Antimicrobial Stewardship

A case-based approach

Sarah Doernberg, MD, MAS

Outline

- Warm-up exercise
- Why is antimicrobial stewardship important?
- What is stewardship?
- Stewardship cases
- ASP case studies

Warm-up

- Find someone sitting next to you
- 2 minutes: Think about a time where you think antibiotic management could have gone better. Please share with the person sitting next to you and share what factors contributed
- Then, summarize with 1-2 words and write on your index card
  - E.g. Treated viral infection with antibiotics due to pressure from patient → Family pressure, treatment of non-bacterial infection

Disclosures: Consultant for Actelion, prior research studies with Cerexa, Merck, Cubist
Factors contributing to imperfect antibiotic management

Almost 40% of inpatients receive antibiotics on a given day

*In 2006, 63.5% of patients at 35 University Health System Consortium hospitals received at least one dose of antibiotics during their hospitalization

30% of inpatient antibiotic use is unnecessary
• 58% received ≥ 1 day of unnecessary antibiotics

30% of outpatient use is unnecessary!
• Over 12% of outpatient visits result in an antibiotic
• 1 outpatient antibiotic prescription per every 2 people annually
• Only half of rx’s for respiratory conditions were estimated to be needed
Sir Alexander Fleming, 1945 Nobel Prize Lecture

**Penicillin**

Overdose and poisoning the patient. There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

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 make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects

---

Prevailing attitude from another Nobel Prize winner, Sir Frank MacFarlane Burnet

“If one looks around the medical scene in North America or Australia, the most important current change he sees is the rapidly diminishing importance of infectious diseases. The fever hospitals are vanishing or being turned to other uses. With full use of the knowledge we already possess, the effective control of every important infectious disease, with the one outstanding exception of poliomyelitis, is possible”

---

Timeline of antibiotic resistance

CDC’s top drug-resistant threats

<table>
<thead>
<tr>
<th>Urgent</th>
<th>Serious</th>
<th>Concerning</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>MDR Acinetobacter</td>
<td>VRE</td>
</tr>
<tr>
<td>CRE</td>
<td>Drug-R Campylobacter</td>
<td>Erythromycin-R Gp A</td>
</tr>
<tr>
<td>Drug-resistant</td>
<td>Candida</td>
<td>Gp B Strep</td>
</tr>
<tr>
<td>genus</td>
<td>Fluoc-R Genitalis</td>
<td>ESBL</td>
</tr>
<tr>
<td></td>
<td>VRE</td>
<td>MDR Pseudomonas</td>
</tr>
<tr>
<td></td>
<td>Drug-R Salmonella</td>
<td>Drug-R Shigella</td>
</tr>
<tr>
<td></td>
<td>MRSAX</td>
<td>MRSA</td>
</tr>
<tr>
<td></td>
<td>Drug-R Strept pneumo</td>
<td>Drug-R Strept pneumo</td>
</tr>
<tr>
<td></td>
<td>MDR/XDR TB</td>
<td></td>
</tr>
</tbody>
</table>

http://chicago-mosaic.medill.northwestern.edu/antibiotic-resistance-superbugs/

https://www.cdc.gov/drugresistance/biggest_threats.html
“Last resort” antibiotics are endangered

Timeline of drug development
Pre-human research
Clinical development
FDA filing, approval, launch preparation

From the IOM
“The absence of new classes in the pipeline… is alarming when one considers the ever-increasing number of antibiotic-resistant organisms.”

New approved antimicrobials in the US
Current pipeline is looking up

Antibiotics in Clinical Development With the Potential to Treat Infectious Caused by Resistant Gram-Negative ESIRAP Pathogens

There is a critical need for new therapies to treat deadly infections caused by Gram-negative ESIRAP pathogens—bacteria that are often resistant to available antibiotics. Only a handful of new treatments with the potential to address these serious threats are currently in development.


87% of physicians agree that AMR is a public health problem, but...

