Antimicrobial Stewardship

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Disclosures

- None
Objectives

- Understand importance of antimicrobial stewardship
- Describe different strategies of antimicrobial stewardship
- Understand what drives prescribers to make antibiotic decisions
- Describe the most effective that YOU can be antimicrobial stewards
Antimicrobial Timeline

1928 1940 1941 1944 1972 2000 2010

- *Time*, February 25, 1966
  - "Nearly all experts agree that [by the year 2000] bacterial and viral diseases will have been wiped out. Probably atherosclerotic heart disease will also have been eliminated. Cells have only a few secrets still hidden from probers, who are confident that before the year 2000 they will have found the secret that causes cancer."

- William H. Stewart, Surgeon General, 1969
  - "It is time to close the book on infectious diseases"

- Robert Petersdorf, President IDSA, 1978
  - "Even with my great personal loyalty to infectious diseases, I cannot conceive of the need for 309 more infectious disease experts [the number taking the boards that year] unless they spend their time culturing each other"
Patient-Level Effects

- Around 5% of hospitalized patients experience an adverse event as a result of antimicrobial therapy
  - Allergic reaction
  - *Clostridium difficile* infection
  - Nephrotoxicity
  - Hepatotoxicity
- Complications of antibiotic use make up 19.3% of all emergency room visits for adverse drug events
- Have lasting effects on the gut microbiome
  - Some studies have linked antibiotic use to childhood obesity
  - Sustained colonization with multidrug-resistant organisms

Trasande, Int J Obes (Lond) 2013.

Inappropriate Antimicrobial Use

- Approximately 30-63% of hospitalized patients receive an antibiotic
  - The average hospital uses 1000 defined daily doses (DDD) of antibiotics per 1000 patient-days
- It is estimated that up to 68% of antibiotic use is inappropriate

Jenkins, CID, 2010.
Polk, CID, 2011.
Ambulatory Setting

- Special considerations:
  - Antibiotic prescription unchecked
  - Frequently encounter conditions (pharyngitis, otitis media, sinusitis, and upper respiratory tract infections) that are >80% caused by viral infection
  - Impractical to change antibiotics after prescription
  - 72% of patients that present with an upper respiratory tract infection expect to receive a prescription for an antibiotic
  - Antibiotics are prescribed in 21% of acute pediatric ambulatory visits (>70% are for upper respiratory tract infections, representing 10 million antibiotic prescriptions per year)
  - Of the providers who gave a prescription for antibiotic, 20% felt the antibiotic was clinically indicated

Bisno, CID, 2002.
Hersh, Pediatrics, 2011.

Antimicrobial Stewardship

- “Coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of healthcare infections, and limit the selection for antimicrobial resistant strains.”

Infectious Diseases Society of America
Antimicrobial Stewardship

“What if there was a quality improvement initiative that had been proven in multiple peer-reviewed publications to improve individual patient outcomes, reduce overall burden of antimicrobial resistance, and save healthcare dollars? Antimicrobial stewardship is just such an intervention.”

- Arjun Srinivasan
**Improve Patient Outcomes**

<table>
<thead>
<tr>
<th>COST</th>
<th>AMP (median)</th>
<th>UP (median)</th>
<th>DIFFERENCE (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>$53</td>
<td>$95</td>
<td>$42 ($-3,$103)</td>
</tr>
<tr>
<td>Infx-assoc costs</td>
<td>$172</td>
<td>$246</td>
<td>$74 ($-40,$197)</td>
</tr>
<tr>
<td>Total costs</td>
<td>$10,021</td>
<td>$10,615</td>
<td>$594 ($-4510,$5331)</td>
</tr>
</tbody>
</table>

**Annual savings**
- Antibiotics: $302,400.00
- Infx-assoc costs: $533,000.00
- Total costs: $4,277,000.00

![Graph showing cost differences between AMP and UP]


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**Reduce Antimicrobial Resistance**

- Clinical Pulmonary Infection Score (CPIS)
  - > 6
  - Antibiotics for 10-21 days
  - Randomize
  - Ciprofloxacin for 3 days
  - Standard Care (antibiotics for 10-21 days)
  - Re-evaluate at 3 days

<table>
<thead>
<tr>
<th></th>
<th>Cipro</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic duration</td>
<td>3 days</td>
<td>10 days</td>
</tr>
<tr>
<td>LOS ICU</td>
<td>9 days</td>
<td>15 days</td>
</tr>
<tr>
<td>Antibiotic resistance/superinfection</td>
<td>15%</td>
<td>35%</td>
</tr>
</tbody>
</table>

