Antimicrobial stewardship and the clinical pharmacist
Gregory Matsuura PharmD. BCPS

Objectives
• Understand the potential “collateral damage” created by antimicrobial use
• Identify the different strategies used to limit antimicrobial overuse
• Describe the prominent role pharmacists can take in antimicrobial stewardship programs
• Discuss the different methods used to monitor the impact of the antimicrobial stewardship programs

Case example
NM is 42 year old male with purulent nasal discharge or facial pain lasting 3 days. He comes into the pharmacy looking for an oral decongestant. He believes he has a sinusitis similar to what he had a few years ago.

Should you recommend he obtain an antibiotic prescription for treatment?
Case an point: sinusitis

- Viral infection is the cause of up to 98% of cases
- Meta-analysis of 57 studies
  - Cure or improvement rate:
    - placebo group (80%) vs. antibiotic group (90%)
- IDSA guidelines → consider antibiotics only if...
  - Severe (≥ 39°C [102°F]): ≥ 3-4 days
  - Worsening after initial (5-6 days) URI: ≥ 3-4 days
  - Persistent symptoms & not improving: >10 days


Antibiotic Collateral Damage

- Broad scale negative events associated with antibiotic use
  - Singular patient events → facility wide effects
  - Development of antibiotic resistance
    - Development multi-drug resistant gram-negatives
    - Colonization with resistant gram-positives
  - Clostridium difficile infection (CDI)

Matsuura GT and Garrison MW. Hosp Pharm 2011;46(10):758-768

Mobile elements of bacterial resistance

- **Transposons**
  - Creation of multiple antibiotic-resistance
  - Can transfer to either chromosomes or plasmids
  - Ex) Vancomycin resistance in enterococcus (*vanA*)

- **Plasmids**
  - Extrachromosomal elements
  - *Extremely common* in bacteria
  - Transfer between different bacterial species
  - Ex) Extended-spectrum β-lactamases

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Gram negative resistance

- **Extended-spectrum β-lactamases (ESBLs)**
  - Broad spectrum β-lactamases identified in 1980’s
  - Associated with broad-spectrum cephalosporin use

- **Carbapenemases**
  - Klebsiella pneumoniae carbapenemase (KPC)
    - Observed in multiple other species
  - New delhi metallo-beta-lactamase 1 (NDM-1)
    - Cross resistance unrelated antimicrobials
    - Medical care in either India or Pakistan

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<table>
<thead>
<tr>
<th>β-Lactamases</th>
<th>Substrates</th>
<th>Method encoded</th>
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<tbody>
<tr>
<td>TEM</td>
<td>Broad spectrum penicillins, extended-spectrum cephalosporins, and aztreonam</td>
<td>Plasmid</td>
</tr>
<tr>
<td>SHV</td>
<td>Same as TEM</td>
<td>Plasmid</td>
</tr>
<tr>
<td>CTX-M</td>
<td>Same as TEM and cefepime for some isolates</td>
<td>Plasmid</td>
</tr>
<tr>
<td>AmpC</td>
<td>Same as TEM plus cephamycins, inhibitor resistant</td>
<td>Chromosomal</td>
</tr>
<tr>
<td>KPC</td>
<td>Same as TEM plus cephamycins and carbapenems</td>
<td>Plasmid</td>
</tr>
</tbody>
</table>
ESBL: Not just a hospital issue

<table>
<thead>
<tr>
<th></th>
<th>Community onset</th>
<th>Hospital onset</th>
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<tbody>
<tr>
<td><strong>ESBL type</strong></td>
<td>CTX-M</td>
<td>TEM and SHV</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td>E. coli</td>
<td>Klebsiella Sp.</td>
</tr>
<tr>
<td><strong>Infection type</strong></td>
<td>Predominately UTIs</td>
<td>Pulmonary, intra-abdominal, bacteremia</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Recurrent UTIs, previous antibiotics (Fluoroquinolones; cephalosporins), nursing-home, previous hospital stay, diabetes</td>
<td>Prolonged hospital stay, ICU (intubations), catheterization (urinary or arterial), previous antibiotics (cephalosporins)</td>
</tr>
</tbody>
</table>

Pout JD and Laupland KB. Lancet Infect Dis 2008;159-166.

