“An Introduction to Judicious Use of Antibiotics

Antibiotic Stewardship Program

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Objectives

-Discuss untoward effects of antibiotic use

-Define antibiotic stewardship

-Describe 6 goals of antibiotic stewardship programs

-Describe a rationale for antibiotic selection

- Describe directed and empiric antibiotic therapy

-Describe and give examples of 4 tenets of appropriate antibiotic use

Outline

- Introduction
- Untoward Effects of Antibiotics
- Antibiotic Stewardship
- Principles of Antibiotic Selection
- Tenets of Appropriate Antibiotic Use
- Conclusion

Introduction

- The modern age of antibiotic therapeutics was launched in the 1930s with sulfonamides and the 1940s with penicillin
- Since then, many antibiotic drugs have been developed, most aimed at the treatment of bacterial infections
- These drugs have played an important role in the dramatic decrease in morbidity and mortality due to infectious diseases
- While the absolute number of antibiotic drugs is large, there are few unique antibiotic targets

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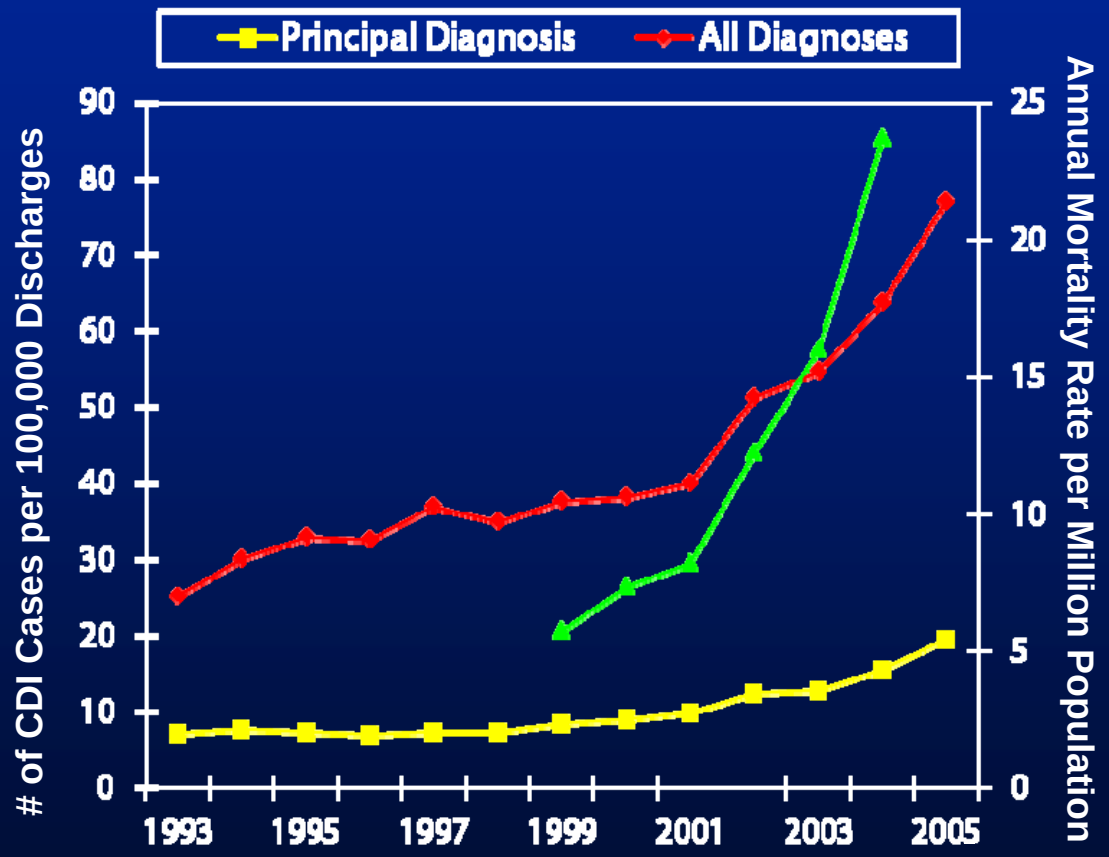
Untoward Effects of Antibiotics

- Antibiotic resistance
- Adverse drug events (ADEs)
  - Hypersensitivity/allergy
  - Drug side effects
  - *Clostridium difficile* infection
  - Antibiotic associated diarrhea/colitis
- Increased health-care costs

