Antibiotic Overuse
“Be Antibiotics Aware: Smart Use, Best Care”

Dena El-sayed
Objectives

• Discuss untoward effects of antibiotic use
• Define antibiotic stewardship
• Describe the goals, and core elements 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
Introduction

- The modern age of antibiotics was introduced in the 1930s with sulfonamides and the 1940s with penicillin.
- Since then, antibiotics have dramatically decreased morbidity and mortality due to infectious diseases.
- There are numerous antibiotics in general but there remain few unique antibiotic targets.

*WHO Global Strategy for Containment of Antimicrobial Resistance, 2000
Cell wall synthesis
- Cycloserine
- Vancomycin, Teichoic planine
- Bacitracin
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

Cell wall
- DNA Gyrase
- Quinolones
- DNA-directed RNA polymerase
- Rifampin

Protein synthesis (50S inhibitors)
- Erythromycin (Macrolides)
- Chloramphenicol
- Clindamycin

Protein synthesis (30S Inhibitors)
- Tetracycline
- Spectinomycin
- Streptomycin
- Gentamicin, Tobramycin (aminoglycosides)
- Amikacin

Folic acid metabolism
- Trimethoprim
- Sulfonamides

Cell Membrane
- PABA
- DHFA
- THFA
- mRNA

Cell wall synthesis enzymes
- DHFA
- THFA
- mRNA
- DNA

Cell wall synthesis inhibitors
- Polymyxins
- Chloramphenicol
- Transacetylase
Excessive Use of Antibiotics

- Prospective observational study in a 650-bed university-affiliated hospital of adult non-ICU care inpatients; new antimicrobials examined over a 2-week period
- Results:
  - 1,941 days of antimicrobial therapy in 129 patients
  - 576 (30%) of 1,941 days of therapy were deemed unnecessary*
  - Total average wholesale price (AWP) of all unnecessary antimicrobials prescribed for the study patients was $14,600, corresponding to an estimated yearly AWP of $350,400

*Given when not needed (viral), at wrong dose, longer durations than necessary, wrong antibiotic is chosen, no longer necessary, broad spectrum agents used to treat very susceptible bacteria.
Problems With Antibiotics

- GI: Nausea, vomiting
- Multidrug-resistant organisms
- HAI: Clostridium difficile
- Drug interaction
- Allergies

GI = gastrointestinal
HAI = healthcare-associated infection
Consequences of Inappropriate Use

- **Antibiotics account for nearly 1 in 5 drug-related adverse events**
  - Between 2004-2006, there were 142,505 estimated ER visits/year due to untoward effects of antibiotics.
    - Antibiotics account for 19.3% of drug-related adverse events in general (e.g. antibiotic associated colitis):
      - 78.7% for allergic events.
      - Approximately 50% due to penicillin & cephalosporin classes.
      - 6.1% required hospital admission.

- **C. difficile Infections**
  - Exposure to antibiotics increases the risk by 3X for at least a month.
  - Up to 85% of patients with *C. diff* have antibiotic exposure in the past 28 days.

- **Antibiotic use drives resistance**
- **Increased health care costs**

C. difficile

**Clostridium Difficile**

- Threat Level: Urgent
- 250,000 Infections per Year
- 14,000 Deaths
- $1,000,000,000,000 In Excess Medical Costs per Year

This bacteria is an immediate public health threat that requires urgent and aggressive action.
**Clostridium difficile Infection**

- Incidence and mortality increasing.
  - When published mortality estimates were applied, the crude case-fatality rate rose from 1.2% in 2000 to 2.3% in 2004.
- A more virulent NAP1/BI strain also seen with increasing frequency, affecting older adults disproportionately.

*Simor AE. J Am Geriatr Soc. 2010 Aug;58(8):1556-64*
Antibiotic Resistance

1. Lots of germs. A few are drug resistant.

2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.

3. The drug-resistant bacteria are now allowed to grow and take over.

4. Some bacteria give their drug-resistance to other bacteria, causing more problems.

Examples of How Antibiotic Resistance Spreads

Animals get antibiotics and develop resistant bacteria in their guts.

Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.

Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.

Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.

Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

http://www.cdc.gov/drugresistance/threat-report-2013/
VANCOMYCIN-RESISTANT ENTEROCOCCUS (VRE)

- 20,000 drug-resistant cases
- 1,300 deaths from drug-resistant cases

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

- 80,461 cases
- 11,285 deaths

DRUG-RESISTANT STREPTOCOCCUS PNEUMONIAE

- 1,200,000 cases
- 19,000 excess hospitalizations
- 7,000 deaths

EXTENDED SPECTRUM β-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

- 26,000 drug-resistant infections
- 1,700 deaths
- 140,000 infections per year

- $40,000 in excess medical costs per year for each infection
Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies.

- From a CDC Study from 2000 to 2007, CRKP isolates went from 1% to 8% of all *Klebsiella* isolates.
- 99 case patients and 99 control patients identified.
- Carbapenem-resistant *K. pneumoniae* infection was independently associated with recent organ or stem-cell transplantation (P=.008), receipt of mechanical ventilation (P=.04), longer length of stay before infection (P=.01), and exposure to cephalosporins (P=.02) and carbapenems (P<.001).
- Case patients were more likely than control patients to die during hospitalization (48% vs 20%; P<.001) and to die from infection (38% vs 12%; P<.001).
- The timely administration of antibiotics with in vitro activity against carbapenem-resistant *K. pneumoniae* was not associated with patient survival.

35,790 GN aerobic isolates from ICU pts from 43 US states Overall susceptibility to ciprofloxacin decreased from 86% in 1994 to 76% in 2000 and was significantly associated with increased national use of fluoroquinolones.

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

- Net present value of antibiotic to a drug company is MINUS $50 million. That compares to a positive $1 billion for a new musculoskeletal drug.

*Spellberg B. APUA Newsletter. 2011;30(1)*
Antimicrobial Approval Timeline

1998
- Rifapentine
- Linezolid

1999
- Quinupristin/Dalfopristin
- Moxifloxacin
- Gatifloxacin

2000
- Cefditoren Ertapenem

2001
- Gemifloxacin
- Daptomycin

2002
- Telithromycin

2003
- Tigecycline

2004
- Doripenem

2005
- Ceftazidime/avibactam

2006
- Ceftaroline

2008
- Ceftolazane/tazobactam

2009
- Telavancin

2010
- Dalbavancin
- Oritavancin

2011
- Fidaxomicin
- Ceftaroline

In development: ceftobiprole, eravacycline, Imipenem-MLK 7655, plazomicin, brilacidin & more...

# Antibiotic Resistance: Who Will Pay the Bills?

Theoklis E. Zaoutis

Division of Infectious Diseases, Center for Pediatric Clinical Effectiveness, The Children’s Hospital of Philadelphia, and Department of Pediatrics and Center for Clinical Epidemiology and Biostatistics, The University of Pennsylvania School of Medicine, Philadelphia

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patients with ARI</th>
<th>Patients without ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1391</td>
<td>188 (13.5)</td>
<td>1203 (86.5)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>42.1</td>
<td>54.8*</td>
<td>40.1*</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>10.2</td>
<td>24.2*</td>
<td>8.0*</td>
</tr>
<tr>
<td>HAI (n)</td>
<td>260</td>
<td>135*</td>
<td>125*</td>
</tr>
<tr>
<td>Cost per day ($)</td>
<td>1651</td>
<td>2098*</td>
<td>1581*</td>
</tr>
<tr>
<td>Total cost ($)</td>
<td>19,267</td>
<td><strong>58,029</strong>*</td>
<td>13,210*</td>
</tr>
<tr>
<td>Death [n (%)]</td>
<td>70</td>
<td>34 (18.1)*</td>
<td>36 (3.0)*</td>
</tr>
</tbody>
</table>

