

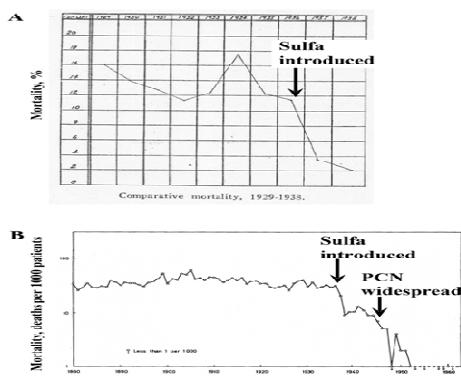
## Antimicrobial Stewardship: Pediatric Perspective

Kari Simonsen, MD  
Assistant Professor of Pediatrics, Division of Infectious Diseases  
University of Nebraska Medical Center  
January 20, 2012

## Objectives

- Describe the impact of the overuse of antimicrobials
- Discuss the importance of antibiotic stewardship
- Discuss opportunities to implement antimicrobial stewardship measures in pediatric hospital care

(A) Mortality rates for erysipelas at Cook County Hospital 1929-1938  
(B) Mortality of erysipelas from Norwegian national registry

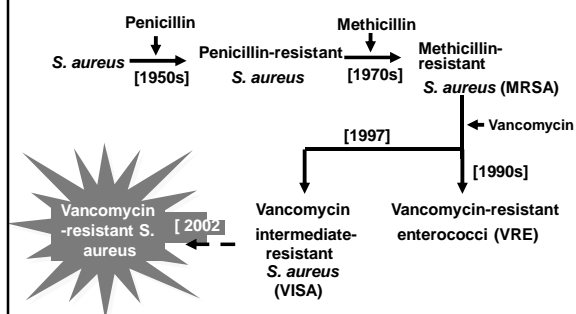


## Alexander Fleming--1945

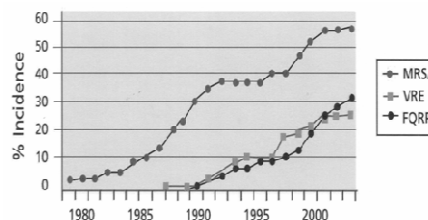


- “The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection the microbes are educated to resist penicillin, and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicaemia or pneumonia which penicillin cannot save.”

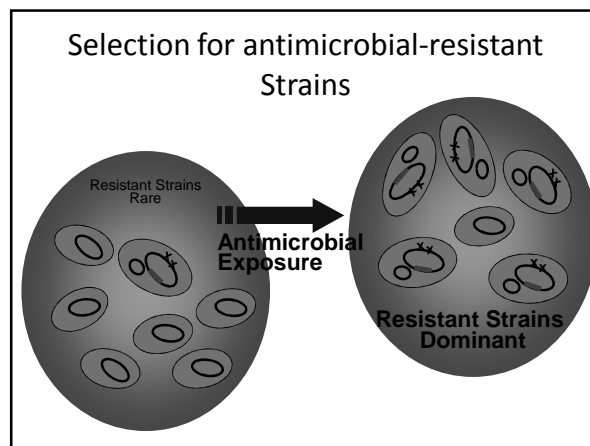
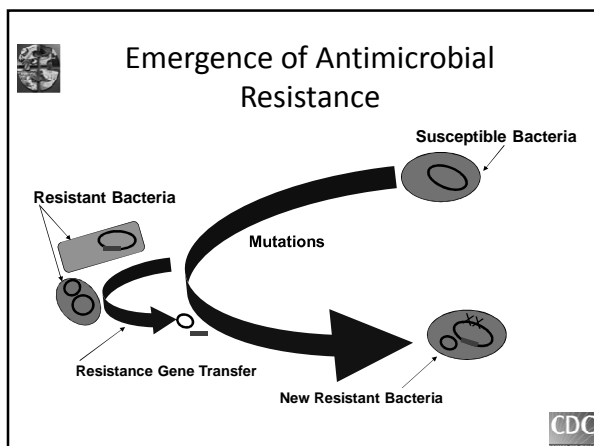
## Evolution of Drug Resistance in *S. aureus*