Antibiotic pressure and MRSA colonization

- β-lactam or fluoroquinolone-treated vs. controls
  - Increased patient MRSA carriage with antibiotic use
  - Median bacterial loads were significantly higher
    - On day 7, 14, and 21 (P<0.05).
  - Two weeks after discontinuation of antibiotics
    - Loads decreased by 2-5log(10)cfu/swab
  - Increased MRSA present in the environment
    - Beta-lactams (relative risk: 3.55; 95% CI 1.30-9.62)
    - Fluoroquinolones (relative risk: 4.32; 95% CI 1.52-12.31)


Vancomycin Resistant enterococcus

- Gastrointestinal colonization
  - Difficult to eradicate
  - Persists up to 3 years
- Associated with antibiotic use
  - Carbapenems, 3rd generation cephalosporins, antibiotics active against anaerobes, and vancomycin
- >1 week survival in the environment
  - Furniture
  - Monitoring devices
  - Automated medication dispensers

The cost of antimicrobial resistance

<table>
<thead>
<tr>
<th></th>
<th>Attributable Length of stay (Days)</th>
<th>Attributable cost</th>
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<tbody>
<tr>
<td>Resistant gram-negative infection</td>
<td>5</td>
<td>$38,121</td>
</tr>
<tr>
<td>VRE infection</td>
<td>6.2</td>
<td>$12,766</td>
</tr>
<tr>
<td>MRSA Surgical site infection</td>
<td>2.6</td>
<td>$13,901</td>
</tr>
<tr>
<td>MRSA Bacteremia</td>
<td>2.2</td>
<td>$6916</td>
</tr>
</tbody>
</table>


Reducing antimicrobial resistance

- Reducing overall exposure
- "just long enough" (but not too long)
  - Comparison of 8 vs 15 days of therapy for VAP
  - Length of ICU stay, and mortality rates on day 60 for the 2 groups did not differ

  Multi-resistant pathogens emerged less frequently in those who had received 8 days of antibiotics (42.1% vs. 62.0% of pulmonary recurrences, P=0.04)


Reducing antimicrobial resistance

- Optimizing dosing — "giving just enough"
  - Selection of single step mutants

<table>
<thead>
<tr>
<th>Development of resistance in 8 strains of P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
</tr>
<tr>
<td>2 x MIC</td>
</tr>
<tr>
<td>4 x MIC</td>
</tr>
<tr>
<td>8 x MIC</td>
</tr>
</tbody>
</table>

**Clostridium difficile**

- Anaerobic spore-forming bacillus
- 2000 to 2009: Primary CDI cases more than tripled
- Hospital onset cost
  - $5,042 – $7,179 per case
  - $897 million to $1.3 billion annually
- Emerging Infections Programs
  - 94% of cases associated with health care

**Transmission of C. difficile**

- Frequently transmitted by health-care workers
- Alcohol based sanitizers
  - Only active against vegetative forms
- Glove use
  - "Even using soap and water, the removal of C. difficile spores is more challenging than the removal or inactivation of other common pathogens"
- Sporicidal disinfectants
  - Hypochlorite-based disinfectants; Bleach (1:10)

**Prevention of CDI**

- Early and reliable detection
  - >3 unformed stools in 24hr period
  - Enzyme immunoassay or nucleic acid amplification
- Isolation of symptomatic cases
- Reducing environmental surface contamination
- Improving antibiotic use
  - Antibiotic use increases CDI risk
    - Seven to ten-fold while taking antibiotic
    - Three-fold for subsequent 2 months
Antibiotic stewardship

- Multidisciplinary activity
- Focused on maximizing therapeutic outcomes
- Minimizing the unintended consequences of antimicrobial use
  - Increased resistance
  - Adverse patient outcomes
  - Increased cost
  - Increased hospital length of stay


Methods of Stewardship

- Preauthorization/Formulary restriction
- Clinical Pathways
- Prospective audit with feedback
- Dose optimization
- IV to PO conversion
- De-escalation/streamlining
Preauthorization/Formulary restriction

- Front end method
  - “On call”: 24/7 coverage (residents/fellows)
  - Delayed review: temporary 24-48 approval
- Depends who is doing it...
  - Chief resident or attending → **No impact** on use
  - Pharmacist and an ID physician
    - Increased clinical cure: 64% vs. 42%
    - Trend ↓ cost attributable to infection: $695

Devito JM, John JE. Arch Intern Med 1985,145:1053-1056

Antibiotic restriction program (ARP)

- Impact of an ARP on antibiotic utilization for CAP
- Multidisciplinary team
  - ID staff physicians and clinical/staff pharmacists
- Results
  - Mean length of stay **reduced** by 1.6 days
  - Associated with $943 savings **per patient**
  - Trend to decreased 30 day readmission rate
  - Decrease in antibiotic use
    - **Both restricted and unrestricted** use declined by 14%


Reducing selective pressure

- Goal: Reducing **overall** antibiotic exposure
- Always look at the big picture
  - Chasing the next problem
  - Monitor overall trends → issues change over time
- “squeezing the balloon”
  - Exchanging on problem for another
Good news! We took care of that first problem...

...The bad news is we created another...

