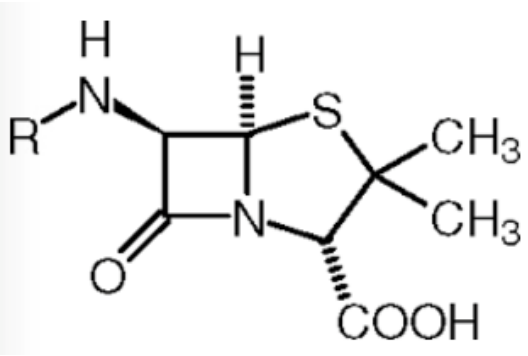

Antimicrobial Stewardship: The Role of the ID Pharmacist

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NewYork-Presbyterian Hospital
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Disclosures

- None

Objectives

1. Describe the infectious diseases (ID) pharmacist's role within an institution well as accompanying priorities and values

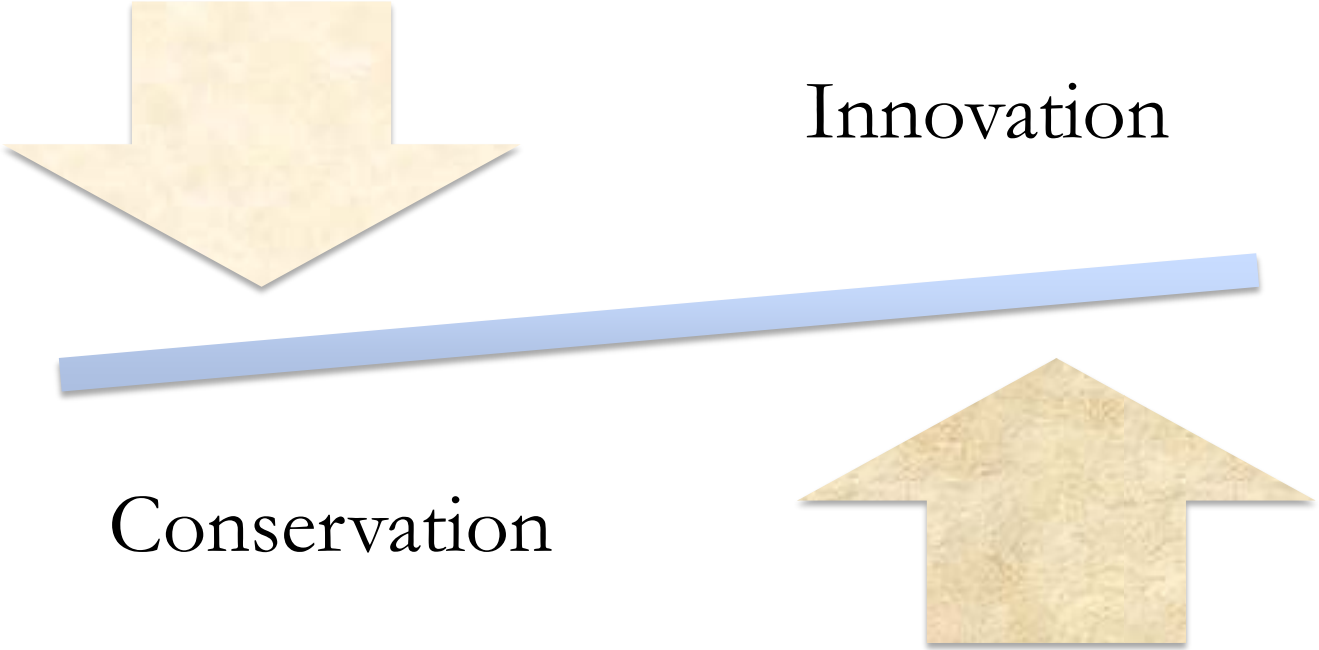
2. Outline antimicrobial stewardship strategies, such as antimicrobial restriction and post-prescription review