## Increasing Prevalence of Antibiotic Resistant Pathogens



Data Source: CDC

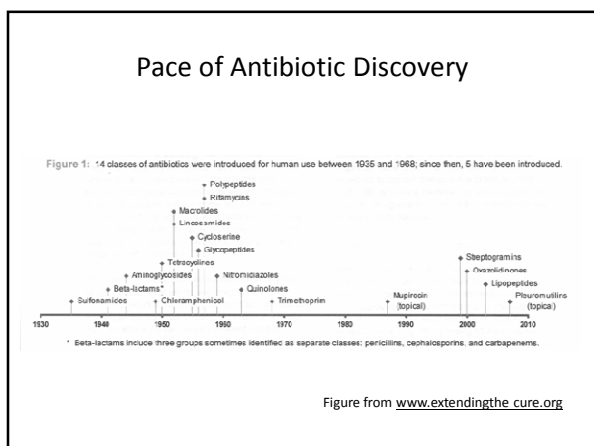
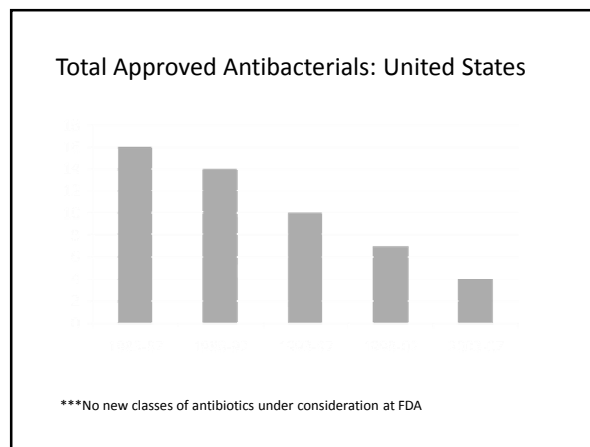


### A Call to Arms!

**BAD BUGS, NO DRUGS**  
 An Antibiotic Discovery Stagnates ... A Public Health Crisis Looms

- The antibiotic pipeline has slowed to a trickle!
- At the time of this publication, only 5 of the 506 drugs in clinical development were antibiotics!

**IDSA**  
 Infectious Diseases Society of America  
 July 2004



### Significance of Nosocomial Infections

- 5% - 10% of all hospitalized patients in the US develop a nosocomial infection; 1.7 million infections per year
- Approximately 100,000 deaths/yr
- 7<sup>th</sup> leading cause of death in the US
  - AIDS: 14,561 deaths (2007), Breast cancer 40,470 deaths (2009), Non-Hodgkins Lymphoma 19,568 deaths (2009)
  - Motor vehicle accidents: 43,788 deaths (2001)
- 25-30 billion dollars/yr

### Improving Patient Outcomes and Resistance Rates Requires Multiple Interventions

- Maximize Hand Hygiene and application of Standard Infection Control Precautions
- Insert and care for devices correctly
- Provide a clean environment
- Eliminate fomites
- Bathe patients with chlorhexidine
- Respiratory etiquette and vaccination
- Antimicrobial stewardship

[www.cdc.gov](http://www.cdc.gov)

### Antibiotic Stewardship

- What is stewardship?
  - The conducting, supervising, or managing of something; *especially* : the careful and responsible management of something entrusted to one's care
- Antibiotics are a shared, limited resource requiring management
- A rational, systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes. Focus = patient and public health.

### Definition of Antimicrobial Stewardship

- IDSA Guidelines:
  - Antimicrobial Stewardship is an activity which promotes:
    1. The appropriate selection of antimicrobials
    2. The appropriate dosing of antimicrobials
    3. The appropriate route and duration of antimicrobial therapy.