Clostridium difficile Infection (CDI)

A potentially deadly colitis

- Antibiotics are the single most important risk factor for CDI
- Incidence and mortality increasing
- A more virulent NAP1/BI strain also seen with increasing frequency



Redelings, et al. EID, 2007;13:1417
CDC. Get Smart for health care. Access at www.cdc.gov/Getsmart/healthcare

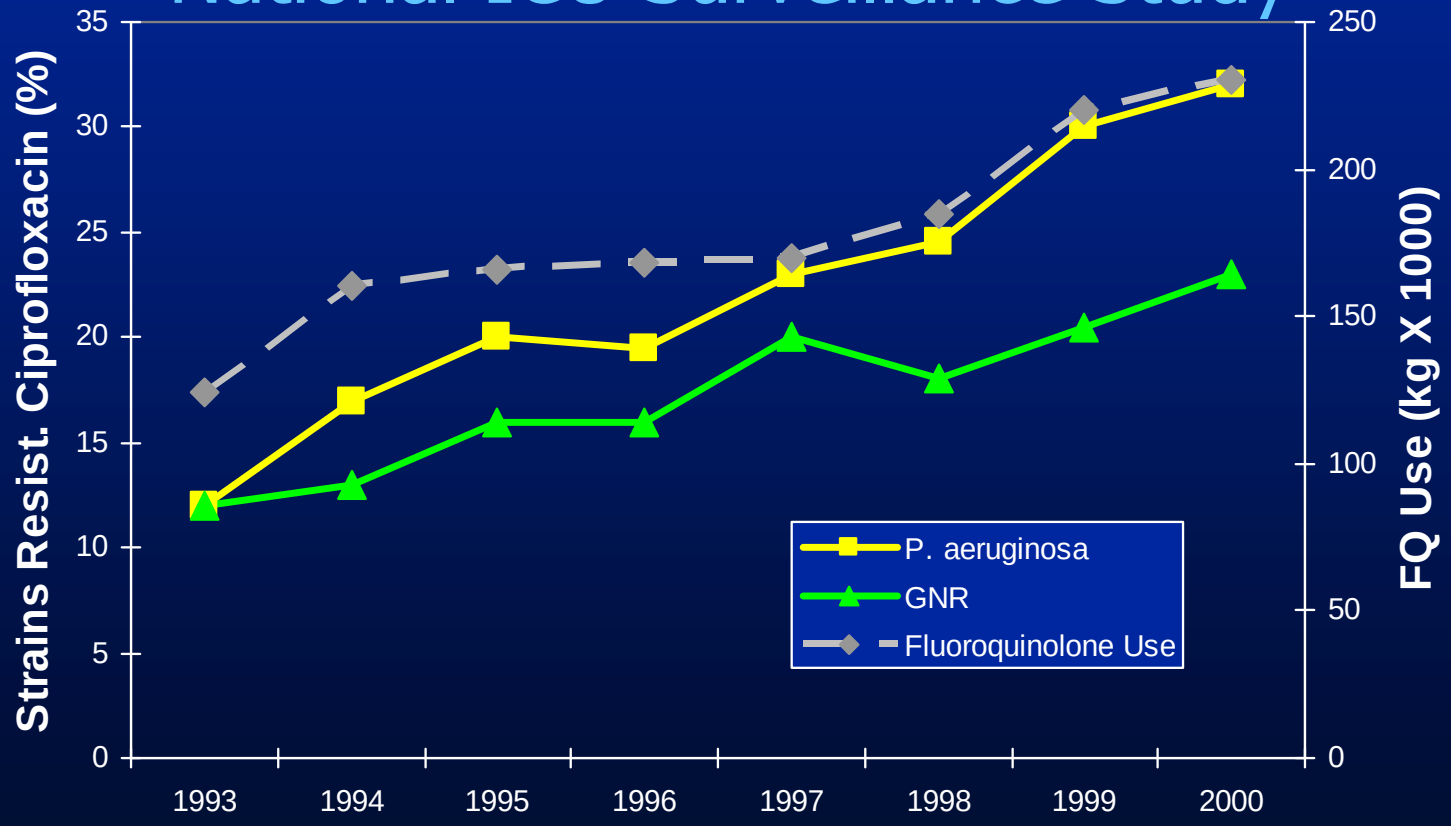
Association Between Antibiotic Use and Nonsusceptible Pneumococcal Infection