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of the drug in treating community-acquired pneumonia</td>
<td>1.6</td>
</tr>
<tr>
<td>Patient severity of illness</td>
<td>3.1</td>
</tr>
<tr>
<td>Previous experience and knowledge about the drug</td>
<td>4.1</td>
</tr>
<tr>
<td>Potential side effects</td>
<td>4.4</td>
</tr>
<tr>
<td>Ease of use</td>
<td>4.6</td>
</tr>
<tr>
<td>Cost to patient</td>
<td>4.9</td>
</tr>
<tr>
<td>Risk of contributing to the problem of antibiotic resistance</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Risk avoidance depends on the clinical population

Antibiotic use also varies by prescribers
% of people in Europe rx’d for cold/flu/sore throat ranges from 11% to 81%

Validated national cultural dimensions explain almost half of this antibiotic variation
- Uncertainty avoidance
  - Extent the society tolerates uncertainty and ambiguity
- Masculinity
  - Distribution of emotional roles between genders
- Assertive and competitive


Borg MA. J Antimicrob Chemother 2012;67:763-768

So what can be done to improve our antibiotic use?

What is antimicrobial stewardship?
Interventions designed to optimize the appropriate use of antimicrobials

Key assumptions
- Prescribing behaviors can be changed
- Antimicrobial use is a primary driving force in the development of AMR
- ↓ in antimicrobial use will ↓ resistance
- Appropriate use improves patient outcomes and reduces costs


The stewardship program

Quality and safety
Pharmacy
IT services
Clinical Services
HEIC

PO+T
Opportunities for stewardship

Diagnostic work-up for suspected infection
- Guidelines
- Stewardship of laboratory testing
- Rapid diagnostics

Empirical therapy started
- Institutional guidelines
- Antibiotic available
- Computerized decision support
- Allergy testing
- Formulary restriction
- Prospective audit and feedback
- Automatic stops

Definitive therapy
- Prospective audit and feedback
- Antibiotic time-out
- Guidelines
- Cascade reporting
- Pharmacy interventions

What are the requirements for antimicrobial stewardship?

- 6/2016 the Joint Commission announced a new Antimicrobial Stewardship standard which will be evaluated starting 1/2017
- CMS has issued a proposed rule that would mandate ASPs in acute care and critical access hospitals as a Condition of Participation (CoP) in the Medicare Program

California Department of Public Health: Abuse Antibiotics, Go to Jail

- 2008: Senate Bill (SB) 739
  - “…all general acute care hospitals develop processes for evaluating the judicious use of antibiotics and monitor results using appropriate quality improvement committees
  - No enforcement provisions or funding
- 2010: SB 739 Enforcement
  - Medical lead for ASP hired, development of ASP programs
  - Evaluation of SB 739 compliance – without consequences
- 2014: SB 1311
  - Adopt and implement ASP policy, identify MD and PharmD leads, ensure formal ASP training, report activities to hospital quality
  - “…violation…constitutes a misdemeanor punishable by a fine not to exceed $1,000, by imprisonment in a county jail, or by both that fine and imprisonment.”

“By 2020, significant outcomes of Goal 1 will include:
- Establishment of antibiotic stewardship programs in all acute care hospitals and improved antibiotic stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.”

https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf

California Department of Public Health: Abuse Antibiotics, Go to Jail

- 2008: Senate Bill (SB) 739
  - “…all general acute care hospitals develop processes for evaluating the judicious use of antibiotics and monitor results using appropriate quality improvement committees
  - No enforcement provisions or funding
- 2010: SB 739 Enforcement
  - Medical lead for ASP hired, development of ASP programs
  - Evaluation of SB 739 compliance – without consequences
- 2014: SB 1311
  - Adopt and implement ASP policy, identify MD and PharmD leads, ensure formal ASP training, report activities to hospital quality
  - “…violation…constitutes a misdemeanor punishable by a fine not to exceed $1,000, by imprisonment in a county jail, or by both that fine and imprisonment.”

http://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201320140SB1311
Case

- A 51 y/o F presents to you in clinic with 1 week of rhinorrhea, facial pain, and low-grade fever. She recalls getting a “Z-pak” the last time she had this, after which she felt better within 3 days.
- She asks you for another course of antibiotics as she has an event approaching and wants to be better by that time.
- What is your next step?