### Primary Goal of Antimicrobial Stewardship

- The over-arching goal is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use.
- (Unintended consequences may include):
  - Drug toxicity/adverse events
  - Selection of pathogenic organisms such as *C. difficile*
  - Emergence of resistant pathogens

### Secondary Goals of Antimicrobial Stewardship

- Limit the emergence and transmission of antimicrobial resistant bacteria (together with appropriate infection prevention measures)
- Reduce healthcare costs without adversely impacting the quality of care

### Magnitude of Antibiotic Usage

- 2<sup>nd</sup> most commonly used drug class in the US
- >8 billion USD spent on anti-infectives annually
- 200-300 million prescriptions annually
- 45% outpatient use/55% inpatient use
- 25-40% of all hospitalized patients receive antibiotics
  - PICU 70% received antimicrobials
  - NICU 43% received antimicrobials

Grohskopf LA et al. *PIDJ* 2005, 24:766-73

### Antibiotics are misused in hospitals

- “It has been recognized for several decades that up to 50% of antimicrobial use is inappropriate”
- IDSA/SHEA Guidelines for Antimicrobial Stewardship Programs
- How are they misused?
  - Given when not needed
  - Continued when no longer necessary
  - Given at wrong dose
  - Broad spectrum agents used unnecessarily
  - Wrong antibiotic given for type of infection

<http://www.journals.uchicago.edu/doi/pdf/10.1086/510393>

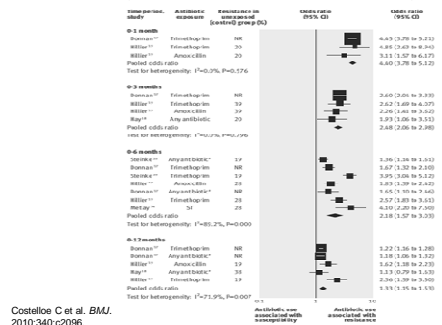
Inappropriate (AND appropriate!) antibiotic use leads to increasing resistance to antibiotics

### Antibiotic exposure increases the risks of resistance

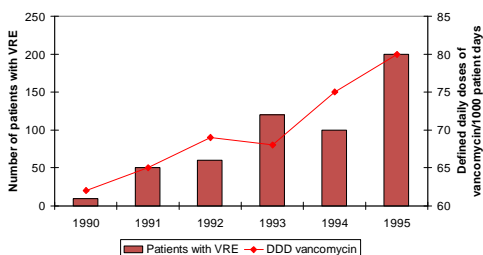
Pathogen and Antibiotic Exposure	Increased Risk
Carbapenem Resistant Enterobacteriaceae and Carbapenems	15 fold 1
ESBL producing organisms and Cephalosporins	6- 29 fold 3,4

Patel G et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106  
 Zapantis TE et al. *Pediatrics* 2005;114:342-9  
 Talon D et al. *Clin Microbiol Infect* 2000;6:375-84

### Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

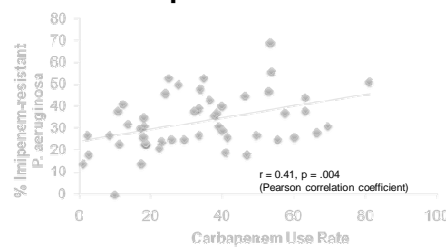


### Association of hospital vancomycin use with resistance (VRE colonization)



(JID 1999;179:163)