Study	Infection	% *S. pneumoniae* who had recent antibiotic use		Odds Ratio	p-value
		Nonsusceptible	Susceptible		
Jackson	Invasive	56%	14%	9.3	0.009
Pallares	Invasive	65%	17%	9.3	<0.001
Tan	Invasive	70%	39%	3.7	0.02
Nava	Invasive	30%	11%	3.5	<0.001
Moreno	Bacteremia	57%	4%	3.6	<0.001
Block	Otitis media	69%	25%	6.7	<0.001

Dowell & Schwartz, Am Fam Physician. 1997 55(5):1647

Fluoroquinolone Use and Resistance among Gram-Negative Isolates, 1993-2000

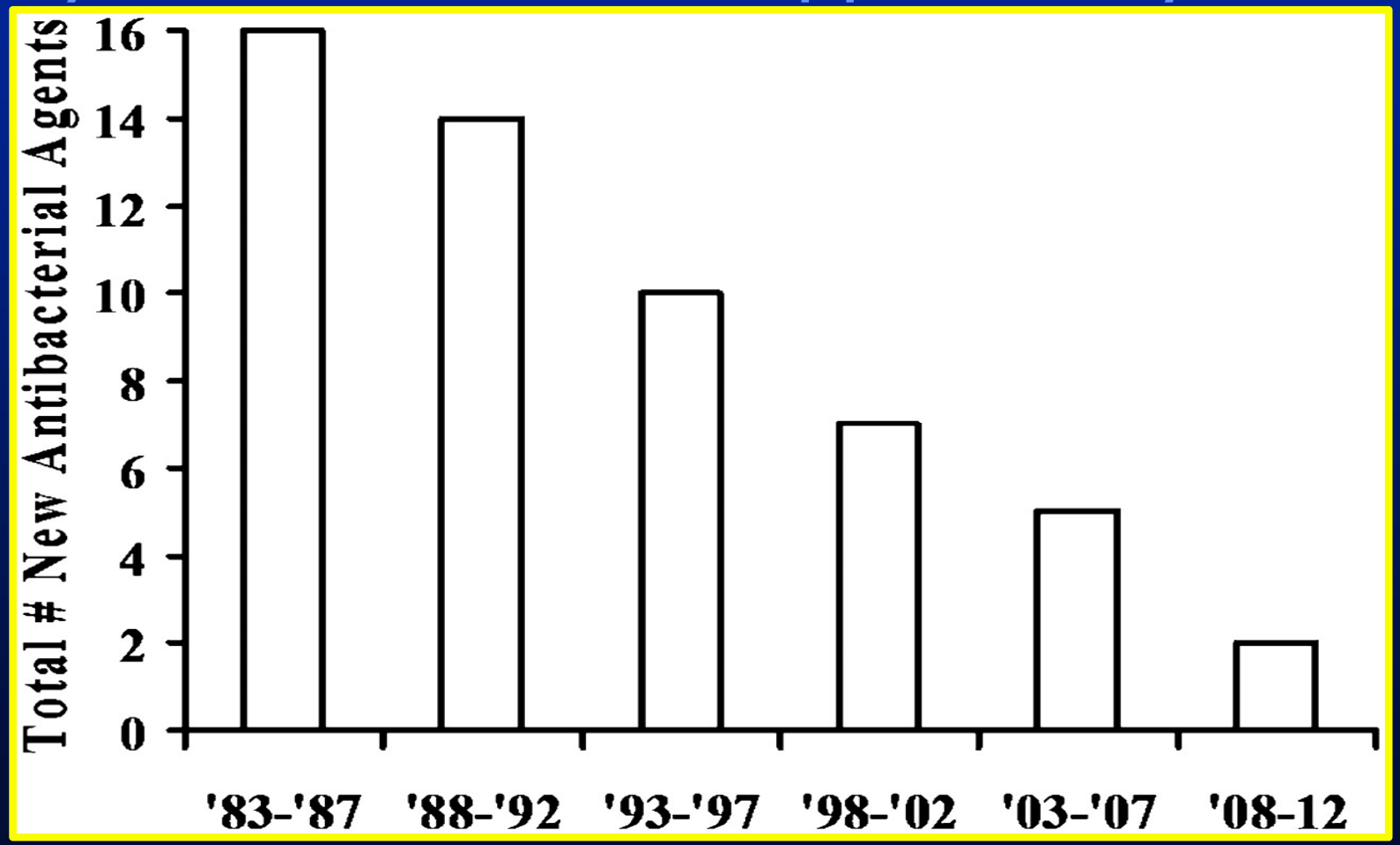
National ICU Surveillance Study



Neuhauser, et al. *JAMA* 2003; 289:885

Limited Number of New Antibiotics to Combat Antibiotic Resistance

New Systemic Antibiotics Approved by the FDA



Clin Infect Dis. 2011;52:S397-S428

Frequency of ADEs due to Antibiotics in Outpatient Setting

- 142,505 estimated emergency department visits/year due to untoward effects of antibiotics
  - Antibiotics account for 19.3% of drug related adverse events
    - 78.7% for allergic events
    - 19.2% for adverse events (e.g. diarrhea, vomiting)
  - Approximately 50% due to penicillin & cephalosporin classes
  - 6.1% required hospital admission

2004-2005 NEISS-CADES project

Shehab N et al. Clin Infect Dis. 2008;47:735

Consequences of Hospital Antibiotic Use

- At one tertiary care center 70% of Medicare patients received an antibiotic in 2010