A. Prescribe a course of azithromycin
B. Obtain further testing
C. Recommend alternative treatments and schedule a follow-up appointment
D. A+C
E. B+C
F. A+B+C

Acute infectious rhinosinusitis

- Other supportive features: HA, fever, fatigue, maxillary dental pain, cough, ear fullness
- 0.5-2% of URIs progress to bacterial infection
- 40-60% of ABRS resolves without treatment, though antibiotics can shorten the course
- Suspect ABRS if:
  - Sxs > 10 days without improvement
  - Sxs < 10 days with initial improvement but then worse (double sickening)

Inappropriate Rx of URI is common

- Study #1: 1662 veterans with URIs
  - 57% got antibiotics when not indicated
  - Predictors for inappropriate treatment: penicillin allergy (OR 2.8), cough (OR 1.6)
- Study #2: 184,032 ambulatory care visits
  - 12.6% associated with antibiotic use
  - 506 rx/1000 US population annually (or, ½ people)
    - 154 million prescriptions in ambulatory care
    - ~50% for respiratory conditions
    - Only 50% of these deemed appropriate
    - 34 million unnecessary rx’s
**CDC/ACP recommendations**

- Do not test or give abx for bronchitis unless you suspect PNA
- Test pts suspected to have gp A Strep pharyngitis. Treat if confirmed positive.
- Treat ARS only if sx > 10 days, severe sx/signs, double sickening
- Do not give antibiotics for the common cold!

**Resources for patients**

**Viruses or Bacteria**
What’s got you sick?

**Tests to support diagnosis of viral URI**

- Procalcitonin for dx of URI in the primary care setting
- PCT is released in response specifically to bacterial infections
  - Rises in 3 – 6 hrs, peaks 12-24 hrs, decline 50% over 24 hours
  - Correlated with infection severity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT (285)</th>
<th>Control (232)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>63 (22%)</td>
<td>68 (28%)</td>
<td>0.812</td>
</tr>
<tr>
<td>Abx initiation</td>
<td>114 (25%)</td>
<td>91 (20%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abx exposure</td>
<td>114 (25%)</td>
<td>91 (20%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Similar results in the ED setting and on the wards (CAP), though attenuated antibiotic results

**Delayed Rx strategies**

- RCT in Spain with 4 strategies for management of acute URIs
  - Immediate Rx (91% used abx)
  - Rx collection after 3 days if sx persisted (23% used abx)
  - Pt led decision about when to fill (33% used abx)
  - No Rx (12% used abx)
- Immediate Rx group had shorter severe sx (0.5-1.5 days)
- Patient satisfaction was high and equal
- Missed work was ↓ in delayed-strategy gps vs. either other group
- Those in the delayed-strategy groups had lower belief that abx worked
Stewardship interventions to improve Rx

- 47 primary care practices in Boston and LA with robust EMRs
- Interventions:
  - Computerized decision support with OTC medications
  - Accountable justification at time of Rx written


Opportunities for stewardship

Diagnostic work-up for suspected infection

- CDC guidelines
- PCT

Empirical therapy started

- Computerized decision support with accountable justification or suggested alternatives
- Peer comparisons

Definitive therapy

- Delayed Rx strategies

Case

- You are admitting a 53 y/o F from the ED with pyelonephritis. She has no risk factors for drug-resistant organisms.
- Her allergy list includes: Penicillin, ciprofloxacin
- What antibiotic will you choose?
  - A. Ceftriaxone
  - B. Aztreonam plus vancomycin
  - C. Ertapenem
  - D. Trimethoprim-sulfamethoxazole
  - E. That’s not a fair question!

Why are drug allergies important?