### Annual prevalence of imipenem resistance in P. aeruginosa vs. carbapenem use rate



45 LTACHs, 2002-03 (59 LTACH years)

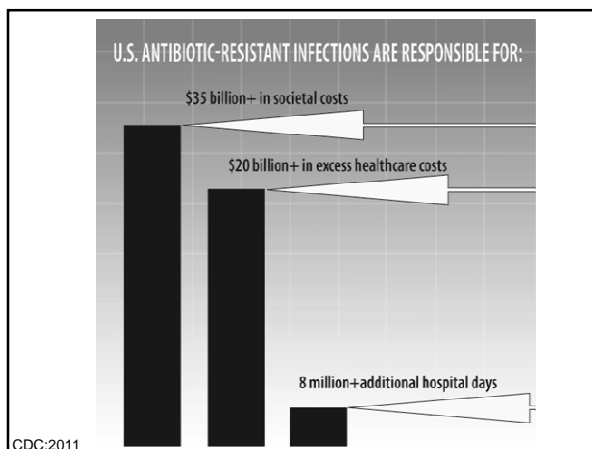
Gould et al. *ICHE* 2006;27:923-5

### Antibiotic misuse adversely impacts patients - resistance

- Getting an antibiotic increases a patient's chance of becoming colonized or infected with a resistant organism.
- Increasing use of antibiotics increases the prevalence of resistant bacteria in hospitals.
- One in every three patients will receive two or more antibiotics in the course of their hospital stay.
- Of the patients receiving antibiotics, three out of every four will receive unnecessary or redundant therapy, resulting in excessive use of antibiotics.

### Options for *Klebsiella* VAP in NYC

1980's	1990's	2000's	2010+
Ampicillin Amoxicillin	Amp/Sulbactam	Piperacillin/ tazobactam	Tigecycline
Amp/Sulbactam	Gentamicin Tobramycin Amikacin	Gentamicin Tobramycin Amikacin	Amikacin
TMP/SMX	Ceftriaxone	Cefepime	Colistin
Gentamicin Tobramycin Amikacin	<b>Cefepime</b>	<b>Tigecycline</b>	
Cefazolin/ Cefuroxime	Ciprofloxacin	Carbapenems	
Ceftriaxone	<b>Carbapenems</b>		
<b>Ciprofloxacin</b>			



### Antibiotic misuse adversely impacts patients - adverse events

- In 2008, there were 142,000 visits to emergency departments for adverse events attributed to antibiotics.
- National estimates for in-patient adverse events are not available, but there are many reports of serious adverse events (aside from *C. difficile* infection) from in-patient antibiotic use.

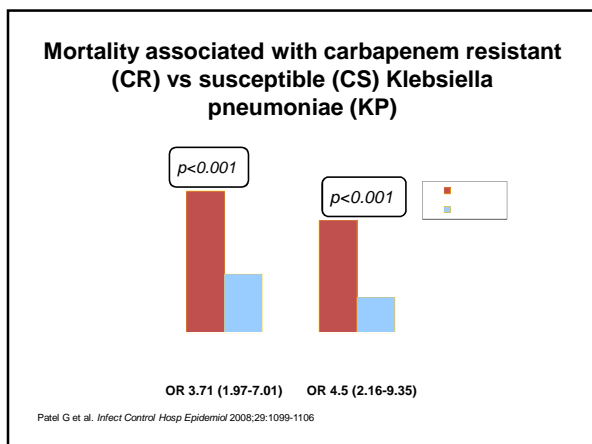
1. Shehab N et al. *Clinical Infectious Diseases* 2008; 15:735-43

### Antibiotic resistance increases mortality

### Mortality of resistant (MRSA) vs. susceptible (MSSA) *S. aureus*

- Mortality risk associated with MRSA bacteremia, relative to MSSA bacteremia: OR: 1.93;  $p < 0.001$ .<sup>1</sup>
- Mortality of MRSA infections was higher than MSSA: relative risk [RR]: 1.7; 95% confidence interval: 1.3–2.4).<sup>2</sup>

1. *Clin. Infect. Dis.* 36(1),53–59 (2003).  
 2. *Infect. Control Hosp. Epidemiol.* 28(3),273–279 (2007).