- Approximately 50% of this use was unnecessary or inappropriate
- Untoward consequences of antibiotic therapy identified in this and other studies:
  - Inadequate treatment of infection
  - Increased hospital readmissions
  - ADEs

Polk et al. In: PPID, 7th ed. 2010
Luther, Ohl. IDSA Abstract 2011

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Antibiotic Stewardship

- Definition: A system of informatics, data collection, personnel, and policy/procedures which promotes the optimal selection, dosing, and duration of therapy for antimicrobial agents throughout the course of their use
- Purpose:
  - Limit inappropriate and excessive antibiotic use
  - Improve and optimize therapy and clinical outcomes for the individual infected patient

Ohl CA. *Seminar Infect Control* 2001;1:210-21.
Dellit TH, et. al. Clin Infect Dis. 2007;44:159-177

Antibiotic Stewardship

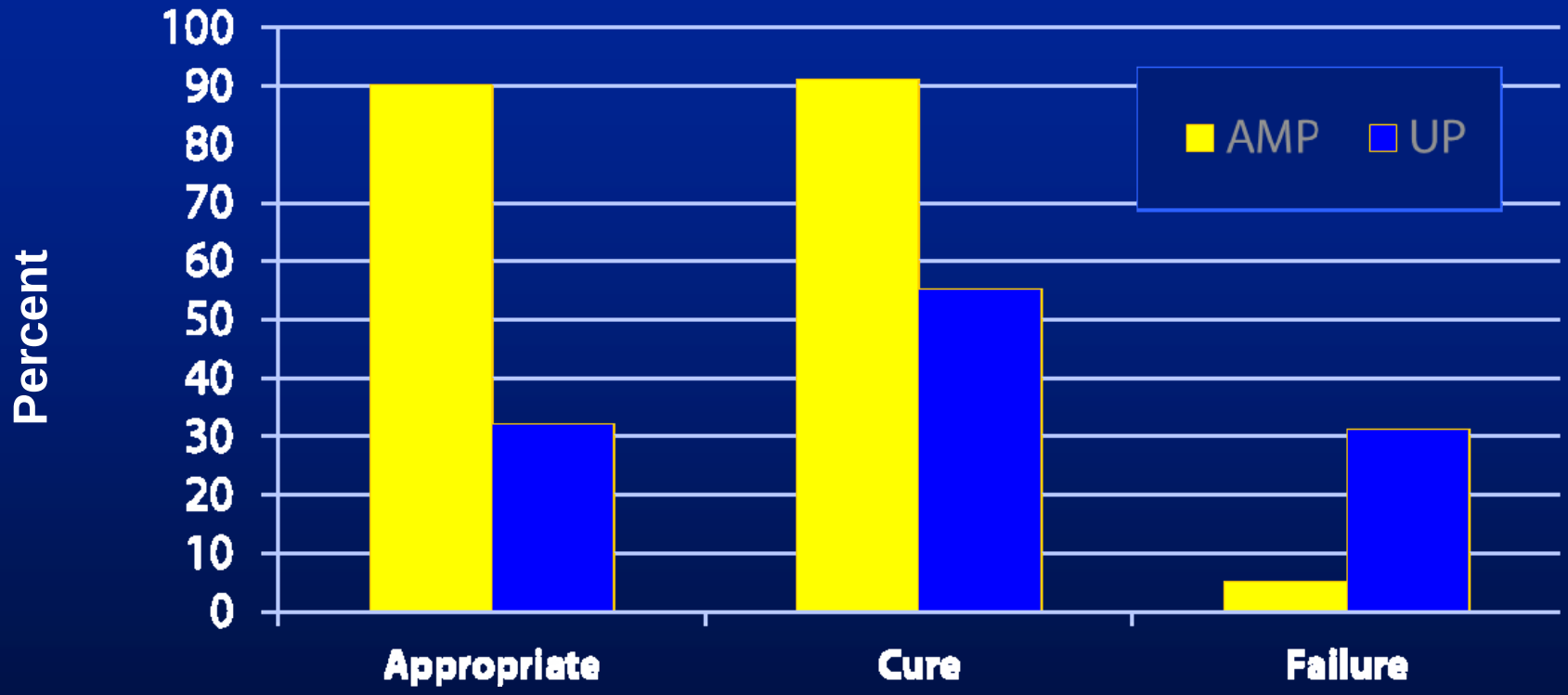
- Is pertinent to inpatient, outpatient, and long-term care settings
- Is practiced at the
  - Level of the patient
  - Level of a health-care facility or system, or network
- Should be a core function of the medical staff (i.e. doctors and other healthcare providers)
- Utilizes the expertise and experience of clinical pharmacists, microbiologists, infection control practitioners and information technologists