3. Discuss challenges of the ID pharmacist from a systems perspective and potential strategies to overcome them

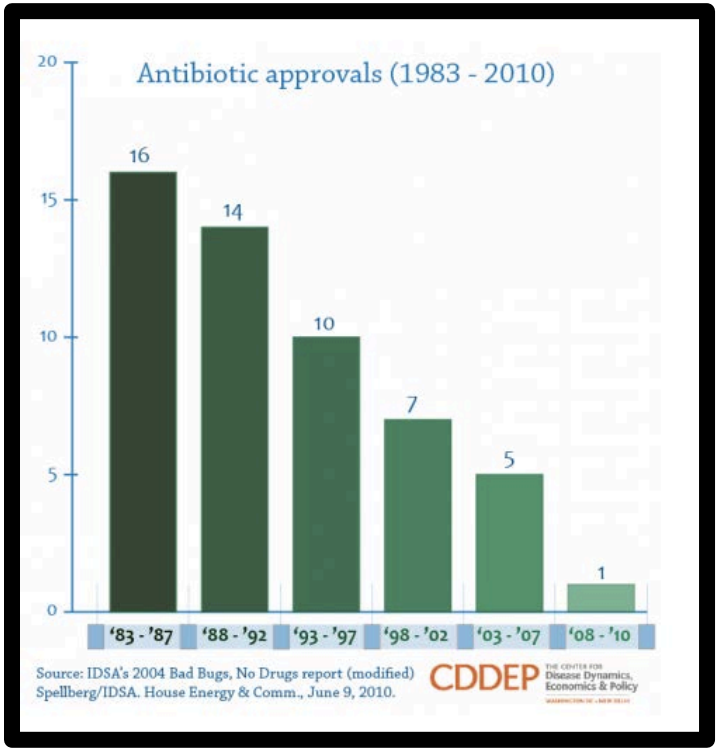
ID Pharmacist Manifesto

- Antibiotic stewardship is a public good
  - Protect resources
  - Value current patients *and* future patients
  - Akin to herd immunity
- Evidence-based medicine beyond the guidelines
- Challenge "provider preference" and then some
- Find the happy place between medicine as an "algorithm" and medicine as an "art-form"
- Embrace uncertainty

Antibiotic Effectiveness



Antimicrobial Market Failure



- Low hanging fruit have been plucked
- Antimicrobial discovery and FDA approval process have become more complex & expensive
- Limited use + shorter durations = decreased revenue
  - New drug for hypertension vs. new drug for invasive aspergillosis?
  - Antimicrobial resistance further decreases lifespan
- Opportunity cost
  - Cost of drug development estimated to be ~$1.2 billion
  - Drug companies may *lose* money on antimicrobials
- Prices are based on public perception and fear
  - Public willing to pay more for cancer than infection?

Public Law 112–144
112th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, to establish user-fee programs for generic drugs and biosimilars, and for other purposes.

July 9, 2012
[S. 3187]

TITLE VIII—GENERATING ANTIBIOTIC INCENTIVES NOW

Sec. 801. Extension of exclusivity period for drugs.
Sec. 802. Priority review.
Sec. 803. Fast track product.
Sec. 804. Clinical trials.
Sec. 805. Reassessment of qualified infectious disease product incentives in 5 years.
Sec. 806. Guidance on pathogen-focused antibacterial drug development.

- The Gain Act (2012)
  - Created an Antibacterial Drug Development Task Force to develop and revise guidance for antibacterial drug development
  - Released a list of pathogens with the potential to pose a public health threat
    - Acinetobacter, Aspergillus, Burkholderia cepacia, Campylobacter spp., Candida, C. diff., Pseudomonas, Non-TB Mycobacteria, Enterococcus
  - Drafted guidance for companies for developing antibiotics that address unmet needs

Recent antimicrobial approvals

- Dalbavancin (Dalvance) 2014
- Oritavancin (Orbactiv) 2014
- Peramivir (Rapivab) 2014
- Tedizolid (Sivextro) 2014
- Ceftolozane-tazobactam (Zerbaxa 2014
- Ceftazidime-avibactam (Avycaz) 2016
- Isavuconazonium sulfate (Cresemba) 2015
- Bezlotoxumab 2016
- Delafloxacin 2017
- Meropenem/vaborbactam (Vabormere) 2017