- Most common cause of fatal anaphylaxis in the United States (59%) and increasing incidence (0.27 to 0.51/million)
- But, still very rare: ~150 deaths annually
- And... Inaccurate PCN allergy label → adverse outcomes
Allergy evaluation for optimal MSSA Rx

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vanc</th>
<th>Hx-guided allergy eval</th>
<th>Skin test allergy eval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured, %</td>
<td>67.3</td>
<td>83.4</td>
<td>84.5</td>
</tr>
<tr>
<td>Recurrence, %</td>
<td>14.8</td>
<td>9.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Death, %</td>
<td>17.9</td>
<td>7.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Allergic reactions, %, total, %</td>
<td>3.0</td>
<td>2.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

What to do if your patient has a reported allergy

- Take a detailed history of the reaction
  - What drug?
  - What situation?
  - Character of rash
  - Mucus membrane involvement?
  - Organ damage?
  - Subsequent exposure (use EMR)

- Options
  - Full-dose challenge
  - Test-dose challenge
  - Desensitization
  - Skin testing

What is safe?

- Type II-IV rxn
  - Serum sickness
  - Stevens-Johnson
  - TEN
  - AIN
  - DRESS

- Type I (IgE-mediated)
  - Anaphylaxis
  - Angioedema
  - Hives
  - Unknown rxn w/o TEN, DRESS, etc.

- Mild
  - Itching
  - Rash (not hives)
  - EMR lists but pt denies

- Avoid PCN or ceph
  - Vancomycin 68 → 37%
  - Aztreonam 12 → 1%
  - Fluoroquinolones 15 → 3%
  - No Δ in adverse drug rxns

- Test dose for 3rd/4th ceph or -penem
  - Desensitization for 3rd/4th ceph or PCN
  - Alternative agent

- Full dose for 3rd/4th ceph or -penem
  - Test dose for 1st/2nd ceph or PCN

Opportunities for stewardship

- Diagnostic work-up for suspected infection
  - Skin testing for allergy

- Empirical therapy started
  - Decision support algorithm
  - Test doses

- Definitive therapy
  - Desensitization
Case

- You inherit the following patient from your colleague when you come on service:
  - 64 y/o M community-dweller with DMII, COPD, CAD
  - Admitted 3 days ago with shortness of breath, fever, cough
  - ROS negative for GI, urinary, neurological complaints
  - CXR with LLL infiltrate
  - UA with +LE, 10-15 WBCs
  - Urine culture with Enterococcus
  - Blood cultures negative
  - Routine MRSA nasal swab: negative
  - Pt is on ceftriaxone, azithromycin, and vancomycin for “CAP and UTI”

What antibiotics would you like to give?

A. Con’t ceftriaxone, azithro, vancomycin x 10 day course
B. Stop the vancomycin, continue ceftriaxone and azithro x 5 day total course
C. Stop the vancomycin, continue ceftriaxone and azithro x 10 day course
D. Stop the ceftriaxone and azithromycin, continue the vancomycin x 10 day course

When to treat MRSA CAP

- Very uncommon: 0.7% of large CAP cohort (n = 2259) had MRSA
- Peaks coincided with respiratory virus season
- Hemodialysis and DM had ↑ rates
- ~30% of patients were given anti-MRSA agents, though!
- MRSA nasal swabs:
  - PPV 11-35% but NPV 84-99% for MRSA pneumonia
- Sputum Gram stain and culture can be useful
- MRSA coverage should not be routine for CAP
- Consider if post-viral, hemodialysis, DM
- Especially if severe