Six Goals of Antibiotic Stewardship Programs

1. Reduce antibiotic consumption and inappropriate use
2. Reduce *Clostridium difficile* infections
3. Improve patient outcomes
4. Increase adherence/utilization of treatment guidelines
5. Reduce adverse drug events
6. Decrease or limit antibiotic resistance
   - Hardest to show
   - Best data for health-care associated gram negative organisms

Tamma PD, Cosgrove SE. Infect Dis Clin North Am. 2011 25:245

Antibiotic Stewardship Improves Clinical Outcomes



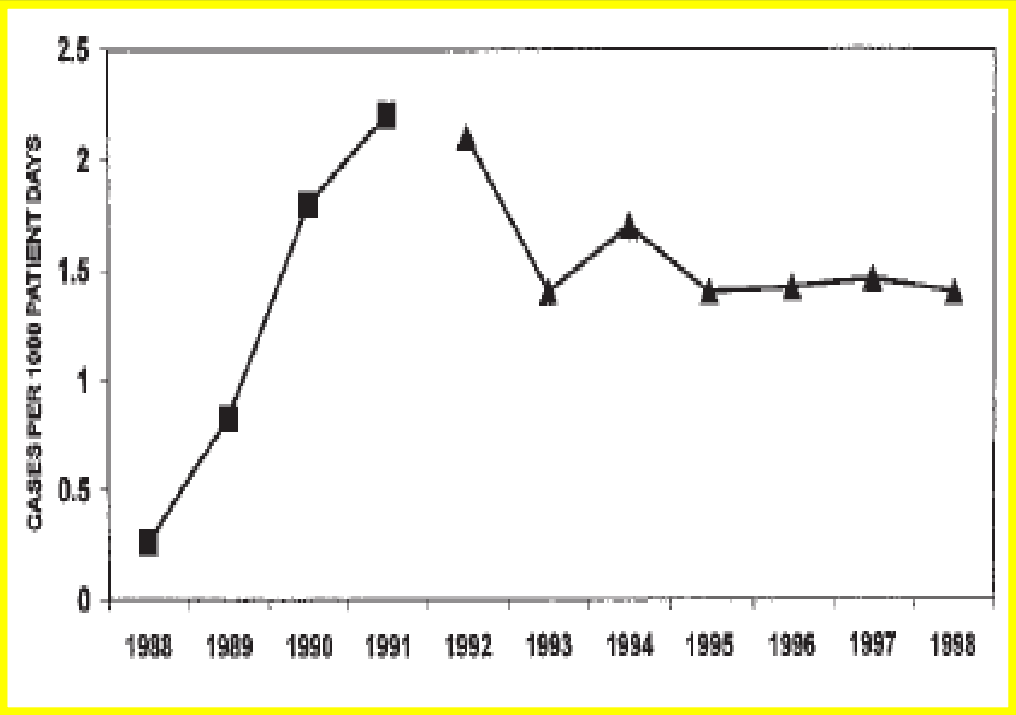
RR 2.8 (2.1-3.8) RR 1.7 (1.3-2.1) RR 0.2 (0.1-0.4)