![Flowchart showing treatment decision tree]

*Fishman, Am J Respir Crit Care Med 2000.*
Reduce Antimicrobial Resistance

- Decreased resistant gram-negative bacilli
- Decreased vancomycin-resistant Enterococcus (VRE)
- Decreased methicillin-resistant S. aureus (MRSA)

Apisarnthanarak A. Clin Infect Dis 2006;42:768
Carling et al. ICHE 2003;24:699-706
Khan et al. J Hosp Infect 2004;54:104-8
Singh et al. Am J Respir Crit Care Med 2000;162:505-11

Decrease Adverse Events

Decrease Adverse Events


Antimicrobial Stewardship

Prior Authorization
Education
IV to PO Transition
Optimize Dosing
Develop Guidelines and Decision Support
Formulary Review and Restriction
Prospective Audit and Feedback
Track Antibiotic Use and Resistance

Antimicrobial Stewardship Team

Penn Medicine
Prevalence of Antimicrobial Stewardship

- 48-60% of US hospitals and long-term care facilities have antimicrobial stewardship programs
  - As few as 15.4% of community hospitals have antimicrobial stewardship or antibiotic subcommittees
  - Varying degrees of activity: most frequent intervention is automatic stop orders and restricted formulary

- Barriers to implementation
  - Lack of personnel (55%)
  - Lack of financial resources (36%)
  - Opposition from prescribers (27%)
  - Resistance from administration (14%)

Essential ASP Team Members

- **Physician(s)**
  - Essential to interact with the medical staff and build political capital
  - Ideally trained in infectious diseases (at least an interest in antibiotic use and patient safety)
  - Diplomatic and collegial

- **Pharmacist(s)**
  - Essential to have a liaison to pharmacy and pharmacy administration
  - Often best poised to make interventions and answer pager
  - Ideally trained in infectious diseases
  - Diplomatic and collegial and comfortable advising physicians

- **Clinical Microbiologist**

- **Link with Infection Prevention and Control Team**
Strategies of Antimicrobial Stewardship

Prior Approval
- **Definition**: Prescribers need to contact ASP team member to request approval
- **Advantages**:
  - Advice on work-up
  - Advice on empiric abx
  - Stop abx before they start
- **Disadvantages**:
  - Time consuming
  - Misses opportunities to de-escalate after
  - Barrier to prompt antibiotic administration

Prospective Audit & Feedback
- **Definition**: ASP team members review antibiotic prescriptions and intervene
- **Advantages**:
  - Schedulable
  - De-escalate antibiotics
  - Can use clinical data
- **Disadvantages**:
  - Harder to stop abx
  - Will not capture unnecessary empiric abx
Prior Authorization

- Arguably the most effective strategy of antimicrobial stewardship
- Very effective at halting use of antimicrobials you really want to restrict
  - High-cost antibiotics
  - “Big-gun” antibiotics

Mehta J, ID Week, 2013.

Prospective Audit & Feedback

- Often requires a focus
  - Drug(s) – expensive or broad-spectrum
    - Easy to find cases from reviewing pharmacy records
  - Disease(s) – asymptomatic bacteriuria, UTI, pneumonia, skin and soft tissue infections
    - More difficult to find cases but can identify “problem areas”
  - IV to PO conversion – typically focus on highly bioavailable agents (linezolid, fluoroquinolones, -azoles, etc.)
    - Cost of actual drugs do not differ much between oral and IV
  - Stopping Unnecessary Antibiotics/De-escalating Tx
    - Biomarkers – procalcitonin
    - Rapid diagnostics – matrix-assisted laser desorption/ionization time of flight (MALDI-TOF)
    - Electronic alerts
Procalcitonin

- Procalcitonin is a biomarker increased in bacterial infections and less so in other types of infections and inflammatory conditions.
- Use of procalcitonin decreased antibiotic consumption with no adverse outcomes (in 11 RCT’s for a variety of conditions including sepsis).
- Using a procalcitonin testing algorithm reduces:
  - Antibiotic treatment duration
  - Length of ICU stay by up to 2 days