The Pipeline

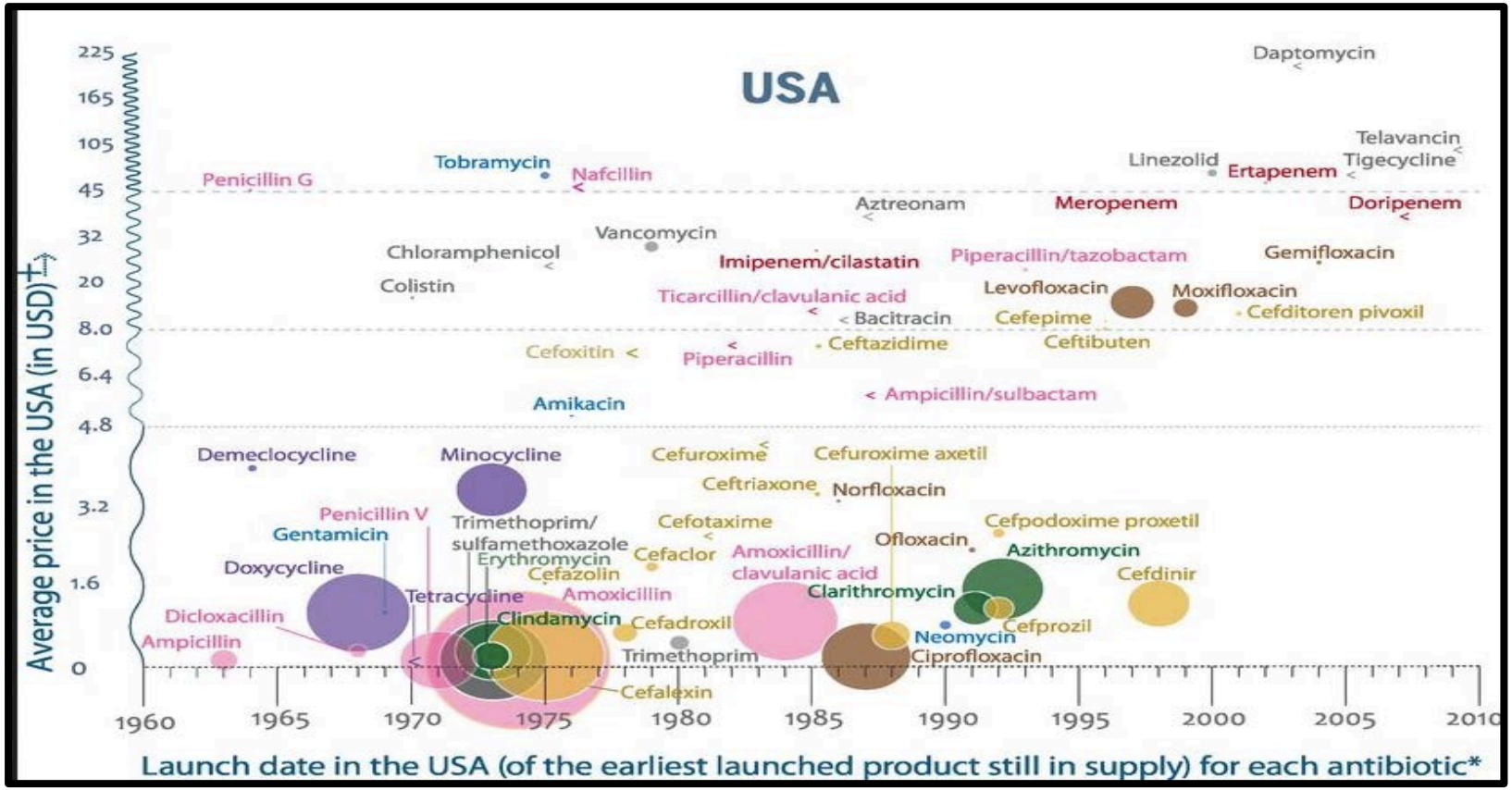
BRIEF

GAIN Act gives Zavante a shot at new antibiotic development

- Fosfomycin IV
- Plazomicin (aminoglycoside)
- Omadacycline (tetracycline)
- Imipenem-relebactam
- Lefamulin (pleuromutilin)

Be careful what you wish for

- Delafloxacin (Baxdela)
  - MRSA
  - MSSA
  - *S. lugdunensis*
  - *Strep spp.*
  - *Enterococcus faecalis*
  - Enterobacteriaceae
  - *Pseudomonas aeruginosa*
  - Very broad spectrum and oral
- Available for prescribing!