*\(p<0.001\)
The Burden of Antimicrobial Resistance

- Bacterial resistance limits the choice of antibiotics which might be effective, often relying on newer and more expensive antibiotics to treat infections.
- Infections due to antibiotic-resistant pathogens have negative clinical and economic consequences compared to infections due to antibiotic-susceptible pathogens \(^1,^2\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Methicillin-susceptible (S) aureus(^7) (n = 165)</th>
<th>Methicillin-resistant (S) aureus(^7) (n = 121)</th>
<th>Imipenem-susceptible (P) aeruginosa(^2) (n = 719)</th>
<th>Imipenem-resistant (P) aeruginosa(^2) (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>6.7%</td>
<td>20.7%(^a)</td>
<td>16.7%</td>
<td>31.1%(^b)</td>
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<tr>
<td>Median Hospital</td>
<td>$52,791</td>
<td>$92,363(^a)</td>
<td>$48,381</td>
<td>$81,330(^c)</td>
</tr>
<tr>
<td>Charges</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

\(a\ p < 0.001 \quad b\) Relative risk, 1.86; 95% CI, 1.38-2.51; \(c\ p < 0.001\)

- As bacterial resistance increases, the accurate selection of appropriate empiric therapy decreases.
- Studies have demonstrated that inappropriate initial therapy is an important independent determinant of mortality \(^3-^6\)

FACT SHEET: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria

Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections

Judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics. The CDC estimates that up to half of all human antibiotic use is unnecessary or inappropriate. The Action Plan includes activities to foster improvements in the appropriate use of antibiotics (i.e., antibiotic stewardship) by improving prescribing practices across all healthcare settings, preventing the spread of drug-resistant threats in healthcare facilities and communities, and continuing to eliminate the use of medically-important antibiotics for growth promotion in animals.

By 2020, significant outcomes in this area will include:

- Establishment of antimicrobial stewardship programs in all acute care hospitals and improved antimicrobial stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.
- Establishment of State Antibiotic Resistance (AR) Prevention (Protect) Programs in all 50 states to monitor regionally.
California Senate Bill 1311

- Law was signed on September 29, 2014
  - Requires all general acute care hospitals to adopt & implement ASP by July 1, 2015
  - Minimum 1 MD or PharmD who is knowledgeable about ASP
  - “Under existing law, a violation of the provisions governing health facilities 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.”
Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America


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Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics.

Keywords. antibiotic stewardship; antibiotic stewardship programs; antibiotics; implementation.
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.
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
• Antibiotic Stewardship and an infection control program, should be a core function of the medical staff.
• Utilizes the expertise and experience of clinical pharmacists, microbiologists, infection control practitioners and information technologists.
IDSA Guidelines: Goals of Antibiotic Stewardship Programs

**Primary Goal**: Optimize clinical outcomes while minimizing unintended consequences of antimicrobial use.

- Reduce *Clostridium difficile* infections
- Reduce adverse drug events
- Decrease or limit antibiotic resistance
  - Hardest to show
  - Best data for health-care associated gram negative organisms

**Secondary Goal**: Reduce healthcare costs without adversely impacting the Quality of care.
Core Elements of Antimicrobial Stewardship Programs