Antibiotic restriction policy: Unforeseen results

- **Restricted** ceftazidime and fluoroquinolones in ICU
  - 18 month intervention period
  - Fluoroquinolone use ↓ 92.1%
  - Ceftazidime use ↓ 96.4%
  - Cefepime use ↑ 270%
- **Increase** in carbapenem-resistance
  - *A. baumannii* and *P. aeruginosa*
- **Decrease** in susceptibility rates
  - *K. pneumoniae* to pip-tazo (65% vs 18% p<0.05)
  - *K. pneumoniae* to cefepime (35% vs 19% p<0.01)


Clinical pathways/Guideline implementation: (It’s not us vs. them)

**Barriers:**
- Fear of liability
- Habit
- Peer influence

**Countering issues:**
- Increased resistance
- Adverse patient outcomes
- Increased cost
- Increased LOS

- Prescribers agree in principle but not in practice
- Passive education only marginally effective

**Guidelines incorporating local microbiology and Resistance patterns**
- Education with prescriber feedback

Dosing optimization

- Vancomycin & MRSA Treatment Failure
  - Initial vancomycin trough <15 mg/L predictor of vancomycin failure (Adjusted odds ratio, 2.00; 95% CI, 1.25–3.22)
- Extended Infusion Pip-Tazo & P. aeruginosa
  - 14-day mortality rate was significantly lower compared to intermittent-infusion (12.2% vs. 31.6%, respectively; P=.04)


Mutant selection by dosing

Knowing the numbers:
Automated susceptibility

- FDA regulates antimicrobial susceptibility testing (AST) devices
  - Breakpoints specified in the antimicrobial drug product’s label
  - “FDA has found it difficult” to ensure labeling is current

Clinical and Laboratory Standards Institute (CLSI)

### CLSI recommended MIC (μg/mL) breakpoints for Enterobacteriaceae

<table>
<thead>
<tr>
<th></th>
<th>Previous MIC (S/I/R)</th>
<th>Revised MIC (S/I/R)</th>
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<tbody>
<tr>
<td>Cefazolin</td>
<td>≤8 / 16 / ≥ 32</td>
<td>≤1 / 2 / ≥ 4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤8 /16-32 / ≥ 16</td>
<td>≤1 / 2 / ≥ 4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≤8 / 16 / ≥ 32</td>
<td>≤4 / 8 / ≥ 16</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤4 / 8 / ≥ 16</td>
<td>≤1 / 2 / ≥ 4</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤2 / 4 / ≥ 8</td>
<td>≤0.5 / 1 / ≥ 2</td>
</tr>
</tbody>
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Parenteral to Oral conversion

- Pharmacist-initiated conversion from IV to PO therapy
- 12-month period
  - Cost savings for drug acquisition were $15,149
  - Decreased length of stay by 1.53 days
  - Cost savings for LOS reduction → $61,072

**A Low-Hanging fruit?**

A study which included 128 VA hospitals evaluated 884,740 IV and 830,572 PO Fluoroquinolone doses:

Avoidable IV FQ accounted for 46.8% of use.


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Prospective audit with intervention and feedback

- IDSA 2007 guidelines: A-I recommendation
- Carney Hospital AST program
  - 7 year period
  - ↓ 22% parenteral broad-spectrum antibiotic use
  - ↓ Ceftazidime resistant enterobacteraceae
  - ↓ rates of C. diff infection

ID pharmacist shares the responsibility for evaluating each patient and making recommendations with an ID specialist physician

Pharmacists as “multipliers”

- Grady Memorial Hospital AST program
  - “Uninvited” patient evaluation by an AST physician
  - Discussed with the critical care pharmacist
  - Associated with protection against emergence of resistance OR 0.42 (95% CI 0.267-0.665)

“...critical care pharmacists, who serve as ambassadors of the antimicrobial utilization physician messages and acted as multipliers of antimicrobial management knowledge and local policies.”

De-escalation/streamlining

- Targets for de-escalation are often continued broad spectrum empiric therapy
- De-escalation can be based on results from
  - Patient presentation → rate of progress
  - Microbiologic data → what has been cultured
- Goal: decrease antimicrobial exposure
  - Reduce incidence of multi-resistant pathogens
  - Reduce CDI risk

Stewardship:
Not a “temporary solution”!!

- University of Maryland medical Center
- Antimicrobial stewardship program
- 45.8% decrease
  - 2001: $44,181 per 1000 patient days
  - 2008: $23,933 per 1000 patient days
- Program discontinued
  - 2010: $31,653 per 1000 patient days
  (32.3% increase)
Examples of antibiotic stewardship programs in Washington State

- Harborview medical center
- UW medical center
- Swedish medical center
- Providence Sacred Heart Medical Center
- Yakima Valley Memorial Hospital
- Providence St Mary Medical Center

Regional/State groups

- Antimicrobial Stewardship Committee of Seattle
- Infectious Diseases Society of Washington
- Providence Health & Services AMS subgroup
- Qualis Health
  - CDI Action network

Lets collaborate!!