Laxminarayan R. *Science* 2014

Everything is investigational

- Ceftazidime-tazobactam
  - Approved for cIAI, cUTI
  - Studied against carbapenems
  - Prescribed for carbapenem-resistant Enterobacteraciae
- Ceftolozane-tazobactam
  - Approved for cIAI, cUTI
  - Studied against carbapenems
  - Prescribed for carbapenem-resistant *Pseudomonas* isolates
- Supporting data is in vitro

Patient care:
Rounding with teams
ID Consult Service
HIV team
Transplant ID
Getting paged re: curbsides

Stewardship:
Approval pager
Post-prescription Review
Medication Use
Evaluations
Active management of high dollar agents or those on shortage

Teaching:
Training PGY-1 and PGY-2 Residents
Training medical residents and other prescribers
Working actively with fellows

Pharmacy Department:
Committees
Training staff
P&T, formulary reviews
Regulatory
Anti-infective inventory
Managing drug shortages

Research:
Retrospective studies
Role in RCTs
Navigating IRB
Presenting at local and national conferences
Publications

CDC: Core Elements of Hospital Antibiotic Stewardship Programs

- Broad interventions
  - Antibiotic time-outs
    - Does this patient have an infection that will respond to antibiotics?
    - If so, is the patient on the right antibiotic(s), dose, and route of administration?
    - Can a more targeted antibiotic be used to treat the infection (de-escalate)?
    - How long should the patient receive the antibiotic(s)?
  - Prior authorization
    - Take the mystery out – read the Antibiotic control program (ACP)
    - Hospital in UK implemented restrictions – decreased CTX by 95%, and cipro by 73%; C diff rate decreased from 2.4 to 0.6 cases/1000 pt-beds) and MRSA by 25% and ESBL by 17%.
  - Prospective audit and feedback (AKA "post-prescription review" or PPR)
- Other: IV to PO, dose optimization, removing duplicates, screening for Ab-related ADR or drug interaction

Dancer S, *Int J of Antimicrob Agents* 2013

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Elements of an antimicrobial stewardship program

- Prospective audit with intervention and feedback
- Formulary restriction and pre-authorization
- Education
- Guidelines and clinical pathways
- Antimicrobial cycling (insufficient data to recommend)
- Streaming or de-escalation of therapy
- Dose optimization
- Parenteral to IV conversion

Table 2. Causal associations between antimicrobial use and the emergence of antimicrobial resistance.

Changes in antimicrobial use are paralleled by changes in the prevalence of resistance.
Antimicrobial resistance is more prevalent in health care–associated bacterial infections, compared with those from community-acquired infections.
Patients with health care–associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials.
Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use.
Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.

Delit T, Clin Infect Dis 2007

Stewardship Activities

Pre-approvals

- AKA Antibiotic Debate Club
- Restrict use of certain antibiotics until approved by ID
- Antibiogram-driven
- Enforce empiric guidelines
- Managing prescriber preferences
- Teaching opportunities
- Can fix doses from day-one

Post-prescription Review

- Reviewing patients downstream; looking for opportunities to de-escalate or discontinue
- Many times culture driven
- Can leave stewardship notes
- Stopping antibiotics tied to decrease in C diff rates