AMP = Antibiotic Management Program
UP = Usual Practice

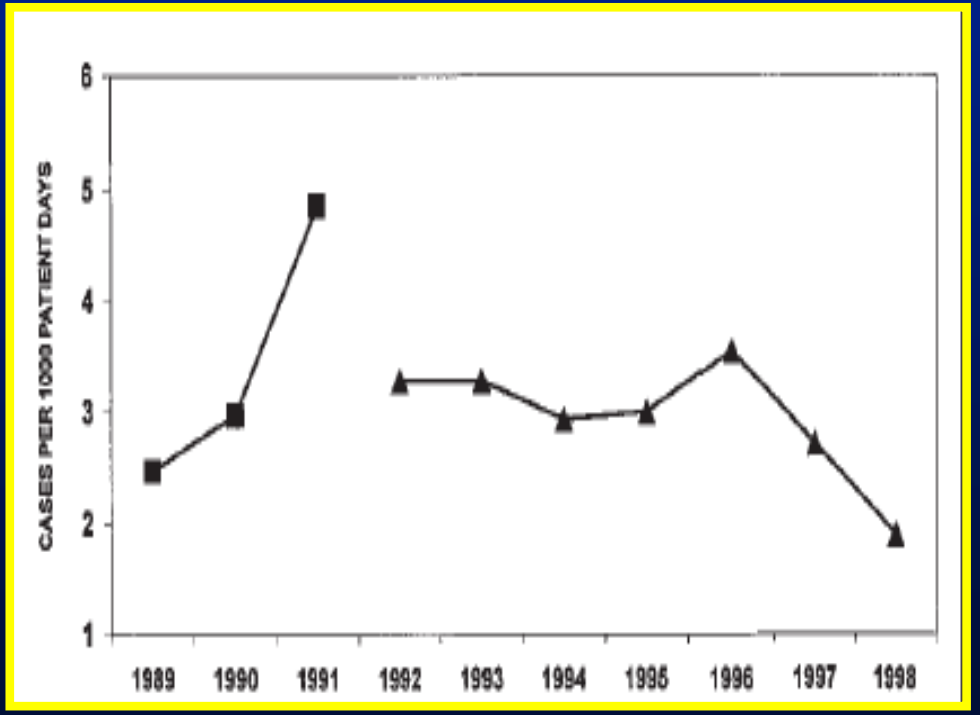
Fishman N. *Am J Med* 2006;119:S53.

Antibiotic Stewardship Reduces *C. difficile* Infection and Gram Negative Resistance

Rates of *C. difficile* AAD



Rates of Resistant Enterobacteriaceae



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

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Nine Factors to Consider When Selecting an Antibiotic

1. Spectrum of coverage
2. Patterns of resistance
3. Evidence or track record for the specified infection
4. Achievable serum, tissue, or body fluid concentration (e.g. cerebrospinal fluid, urine)
5. Allergy
6. Toxicity
7. Formulation (IV vs. PO); if PO assess bioavailability
8. Adherence/convenience (e.g. 2x/day vs. 6x/day)
9. Cost

Principles of Antibiotic Therapy

Empiric Therapy (85%)

- Infection not well defined ("best guess")
- Broad spectrum
- Multiple drugs
- Evidence usually only 2 randomized controlled trials
- More adverse reactions
- More expensive

Directed Therapy (15%)

- Infection well defined
- Narrow spectrum
- One, seldom two drugs
- Evidence usually stronger
- Less adverse reactions
- Less expensive

Why So Much Empiric Therapy?

- Need for prompt therapy with certain infections
  - Life or limb threatening infection
  - Mortality increases with delay in these cases
- Cultures difficult to do to provide microbiologic definition (i.e. pneumonia, sinusitis, cellulitis)
- Negative cultures
- Provider Beliefs
  - Fear of error or missing something
  - Not believing culture data available
  - "Patient is really sick, they should have 'more' antibiotics"
  - Myth of "double coverage" for gram-negatives e.g. pseudomonas
  - "They got better on drug X, Y, and Z so I will just continue those"

To Increase Directed Therapy for Inpatients:

- Define the infection 3 ways
  - Anatomically, microbiologically, pathophysiologically
- Obtain cultures before starting antibiotics
- Use imaging, rapid diagnostics and special procedures early in the course of infection
- Have the courage to make a diagnosis
- Do not rely solely on “response to therapy” to guide therapeutic decisions; follow recommended guidelines
- If empiric therapy is started, reassess at 48-72 hours
  - Move to directed therapy (de-escalation or streamlining)

To Increase use of Directed Therapy for Outpatients:

- Define the infection 3 ways
  - Anatomically, microbiologically, pathophysiologically
- Obtain cultures before starting antibiotics
  - Often difficult in outpatients (acute otitis media, sinusitis, community-acquired pneumonia)
- Narrow therapy often with good supporting evidence
  - Amoxicillin or amoxicillin/clavulinate for AOM, sinusitis and CAP
  - Penicillin for Group A Streptococcal pharyngitis
  - 1st generation cephalosporin or clindamycin for simple cellulitis
  - Trimethoprim/sulfamethoxazole or cipro/levofloxacin for cystitis

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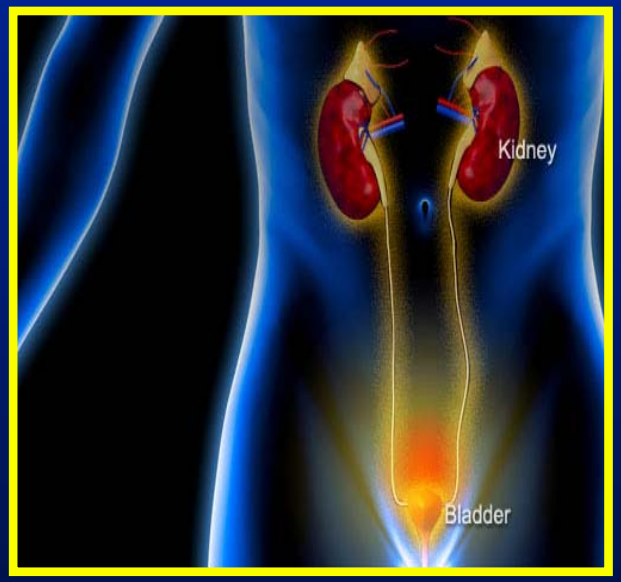
Tenet 1: Treat Bacterial Infection, not Colonization

- Many patients become colonized with potentially pathogenic bacteria but are not infected
  - Asymptomatic bacteriuria or foley catheter colonization
  - Tracheostomy colonization in chronic respiratory failure
  - Chronic wounds and decubiti
  - Lower extremity stasis ulcers
  - Chronic bronchitis
- Can be difficult to differentiate
  - Presence of WBCs not always indicative of infection
  - Fever may be due to another reason, not the positive culture

Tenet 1: Treat Bacterial Infection, not Colonization

Example: Asymptomatic bacteriuria

- $\geq 10^5$ colony forming units is often used as a diagnostic criteria for a positive urine culture
- It does NOT prove infection; it is just a number to state that the culture is unlikely due to contamination
- Pyuria also is not predictive on its own
- It is the presence of symptoms AND pyuria AND bacteruria that denotes infection



Prevalence of Asymptomatic Bacteriuria

Age (years)	Women	Men
20	1%	1%
70	20%	15%
>70 + long-term care	50%	40%
Spinal cord injury (with intermittent catheterization)	50%	50%
Chronic urinary catheter	100%	100%
Ileal loop conduit	100%	100%

Nicolle LE. *Int J Antimicrob Agents*. 2006 Aug;28 Suppl 1:S42-8.

Treatment of Asymptomatic Bacteriuria in the Elderly

Multiple prospective randomized clinical trials have shown no benefit

- No improvement in "mental status"
- No difference in the number of symptomatic UTIs
- No improvement in chronic urinary incontinence
- No improvement in survival