...That’s great!! Um...why do your numbers look different...
Benchmarking

- Antimicrobial use and resistance reports
  - Reliable reports to clinicians can improve the appropriateness of antimicrobial usage
  - Variety of methods exist
    - Doses dispensed
    - Doses billed
    - Cost per patient
    - Defined daily doses


Defined daily doses

- Defined daily doses (DDD) conversion factors
  - Developed from the World Health Organization
  - [http://www.whocc.no/atc_ddd_index](http://www.whocc.no/atc_ddd_index)

Example: Ampicillin

Overestimates the number of days of therapy by ~4-fold, because the WHO-recommended DDD for ampicillin (alone or combined with sulbactam) is 2 g, whereas the mean administered daily dose was >8 g.


National Healthcare Safety Network (NHSN) AUR Option

- Objectives:
  - Assist hospitals in collecting data on antimicrobial use and/or resistance
  - Feedback rates to encourage appropriate prescribing as part of antimicrobial stewardship
  - Provide risk-adjusted inter- and intra-facility comparisons
Data Elements for Antimicrobial Days

- Days of therapy (DOT)
- Days present by month, patient location
- Only computerized administered data
  - Electronic medication administration record (eMAR)
  - Bar code medication administration (BCMA)
- Usage derived from other data sources (i.e., pharmacy orders, doses dispensed, doses billed) cannot be submitted.

Antimicrobial Use Reporting

CDC
NHSN

Facility
Vendor

For more information (and updates)

- CDC website
- Society of infectious disease pharmacists
  - http://www.sidp.org/
Yakima Valley Memorial Hospital

- 225 bed acute care community hospital
- Community & hospitalist providers
- 3 independent ID specialists
- AMS Team:
  - 0.5 FTE pharmacist (AMS/clinical informatics)
  - ≈1 hour/week ID physician
- Infection control
- Microbiology
- Clinical Floor pharmacists (5 teams)
PDF report of patients on Abx therapy, “Follow-up” notes by pharmacists

EMR reviewed → Additional sources (RNs, Floor pharmacists, Micro lab)

Discussion with ID physician

Direct case discussion with physician

Targeted review

• Patients with initial diagnosis-therapy mismatch
• Targeted antimicrobials
• Isolate resistant/not covered by current abx
• Potential IV – PO switch
• Broad spectrum abx >3 days
• Duration >7 days
Clinical timeline

- Clinical response; Preliminary cx; IV to PO
- Final culture results
- Planned duration; Infusion care
- Review long term plan

Documented Antibiotic Review Team Interventions
- 1/1/2010-12/31/11 (n=645)
  - Streamline/de-escalate coverage 27%
  - Dosing change 29.7%
  - Antibiotic mis-match 13%
  - IV to PO 10.2%

A minor example: Aztreonam

<table>
<thead>
<tr>
<th>Year</th>
<th>DDD/1000</th>
<th>DOT/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2009</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2010</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2011</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Target antibiotic example: Pip-Tazo

<table>
<thead>
<tr>
<th></th>
<th>DDD/ 1000 pt days</th>
<th>DOT/ 1000 pt days</th>
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<tbody>
<tr>
<td>2009</td>
<td>75.6</td>
<td>105.1</td>
</tr>
<tr>
<td>2010</td>
<td>73.4</td>
<td>98.6</td>
</tr>
<tr>
<td>2011</td>
<td>74.8</td>
<td>96.2</td>
</tr>
</tbody>
</table>

A few resources

- Society of infectious diseases pharmacists
  - Antibiotic Stewardship Certification Program for Pharmacists
- Mad ID [http://mad-id.org/](http://mad-id.org/)
  - Antimicrobial Stewardship Training Programs
- ASHP
- Nebraska medical center

Question #1

- How long can gastrointestinal VRE colonization persist?

  a) 1 – 2 weeks
  b) 2-6 months
  c) 1-2 years
  d) Up to 3 years
Question #2
• Which of the following is a plasmid-mediated broad-spectrum resistance that includes carbapenems?
  a) TEM
  b) SHC
  c) KPC
  d) CTX-M

Question #3
• How much of an increased risk of developing a *Clostridium difficile* Infection does a patient have while taking antibiotics?
  a) Two-fold
  b) Three to four-fold
  c) Five to six-fold
  d) Seven to ten-fold

Question #4
• Which of the following methods of reducing antibiotic use has been associated with the “squeezing the balloon” effect?
  a) IV to PO switch
  b) Prospective review with feedback
  c) Preauthorization/Formulary restriction
  d) De-escalation/streamlining
Question #5

• Which is not an effective method in reducing patient to patient transmission in a health care setting?

a) Alcohol based hand sanitizer  
b) Glove use  
c) Isolation of symptomatic cases  
d) Hypochlorite-based disinfectants