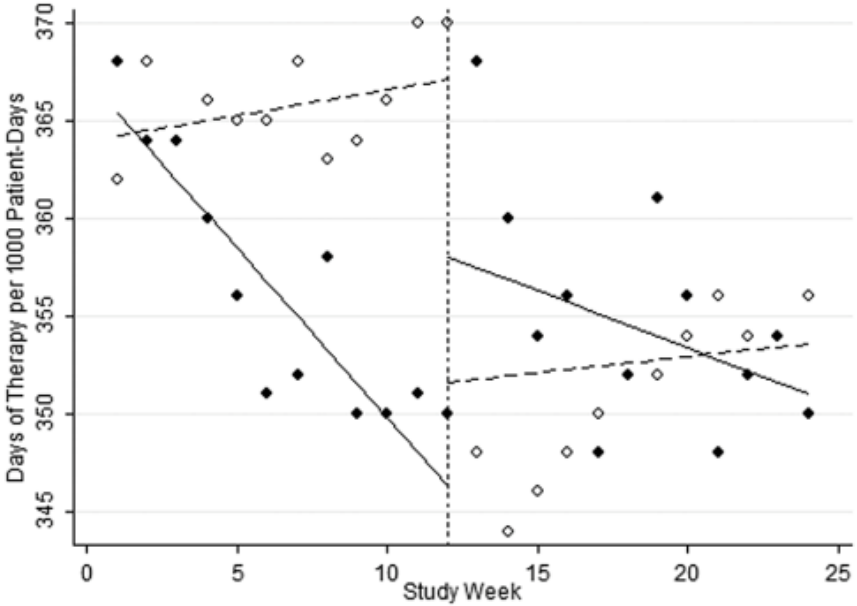
Clinical Infectious Diseases

MAJOR ARTICLE

What Is the More Effective Antibiotic Stewardship Intervention: Preprescription Authorization or Postprescription Review With Feedback?

Pranita D. Tamma,[1] Edina Avdic,[2] John F. Keenan,[3] Yuan Zhao,[4] Gobind Anand,[5] James Cooper,[6] Rebecca De

[1]Division of Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, and [2]Department of Pharmacy, of Family Medicine, Lynchburg General and Virginia Baptist Hospital, Lynchburg; [4]Department of Epidemiology, Johns Hopkins Bloomberg of Gastroenterology, Department of Medicine, University of California, San Diego; [6]Division of Hematology, Department of Medicine, Na Critical Care Medicine, [8]Cardiology, and [9]Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Ba



Tamma P, Clin Infect Dis 2017

Tension #1

- When two disciplines read the exact same study in polar opposite ways

Annals of Internal Medicine

ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Background: Invasive aspergillosis (IA) is associated with poor outcomes in patients with hematologic malignancies (HMs) and hematopoietic cell transplantation (HCT). Small studies suggest a role for combination antifungal therapy.

Objective: To assess the safety and efficacy of voriconazole and anidulafungin compared with voriconazole monotherapy for treatment of IA.

Design: Randomized, double-blind, placebo-controlled multicenter trial. (ClinicalTrials.gov: NCT00531479)

Setting: 93 international sites.

Patients: 454 patients with HM or HCT and suspected or documented IA were randomly assigned to treatment with voriconazole and anidulafungin or placebo. Primary analysis was done in the modified intention-to-treat population of 277 patients in whom IA was confirmed.

Measurements: The primary outcome was 6-week mortality; secondary outcomes included 12-week mortality, mortality in major subgroups, and safety measures.

Results: Mortality rates at 6 weeks were 19.3% (26 of 135) for combination therapy and 27.5% (39 of 142) for monotherapy (difference, −8.2 percentage points [95% CI, −19.0 to 1.5]; P = 0.087). Secondary mortality outcomes favored combination therapy. Multivariable regression analysis suggested that maximum galactomannan value, Karnofsky score, and baseline platelet count had prognostic significance. Most patients (218 of 277 [78.7%]) had IA diagnosis established by radiographic findings and maximum galactomannan positivity. In a post hoc analysis of this dominant subgroup, 6-week mortality was lower in combination therapy than monotherapy (15.7% [17 of 108] vs. 27.3% [30 of 110]; difference, −11.5 percentage points [CI, −22.7 to −0.4]; P = 0.037). Safety measures, including hepatotoxicity, were not different.

Limitations: Mortality at 6 weeks was higher than expected, and the difference in mortality was lower than expected, which reduced power to detect a treatment effect. Enrollment was restricted to patients with HM or HCT, which limited generalizability.