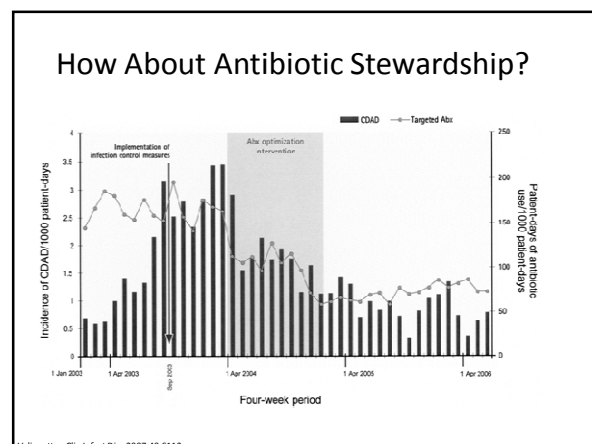
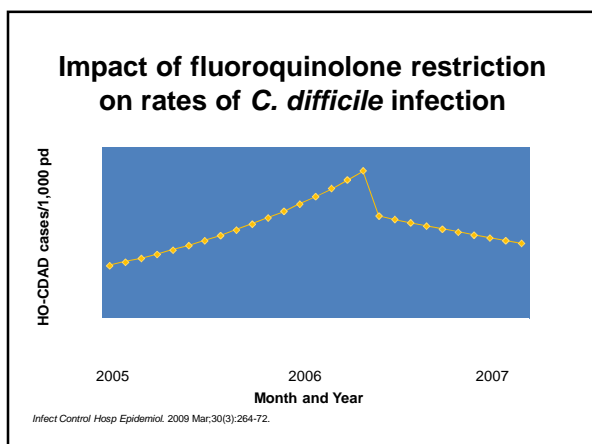
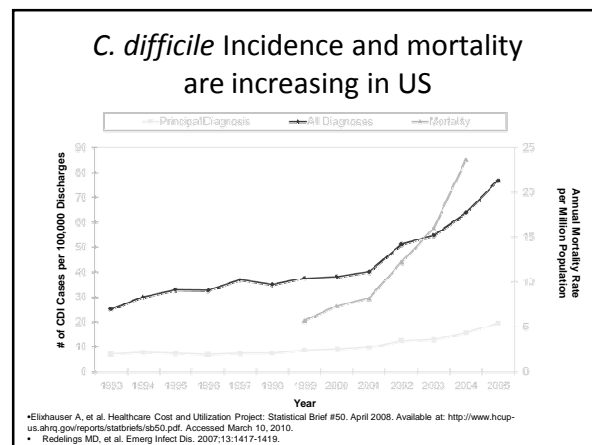


## Improving antibiotic use reduces *C. difficile* infections

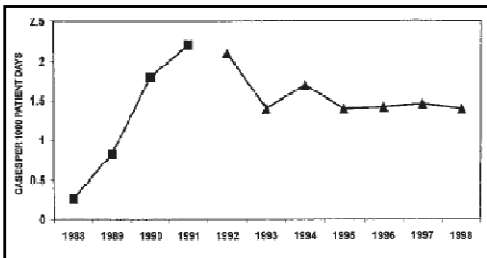
### Antibiotic misuse adversely impacts patients- *C. difficile*

- Antibiotic exposure is the single most important risk factor for the development of *Clostridium difficile* associated disease (CDAD).
  - Up to 85% of patients with CDAD have antibiotic exposure in the 28 days before infection<sup>1</sup>
- Emergence of the NAP-1/BI or “epidemic” strain of *C. difficile* has intensified the risks associated with antibiotic exposure.
- Epidemic strain is resistant to fluoroquinolone antibiotics, which confers a selective advantage.<sup>2</sup>

<sup>1</sup> Chang HT et al. *Infect Control Hosp Epidemiol* 2007; 28:926-931.  
<sup>2</sup> McDonald LC et al. *New England Journal of Medicine* 2005;353:2433-41



### Impact of improving antibiotic use on rates of *C. difficile*



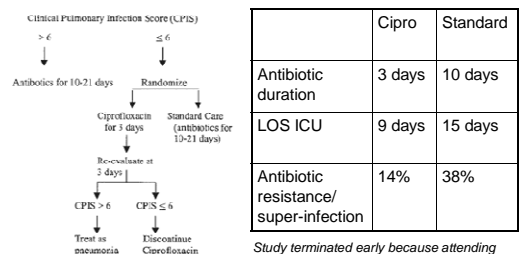
Carling P et al. *Infect Control Hosp Epidemiol.* 2003;24(9):699-706.