MALDI-TOF

- Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can rapidly identify organisms following isolation from clinical specimens.
- Decreases time to organism identification by 1.2-1.5 days compared to traditional culture methods (84.0 to 55.9 hours, p < 0.001).
- When MALDI-TOF is linked with an antimicrobial stewardship program, it can:
  - Improve time to effective antibiotic (30.1 to 20.3 hours, p = 0.021)
  - Improve time to streamlined antibiotics (90.3 to 47.3 hours, p < 0.001)
  - Decrease hospital stay (11.9 to 9.3 days, p = 0.01)
  - Mean hospital costs ($45,709 to $26,162, p = 0.009)
  - May also decrease mortality and recurrence of bacteremia

Prescriber Interventions

- Those that prescribe the most know the least and most of the issues that exist are a result of a knowledge deficit on best practices in antimicrobial practices
- The prescribers may understand basic principles, but they often lack the basic point-of-care information on how to put knowledge into practice

Changing Behavior

• Antibiotic prescription is motivated by a variety of factors:
  • To cover gaps that exist in their own knowledge
  • Fear
  • Personal experience
  • Literature and evidence-based practice
  • Level of training
  • Try to do the best for the patient
    – The more the better
    – The earlier the better
    – Just in case
  • Medical hierarchy
• Understanding these barriers to change is crucial to overcome (or bypass them)
• Understanding the audience allows for targeted approach

Antimicrobial Stewardship in Daily Practice

• Order the appropriate diagnostic studies
• Prescribe appropriate antibiotics based on indication
• Re-evaluate and streamline antibiotics based on results of diagnostic studies (24 hours, 48 hours, 72 hours, etc.)
• Clearly define duration of therapy
Antimicrobial Stewardship in Daily Practice

- Order the appropriate diagnostic studies
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Diagnostic Studies: A Common Example

- 70-year-old male with traumatic brain injury sedated on the ventilator with indwelling urinary catheter, central line, sacral decubitus ulcer on phenytoin who has been febrile for 7 days
- Fever and leukocytosis are common in the ICU setting
  - 79% of patients in ICU are febrile at least once
  - 85% of patients in ICU have leukocytosis
  - 42% of patients in ICU have both during first week
- A fever and leukocytosis frequently trigger a battery of diagnostic tests that are costly and produce misleading results, thereby exposing patients to unnecessary antibiotics

Diagnostic Studies

- Appropriate specimens should be obtained prior to initiating antibiotics
- Some centers have suppressed overly broad and inappropriate antibiotics should be suppressed with susceptibility results
- Treatment of colonizing organisms should be avoided

Urine Cultures

- Asymptomatic bacteriuria is common
  - Post-menopausal females: 2.8-8.6%
  - Long-term care residents: 15-50%
- Pyuria (in the absence of symptoms) is not an acceptable treatment indication
- Treatment of asymptomatic bacteriuria is associated with no decreased risk of UTI and is associated with increased adverse events
- Algorithms to promote appropriate interpretation of urine cultures have decreased antibiotic use by 50%

Respiratory Cultures

- The average ICU patient who has respiratory cultures sent had > 2 respiratory cultures sent during their hospitalization.
- Specificity of respiratory cultures for infection is as low as 46%.
- Treatment is directed against positive respiratory cultures in 76% of cases.
- Evaluation for leukocytes in respiratory specimen indicative of purulent sputum and rejection of specimens if these conditions are not met can increase specificity.


Mandatory Antibiotic “Time-Out”

- Mandatory reassessment at days 3, 7, and 10 also showed decrease in MDROs causing nosocomial infections:
  - All: 37% to 13%, p < 0.001
  - MRSA: 61% to 13%, p < 0.001
  - Ceftriaxone-resistant Enterobacteriaceae: 37% to 13%, p < 0.001

- A mandatory day 3 reassessment for all patients receiving an antibiotic reduced average treatment durations in the ICU from 14.1 to 11.9 days (p < 0.001).

- None of these interventions associated with any worse clinical outcomes.

Antimicrobial Stewardship in Daily Practice

- Order the appropriate diagnostic studies
- Prescribe appropriate antibiotics based on indication
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- Clearly define duration of therapy
Prescribe Antibiotics Based on Indication

- The administrative wheels are moving towards requiring antibiotics prescriptions be tied to an indication
- Understanding local treatment guidelines is essential
- Understanding areas where providers often deviate from the guidelines is just as essential
  - Skin in soft tissue infections (SSTI)
    - *Streptococcus* and *Staphylococcus aureus* make up to > 90% of SSTIs
    - 60-81% of patients receive broad-spectrum gram-negative coverage
    - 72-83% of patients receive anaerobic coverage
  - Healthcare-associated pneumonia (HCAP)
    - Vancomycin is frequently used for treatment of HCAP, but infrequently discontinued
    - Negative throat and nasal culture for MRSA (or negative nasal PCR for MRSA) has ~98% negative predictive value for MRSA pneumonia
    - Discontinuation of vancomycin with negative throat and nasal cultures in patients with clinical pulmonary infection score (CPIS) < 6 showed no change in mortality
      