Conclusion: Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in subgroups of patients with IA. Limitations in power preclude definitive conclusions about superiority.

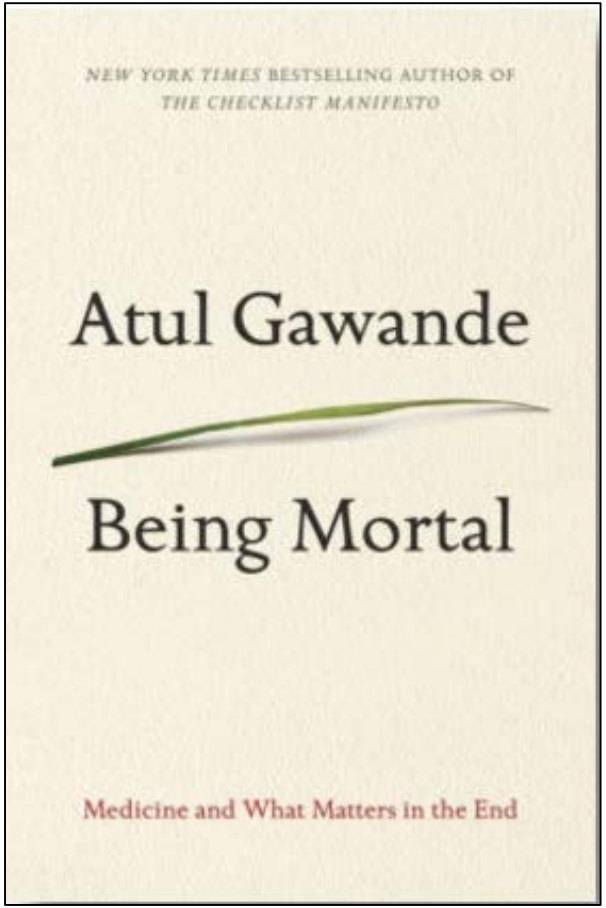
Primary Funding Source: Pfizer.

Ann Intern Med. 2015;162:81-89. doi:10.7326/M13-2508 www.annals.org
For author affiliations, see end of text.

Marr K, Ann Intern Med 2015

Tension #2

- Antibiotic last rights
- "Patient is on max dose pressors & we want to escalate empirically"



Tension #3

- Choosing between:
  - A more narrow spectrum agent that is costly vs. a more broad agent that is less costly
  - A more narrow spectrum agent that carries a higher risk of *C diff* vs a more broad agent that has a lower risk of *C diff*

Tension #4

- Temporal discounting: using levofloxacin today versus levofloxacin susceptibility next month

- Flip-side: Using a broader agent on second course empirically

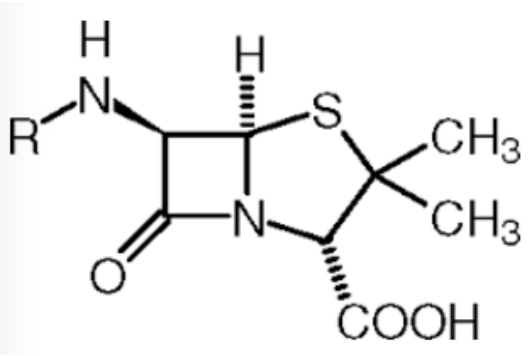
Antibiotic exposure and resistance development in *Pseudomonas aeruginosa* and *Enterobacter* species in intensive care units*

David S. Y. Ong, MD, PharmD; Irene P. Jongerden, RN, PhD; Anton G. Buiting, MD, PhD; Maurine A. Leverstein-van Hall, MD, PhD; Ben Speelberg, MD, PhD; Jozef Kesecioglu, MD, PhD; Marc J. M. Bonten, MD, PhD

Ong D, Crit Care Med 2011

Challenges

- Making stewardship matter to others
- Outpatient stewardship
- Changing patient population
- How to risk adjust metrics
- Sharing micro data when patients transfer
- The dreaded calls: *M. abscessus*, XDR TB, middle-of-the-night malaria (bad bugs no drugs part deux)



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