### Pediatric Perspective: *C. difficile*

- Epidemiology of disease is changing, and pediatric patients are at greater risk than ever before
- Decreasing rates of *C. difficile* infection (CDI) requires both infection control and antibiotic control
- Improvements in antimicrobial use in pediatric settings may continue to keep pediatric rates of CDI much lower than adult rates

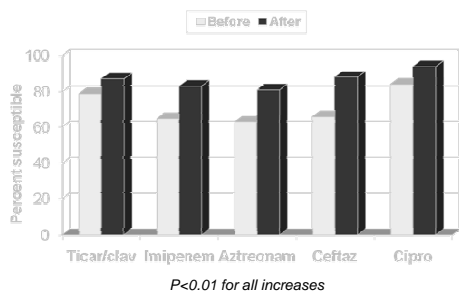
### Improving antibiotic use *reduces* resistance

### Stewardship optimizes patient safety: decreased patient-level resistance



Singh N et al. *Am J Respir Crit Care Med.* 2000;162:505-11.

### *P. aeruginosa* susceptibilities before and after implementation of antibiotic restrictions (CID 1997;25:230)



### Implementation of an Antibiotic Stewardship Program

- Core strategies
  - Prospective audit with intervention & feedback
  - Formulary restriction and preauthorization
- Supplements
  - Education, guidelines/clinical pathways, antimicrobial order forms, de-escalation, dose optimization, IV to PO conversion

Dellit TH, et al. *Clin Infect Dis.* 2007;44.

### Personnel Necessary

- High level executive commitment necessary!
- Engage and gain trust/buy-in from stakeholders:
  - Senior clinicians
  - RN leadership
  - Pharmacy
  - Infection Prevention
  - Trainees

### Personnel Necessary

- Institution specific team members:
  - Pharm D involvement essential
  - ID physician
  - If not available, physician champion
  - Data analyst
  - Administrative support/buy-in!

Septimus EJ, Owens Jr RC. CID 2011;53(suppl 1);S8-14.

### Links to Infection Control

- Antimicrobial Stewardship is one component of a comprehensive plan to prevent resistance and minimize spread of resistant organisms
- Harnessing work already underway for stewardship activities--electronic surveillance
- Reduces cost by allowing multiple aims from daily work already ongoing
- Preventing resistance reduces future infection control costs


### Audit and Feedback


- Process of reviewing patients who are receiving antibiotics and giving “unsolicited” advice
- Advantages
  - Customization
  - Educational
  - No delays in therapy
- Disadvantages
  - Optional
  - Time intensive
  - Person performing intervention needs broad knowledge base

### Formulary Control

- Restrictions
  - Involves restricting the use of antibiotics to approved choices
- Preauthorization
  - Clinicians are unable to obtain specific antibiotics unless approved by reviewer
- Microbiology Report Format
  - Provide culture results based on formulary to reduce requests for non-formulary agents
  - Minimize utilization of broad-spectrum agents for sensitive organisms

### Clinical Pathways Example: Surgical Prophylaxis Order Form





\* 0 2 0 2 0 2 0 2 \*

PT NAME

MR #

**FOR USE IN ADULT PATIENTS ONLY - Use Back or Blue Ball Point Pen - All Entries Must Be Dated and Signed**

If active infection is present at time of surgery, or the antibiotic on standard order sheet, mark correct procedure and drug choice below.