Antimicrobial Stewardship in Daily Practice

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Antimicrobial Stewardship in Daily Practice

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Define Duration of Therapy

- Use the shortest effective course

<table>
<thead>
<tr>
<th>Type of Infectious Diseases</th>
<th>Recommended duration of antimicrobial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>≥ 5 days</td>
</tr>
<tr>
<td>HAP, VAP, and HCAP</td>
<td></td>
</tr>
<tr>
<td>Bacteria other than NFGNB</td>
<td>7 days</td>
</tr>
<tr>
<td>NFGNB</td>
<td>14 days</td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>7 days</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>7 days</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>21 days</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>21 days</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>21 days</td>
</tr>
<tr>
<td>CRSI</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus spp.</td>
<td>5–7 days</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4–6 weeks*</td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>4–6 weeks*</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>7–14 days</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>7–14 days</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>14 days after the first negative BC</td>
</tr>
<tr>
<td>Native valve endocarditis</td>
<td></td>
</tr>
<tr>
<td>Viridans Group and S. bovis (MIC &gt; 12, ≤0.5μg/mL)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Viridans Group and S. bovis (MIC ≤ 12μg/mL)</td>
<td>14 days</td>
</tr>
<tr>
<td>MSSA Uncomplicated right-sided</td>
<td>14 days</td>
</tr>
<tr>
<td>MRSA</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td></td>
</tr>
<tr>
<td>Viridans Group and S. bovis (MIC ≤ 12μg/mL)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>MSSA and MRSA</td>
<td>≥6 weeks</td>
</tr>
<tr>
<td>Complicated intra-abdominal infection</td>
<td>4–7 days</td>
</tr>
<tr>
<td>Peptostreptococci</td>
<td>14 days</td>
</tr>
</tbody>
</table>
**Ventilator-Associated Pneumonia**

- Prospective, randomized, double-blind trial for treatment of VAP comparing 8 days to 15 days of treatment showed no difference in mortality or recurrence of infection
  - All patients received initial appropriate empiric therapy
  - Non-fermenters (*Acinetobacter, Burkholderia, Pseudomonas, Stenotrophomonas*, etc.) did not have higher mortality when 8 days compared to 15 days, but had higher rates of recurrence (40.6% vs. 25.4%)
- Formal daily guideline reassessment by an infectious diseases consultant for VAP resulted in:
  - Shorter duration of treatment: 6.0 vs. 8.0 days ($p = 0.001$)
  - Less antibiotic-resistant superinfections in the intervention group (14% vs. 38%, $p = 0.017$)
- Mandatory reevaluation of clinical, radiographic, and laboratory data at day 3 for patients with pulmonary infiltrates led to:
  - Less patients being treated beyond 3 days (28% vs. 93%, $p < 0.001$)
  - Shorter duration of therapy (3.0 vs. 9.8 days, $p < 0.001$)
  - Reduction in ESBL *Klebsiella* (68% to 44%, $p < 0.001$) and carbapenem-resistant *Pseudomonas* (61% to 41%, $p < 0.001$)


**Community-Acquired Pneumonia (CAP)**

- Randomized, double-blind study compared 3-day v. 8-day duration of therapy for mild-moderate CAP
  - 28-day clinical cure rates in 3-day (90%) and 8-day (88%) groups similar
  - Decreased adverse events in 3-day (11%) versus 8-day group (22%)
- Despite evidence for VAP duration, average duration of therapy for VAP is 15 days!
- Education followed by prospective audit and feedback decreases duration of antibiotic therapy for pneumonia
  - Duration of therapy decreased from 10 to 7 days
  - Antibiotics narrowed more frequency (67% vs. 19%)

Urinary Tract Infections

- **Uncomplicated cystitis**
  - 3 days if using TMP-SMX or fluoroquinolone
  - 5 days if using nitrofurantoin
  - 7 days if using cephalosporins

- **Pyelonephritis**
  - 7 days if using ciprofloxacin
  - 5 days if using high-dose levofloxacin (750 mg)

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**Full Circle?**

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and, by exposing his microbes to non-lethal quantities of the drug, educate them to resist penicillin…. *I hope this evil can be averted.*”

- Sir Alexander Fleming (1945)