
<tr>
<td>I (intermediate)</td>
<td>Effectiveness ~ urinary concentration</td>
</tr>
<tr>
<td>R (non-susceptible)</td>
<td>Maybe susceptible</td>
</tr>
</tbody>
</table>

*depending on urinary pH, antibiotic dose, and renal function
† if in vitro = in vivo susceptibility
### Susceptibilities of "Ampicillin Resistant E. coli" Tested in Human Urine at Urinary pH and Urinary Concentrations

<table>
<thead>
<tr>
<th>Oral Antibiotic</th>
<th>Broth pH 7.4</th>
<th>Urine* pH 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Susceptible</td>
<td>% Resistant</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0% (0/25)</td>
<td>100% (25/25)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>28% (7/25)</td>
<td>72% (18/25)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>40% (10/25)</td>
<td>60% (15/25)</td>
</tr>
</tbody>
</table>

* Human urine heat treated to remove thermolabile anti-bacterial activity

### Penicillin G: E. coli Urine vs Serum Spectrum

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Serum Concentration</th>
<th>Minimal Urine Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>800,000 units q6h</td>
<td>&lt; 0.5 mcg/mL</td>
<td>100 mcg/mL</td>
</tr>
<tr>
<td>Penicillin – G Concentration</td>
<td>% E. coli killed</td>
<td></td>
</tr>
<tr>
<td>0.5 mcg/ml</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>100 mcg/ml</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

### Urinary Spectrum of Oral Penicillins

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Penicillin</th>
<th>Ampicillin</th>
<th>Amoxicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dose</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Serum levels</td>
<td>0.5 mcg/ml</td>
<td>2 mcg/ml</td>
<td>4 mcg/ml</td>
</tr>
<tr>
<td>Urine levels</td>
<td>&gt; 100 mcg/ml</td>
<td>&gt; 300 mcg/ml</td>
<td>&gt; 600 mcg/ml</td>
</tr>
<tr>
<td>Urinary spectrum</td>
<td>E. coli, P. mirabilis, E. faecalis (VSE)</td>
<td>E. coli, P. mirabilis, E. faecalis (VSE)</td>
<td>E. coli, P. mirabilis, E. faecalis (VSE)</td>
</tr>
</tbody>
</table>

* With normal renal function

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**Reference:**
Penicillin G Concentration % E. coli killed 0.5 mcg/ml 0 100 mcg/ml 85
Parameters | Tetracycline | Doxycycline
--- | --- | ---
Oral dose | 500 mg | 100 mg
Serum levels | 2 mcg/ml | 4 mcg/ml
Urine levels | > 300 mcg/ml | > 150 mcg/ml
Urinary spectrum | E. coli, Klebsiella sp., Enterobacter sp., Indole + Proteus sp., Pseudomonas aeruginosaa | E. coli, Klebsiella sp., Enterobacter sp., Indole + Proteus sp., Pseudomonas aeruginosaa

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**Urinary Spectrum of Oral Tetracyclines a**

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**Tetracycline: Urinary Spectrum**

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Parameters | Methenamine salts (methenamine hippurate/mandelate) | Fosfomycin
--- | --- | ---
Oral dose | 100 mg | 3 gm
Serum levels | Formaldehyde level = 0 | 26 mcg/ml
Urine levels | Formaldehyde > 20 mcg/ml (dependent on urine pH, time, volume) | 1000-4000 mcg/ml
Urinary spectrum | E. coli, Klebsiella sp., Enterobacter sp., Serratia marcescens, P. aeruginosaa | E. coli, Klebsiella sp., Enterobacter sp., Serratia marcescens, P. aeruginosaa

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Nitrofurantoin

• Spectrum includes all GNB uropathogens except:
  – *Pseudomonas aeruginosa*
  – *Serratia marcescens*
  – *Proteus mirabilis*

• Also effective against all Gram positive uropathogens (VSE & VRE) except:
  – Group B streptococci

• Resistance is rare after decades of worldwide use

Nitrofurantoin

• For MDR GNB AUC, there are few oral alternatives, particularly for carbapenem resistant Enterobacteriaceae (CRE)
  – Doxycycline
  – Fosfomycin
  – Fluoroquinolones

• Antimicrobial activity is pH dependent

• Renal tubular re-absorption is pH dependent

The Effects of Urinary pH on Antibiotic Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal activity at urinary pH (pH 5.5-6)</td>
<td>Penicillin G</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMZ)</td>
</tr>
<tr>
<td></td>
<td>Oral cephalosporins</td>
</tr>
<tr>
<td>Activity not affected by urinary pH</td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td>Naldixic acid / oxolinic acid</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Activity increased by acid urine (pH &lt; 6)</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Activity requires an acid urine (pH &lt; 6)</td>
<td>Methenamine mandelate / methenamine hippurate</td>
</tr>
<tr>
<td>Activity increased by alkaline urine (pH &gt; 6)</td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
</tr>
</tbody>
</table>
Nitrofurantoin

• After appropriate spectrum, main concern of nitrofurantoin efficacy is renal insufficiency, i.e., reduced CrCl (< 60 ml/min)

• Currently, nitrofurantoin is not recommended for CrCl < 60 ml/min

• There is little clinical data to support this breakpoint

• Clinically, nitrofurantoin is highly effective in patients with CrCl > 30 ml/min

Nitrofurantoin

• Nitrofurantoin is effective oral therapy for AUC (due to susceptible organisms) in patients who have renal insufficiency (CrCl = 30-60 ml/min), particularly in those with an optimal urinary pH (acidic)

• Nitrofurantoin has several advantages:
  – Oral vs IV option
  – Low resistance potential
  – Useful in renal insufficiency

Nitrofurantoin

• Patient presenting with AUC / CAUTI caused by MDR uropathogens may be treated with oral antibiotics
  – Doxycycline
  – Nitrofurantoin
  – Fosfomycin
  – Methanamine salts

• Oral options provide cephalosporin, aminoglycoside, quinolone, and carbapenem sparing therapies

• Oral options often less expensive, have lower resistance potential, lower C. diff potential and may prevent hospitalization
Conclusion

• Successful ASPs require adequate resources, collaboration, and expertise

• Excessive / poorly chosen antibiotic therapy will impact both individual patients and the community at large

• Using existing antibiotics wisely can minimize development of MDROs

Be Good Antimicrobial Stewards

How we use antibiotics today or in one patient directly impacts how effective they will be tomorrow or in another patient; they are a shared resource

- Centers for Disease Control and Prevention