Procedure (and date):	Pre-op Antimicrobial and Dose	Post-op Antimicrobial and Dose
Weight: _____ kg    Allergies/reaction (see below): _____    Physician: _____ Reason: _____ True drug allergy is based on the presence of a patient response with one or more of the following signs/symptoms: respiratory difficulty, hypotension, rash, or hives. In the absence of these findings, an antibiotic of the same classification may be used for surgical prophylaxis.		
<b>1</b> <b>Indication</b> Abdominal, upper extremity (non-perforated), biliary, colorectal surgery or any type, orthotopical or sternal, bowel surgery	☐ Cefazolin 1 g (2 g if greater than 80 kg) IV x 1 dose ☐ cefuroxime 1.5 g IV x 1 dose ☐ ceftriaxone 1 g IV x 1 dose ☐ clindamycin 900 mg IV x 1 dose ☐ vancomycin 1 g IV x 1 dose ☐ meropenem 1 g IV x 1 dose ☐ piperacillin-tazobactam 4.5 g IV x 1 dose	No post-op dose needed.
<b>Cardiac</b> coronary artery bypass graft (CABG), CABG with valve implant, pacemaker and other implants	☐ cefazolin 1 g (2 g if greater than 80 kg) IV x 1 dose ☐ cefuroxime 1.5 g IV x 1 dose ☐ ceftriaxone 1 g IV x 1 dose ☐ clindamycin 900 mg IV x 1 dose ☐ vancomycin 1 g IV x 1 dose ☐ meropenem 1 g IV x 1 dose ☐ piperacillin-tazobactam 4.5 g IV x 1 dose	☐ cefazolin 1 g (2 g if greater than 80 kg) IV q8h x 24h ☐ Allergy: vancomycin 1 g IV q12h X 24h + gentamicin 80 mg (160 mg if greater than 80 kg) IV x 1 dose (8h after pre-op dose) MDRSA coverage: ☐ vancomycin 1 g IV q12h x 1 dose + cefazolin 1 g (2 g if greater than 80 kg) IV q8h x 24h ☐ vancomycin 1 g IV q12h x 24h + gentamicin 80 mg (160 mg if greater than 80 kg) IV x 1 dose (8h after pre-op dose)
<b>General</b> any implanted foreign body (e.g. hernia patch)	☐ cefazolin 1 g (2 g if greater than 80 kg) IV x 1 dose ☐ Allergy: vancomycin 1 g IV x 1 dose	No post-op dose needed.

### Potential Initial ASP Projects:

- Renal dosing protocol
- IV to PO conversions (reduce need for IV therapy, reduce adverse effects, reduce length of stay) Good examples for this:
  - Fluoroquinolones
  - Metronidazole
  - Fluconazole
  - Clindamycin
  - Linezolid

### IT Solutions

- Many programs exist to facilitate antimicrobial stewardship specifically, or can be done by enhancing other systems already in place
  - Infection Prevention
  - Pharmacy
  - Microbiology
  - Clinician (CPOE)
  - Performance Improvement/Administrative

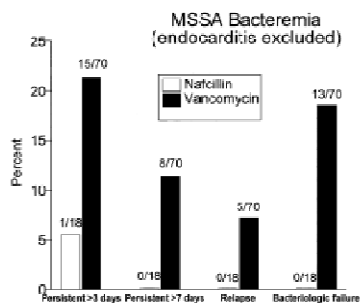
### Combination Therapy

- Where is it appropriate?
  - Severe infections caused by a broad range of pathogens
    - Ventilator associated pneumonia, sepsis of unknown source, meningitis
  - When is it not
    - Skin/soft tissue infection, UTI
  - Where is it an option
    - CAP, intra-abdominal infections
- So we started it, when do we stop it?

### De-escalation

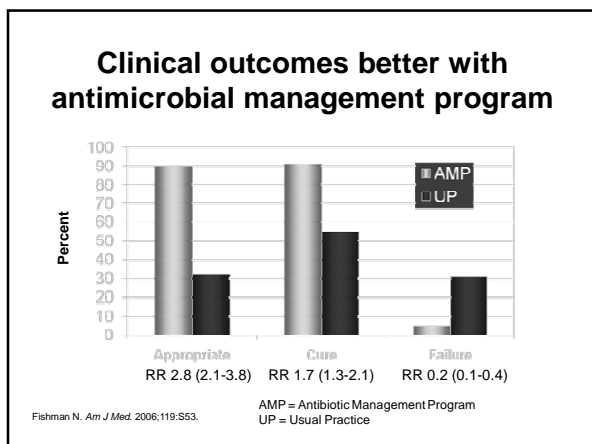
- Driven by data
  - Get appropriate cultures!!
  - Published guidelines
    - Help decide when/what to culture
    - How to interpret results
- Careful initial work-up with collection of appropriate cultures allows for de-escalation to occur quickly and safely