Summary of Asymptomatic Bacteriuria Treatment

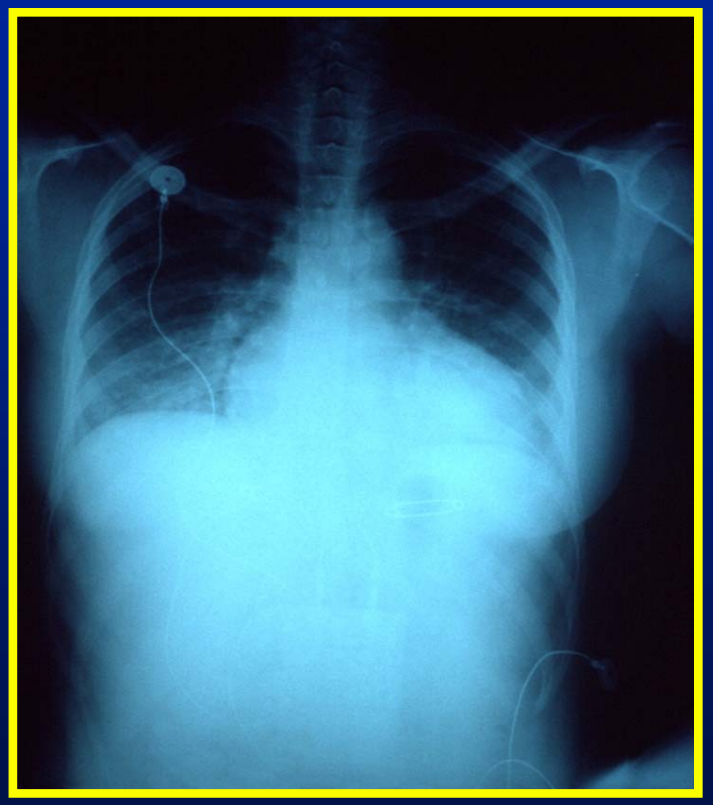
- Treat symptomatic patients with pyuria and bacteriuria
- Don't treat asymptomatic patients with pyuria and/or bacteriuria
- Define the symptomatic infection anatomically
- Dysuria and frequency without fever equals cystitis
- Dysuria and frequency with fever, flank pain, and/or nausea and vomiting equals pyelonephritis
- Remember prostatitis in the male with cystitis symptoms

Tenet 2: Do not Treat Sterile Inflammation or Abnormal Imaging Without Infection

Example: community-acquired pneumonia (CAP)

- CAP: often a difficult diagnosis
- X-rays can be difficult to interpret. Infiltrates may be due to non-infectious causes.
- Examples:
  - –Atelectasis
  - –Malignancy
  - –Hemorrhage
  - –Pulmonary edema

Community-Acquired Pneumonia (CAP)



- Pneumonia is not present in up to 30% of patients treated
- Do not treat abnormal x-rays with antibiotics if the patient does not have systemic evidence of inflammation (fever, wbc, sputum production, etc)
- Discontinue antibiotics initially started for pneumonia if alternative diagnosis revealed

Tenet 3: Do not Treat Viral Infections with Antibiotics

- Acute bronchitis
- Common colds
- Sinusitis with symptoms less than 7 days
- Sinusitis not localized to the maxillary sinuses
- Pharyngitis not due to Group A *Streptococcus spp.*

Gonzales R, et al. Annals of Intern Med 2001;134:479
Gonzales R, et al. Annals of Intern Med 2001;134:400
Gonzales R, et al. Annals of Intern Med 2001;134:521

Tenet 4: Limit Duration of Antibiotic Therapy to the Appropriate Length

- Ventilator-associated pneumonia: 8 days
- Most community-acquired pneumonia: 5 days
- Cystitis: 3 days
- Pyelonephritis: 7 days if fluoroquinolone used
- Intra-abdominal with source control: 4-7 days
- Cellulitis: 5-7 days

Hayashi Y, Paterson DL. Clin Infect Dis 2011; 52:1232

Other Tenets of Antibiotic Stewardship

- Re-evaluate, de-escalate or stop therapy at 48-72 hours based on diagnosis and microbiologic results
- Re-evaluate, de-escalate or stop therapy with transitions of care (e.g. ICU to step-down or ward)
- Do not give antibiotic with overlapping activity
- Do not “double-cover” gram-negative rods (i.e. *Pseudomonas sp.*) with 2 drugs with overlapping activity

Other Tenets of Antibiotic Stewardship

- Limit duration of surgical prophylaxis to <24 hours perioperatively
- Use rapid diagnostics if available

  (e.g. respiratory viral PCR)
- Solicit expert opinion if needed
- Prevent infection
  - Use good hand hygiene and infection control practices
  - Remove catheters

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- The therapeutic benefit of antibiotics should be balanced with their unintended adverse consequences
- Inappropriate antibiotic use is associated with increased antibiotic resistance, adverse drug effects and *Clostridium difficile* infection
- Antibiotic stewardship is important for preserving existing antibiotics and improving patient outcomes
- Antibiotic prescribing should be prudent, thoughtful and rational