Duration of therapy for CAP

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uranga A et al.</td>
<td>Non-blinded RCT of CAP patients in Spain (n = 312), most rx FQ</td>
<td>5 days, afebrile, and stable vs. treating MD discretion (median 10 days)</td>
</tr>
<tr>
<td>el Moussaoui R et al.</td>
<td>Blinded RCT in inpatients with mild to moderate CAP who have initial improvement</td>
<td>3 days vs. 8 days of rx in patients with initial improvement</td>
</tr>
<tr>
<td>Li JZ et al.</td>
<td>Meta-analysis of RCTs of CAP treatment duration in adults, 1980-2006 (n = 15)</td>
<td>≤ 7 days vs &gt; 7 days Macrolides more common</td>
</tr>
<tr>
<td>Dimopoulos G et al.</td>
<td>Meta-analysis of RCTs of CAP treatment duration in adults and kids (n = 7), 3-7 days vs. 7-10 days (adults) 3 days vs. 5 days (push)</td>
<td>No Δ in cure, mortality, relapse</td>
</tr>
</tbody>
</table>

References:
Asymptomatic bacteriuria

- Bacteria in the urine without any symptoms
- 50-100% also have pyuria
- Returning to our patient:
  - Admitted 3 days ago with shortness of breath, fever, cough
  - ROS negative for GI, urinary, neurological complaints
  - CXR with LLL infiltrate

Our patient: No treat

Disease probability

Take an antibiotic time-out!

- Consider:
  - Does this patient have a bacterial infection?
  - If so, is the patient on the right antibiotic(s), dose, and route?
  - Can a more targeted antibiotic be used (de-escalate)?
  - How long should the patient receive the antibiotic(s)?

Opportunities for stewardship

Diagnostic work-up for suspected infection

Think about No treat/Test threshold
MRSA nasal swab NPV can be useful

Empirical therapy started

Definitive therapy

Take an antibiotic time-out!

Shorten duration when able
Some ASP case studies

**CDC Core Elements**

<table>
<thead>
<tr>
<th>Element</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leadership support</td>
<td>Written statement, Financial support</td>
</tr>
<tr>
<td>Accountability</td>
<td>Physician leader</td>
</tr>
<tr>
<td>Drug expertise</td>
<td>PharmD leader</td>
</tr>
<tr>
<td>Multidisciplinary ASP</td>
<td>Clinicians, ICPS, QI, Micro, RN, IT</td>
</tr>
<tr>
<td>Policies and guidelines</td>
<td>Document dose/duration/indication, Local treatment guidelines</td>
</tr>
<tr>
<td>Specific interventions</td>
<td>Time-out, Prior authorization, Prospective audit and feedback</td>
</tr>
<tr>
<td>Pharmacy interventions</td>
<td>IV→PO, dose adjustment, PK/PD, duplicative rx alerts, stop orders</td>
</tr>
<tr>
<td>Diagnosis-specific guidelines</td>
<td>CAP, UTI, surgical pps, culture-proven ifxns, SSTI, MRSA, CDI</td>
</tr>
<tr>
<td>Tracking and reporting</td>
<td>Process, usage, outcomes, communication to prescribers</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
</tbody>
</table>

Rapid diagnostic testing +ASP for BSIs improves mortality

- With ASP: OR 0.64 (95% CI, 0.51–0.79)
- Without ASP: OR 0.72 (95% CI, 0.46–1.12)
- Time to effective Rx ↓ 5 hours
- LOS ↓ 2.5 days


Real-world example: Formulary restriction

After implementation of a prior auth system, one center reported:
- ↓ antimicrobials $70K
- ↑ susceptibility to antibiotics
- 83% → 95% (PsA imipenem)
- 84% → 98% (Klebsiella imipenem)
- No Δ LOS or mortality

Formulary restriction examples

Collateral damage of formulary restriction

- 80% ↓ cephalosporin use
- 44% ↓ ceftaz-R Klebsiella
- ↑69% imipenem-R PsA

Real-world example: Prospective audit and feedback
Real-world example: Prospective audit and feedback


Real-world example: Antibiotic guidelines

Take-home

- Antibiotics are limited resources
- Inappropriate or unnecessary antibiotic use is common
- Antibiotic stewardship is an approach to improving antibiotic use with the hopes of enhancing individual and societal outcomes
- There are many approaches you can use to improve your own antibiotic use
- Antibiotic stewardship programs also have multiple tools, of which formulary restriction and prospective audit and feedback are the backbone
Thank you!

Questions?