### MSSA Bacteremia: Beta-lactams are superior

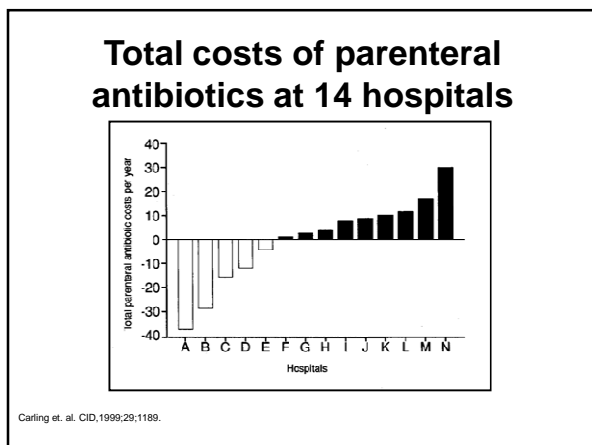


Chang, Medicine. 2003;82:333.

**Improving antibiotic use  
improves infection cure rates**



### Improving Antibiotic Use SAVES Money



### Improving antibiotic use saves money

- “Comprehensive programs have consistently demonstrated a decrease in antimicrobial use with annual savings of \$200,000 - \$900,000”
- IDSA/SHEA Guidelines for Antimicrobial Stewardship Programs

<http://www.journals.uchicago.edu/doi/pdf/10.1086/510393>

### ANTIMICROBIAL STEWARDSHIP IS A PUBLIC HEALTH IMPERATIVE

Antibiotics are an endangered species

### Improving antibiotic use is a public health imperative

- Antibiotics are the only drug where use in one patient can impact the effectiveness in another.
- If everyone does not use antibiotics well, we will all suffer the consequences.
- Antibiotics are a shared resource, (and becoming a scarce resource).
- Using antibiotics properly is analogous to developing and maintaining good roads.

## Improving antibiotic use is a public health imperative

- Bringing new antibiotics into our current environment is akin to buying a new car because you hit a pot hole, but doing nothing to fix the road.
- Fixing the “antibiotic use road” is part of the mission of public health.
- We must all participate in maintaining the “antibiotic road” through stewardship

## What Can I do Today?

- ❑ *Ensure all orders have dose, duration, and indications*
- ❑ *Get cultures before starting antibiotics*
- ❑ *Take an “antibiotic time-out,” reassessing antibiotics after 48-72 hours*

CDC- Get Smart/Healthcare

## Goals- Get Smart for Healthcare

- Improve patient safety through better treatment of infections.
- Reduce the emergence of anti-microbial resistant pathogens and *Clostridium difficile*.
- Heighten awareness of the challenges posed by antimicrobial resistance in healthcare and encourage better use of antimicrobials as one solution.



## Summary

- Resistance is a worsening problem, years of antibiotic overuse has contributed
  - Infection control has a key role in the control of resistance
- Antibiotics are a limited resource, requiring careful management
  - Antibiotic stewardship is working in many ways to improve this
  - Antimicrobial Stewardship teams can facilitate improvements in utilization in your hospital!

## Resources to Help YOU start:

- CDC
  - Antimicrobial Stewardship for the Community Hospital [www.Rockpointe.com/ASPToolkit](http://www.Rockpointe.com/ASPToolkit)
  - <http://www.cdc.gov/drugresistance/campaigns.html>
  - [www.cdc.gov/getsmart/healthcare/](http://www.cdc.gov/getsmart/healthcare/)
- IDSA/SHEA Guidelines [www.idsociety.org](http://www.idsociety.org)
- [www.extendingthecure.org](http://www.extendingthecure.org)