- **Leadership Commitment**: funding (often pays for itself), assurance, training.
- **Accountability**: identify a single leader responsible (MD, PharmD), provide dedicated time. Partnerships with health department/labs.
- **Drug Expertise**: Pharmacist trained in ID/ASP, ID MD.
- **Action**: Facility specific guidelines, order sets, chart review
  - Interventions: prospective audit, formulary restriction and preauthorization, antibiotic ‘time out’ (review antibiotics at a concrete point in time).
- **Tracking**: monitoring antibiotic prescribing and resistance patterns.
- **Reporting**: regular reporting information on antibiotic use and resistance to staff.
- **Education**: educating clinicians about resistance and optimal prescribing.
### VCMC
#### ANTIBIOTIC 2017
**GRAM NEGATIVE**
(of isolates tested)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Amp/Clavulanate</th>
<th>Amp/Sulbactam</th>
<th>Ampiillin</th>
<th>Azithromycin</th>
<th>Cefazolin</th>
<th>Cefepime</th>
<th>Ceftriaxone</th>
<th>Cefuroxime</th>
<th>Ciprofloxacin</th>
<th>Erifapenem</th>
<th>Gentamicin</th>
<th>Levofloxacin</th>
<th>Meropenem</th>
<th>Nitrofurantoin</th>
<th>Pip/Tazobactam</th>
<th>Tobramycin</th>
<th>Trimethoprim/Sulfamethaxasole</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. Coli</em></td>
<td>225</td>
<td>51</td>
<td>68</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>89</td>
<td>74</td>
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<td>99</td>
<td>88</td>
<td>94</td>
<td>94</td>
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<td><em>Enterobacter spp.</em></td>
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<td>95</td>
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<td>88</td>
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<td>88</td>
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<td>75</td>
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<td><em>Serratia spp.</em></td>
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<td>100</td>
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</tr>
</tbody>
</table>

Nitrofurantoin reported only on urinary isolates
X: not tested
N: not recommended

12% of *E.Coli* are Extended Spectrum Beta Lactamase (ESBL) Producing

12% of *Klebsiella spp* are ESBL producing

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### VCMC
#### ANTIBIOTIC 2017
**GRAM POSITIVE**
(of isolates tested)

<table>
<thead>
<tr>
<th>Strain</th>
<th># of isolates tested</th>
<th>Amox/Clavulinate</th>
<th>Amp/Sulbactam</th>
<th>Ampiillin</th>
<th>Azithromycin</th>
<th>Cefazolin</th>
<th>Cefepime</th>
<th>Ceftriaxone</th>
<th>Cefuroxime</th>
<th>Ciprofloxacin</th>
<th>Erifapenem</th>
<th>Gentamicin</th>
<th>Levofloxacin</th>
<th>Meropenem</th>
<th>Nitrofurantoin</th>
<th>Pip/Tazobactam</th>
<th>Tobramycin</th>
<th>Trimethoprim/Sulfamethaxasole</th>
<th>Vancomycin</th>
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<td><em>Strep. Pneumonia</em></td>
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<td>X</td>
<td>100</td>
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<td>72</td>
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<td>96</td>
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<td><em>Staph coag negative</em></td>
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<tr>
<td><em>Enterococcus Faecalis</em></td>
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<td>X</td>
<td>33</td>
<td>50</td>
<td>67</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

X: not tested
N: not recommended

33% of *Staph aureus* are Methicillin Resistant (MRSA)

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VCMC/SPH Antimicrobial Stewardship Committee 03/2018, P&T Committee 03/2018
Antimicrobial Prescribing Process & Antimicrobial Stewardship Strategies

1. Patient evaluation
   - Education/guideline strategies
   - Antibiotic cycling strategies
   - Formulary/restriction strategies
   - Computer-assisted strategies

2. Choice of antimicrobial to prescribe

3. Prescription ordering
   - Review and feedback strategies

4. Dispensing of antimicrobial
Antibiotic Stewardship Strategies: IDSA Guidelines

• Formulary restriction and preauthorization (A-II)
  – Can lead to immediate and significant reduction in antimicrobial use and cost.
  – May delay therapy. Loss of prescriber autonomy.
  – *Report rates of resistance to show effects: ESBL, CDAD, MRSA, SPACE, KPC 1-3 rates.*

• Prospective audit with intervention and feedback (A-I)
  – Review when more clinical data available. Prescriber autonomy maintained. Can re-address de-escalation, duration, switch to PO.
  – Compliance voluntary. Labor-intensive. Technology support.

• Education programs, with active intervention (AIII, B-II)
Antibiotic Stewardship Strategies: IDSA Guidelines

• Clinical Guidelines (A-I)
  – Incorporate local antimicrobial resistance patterns. Provide education and feedback.

• Stream-lining or de-escalation therapy (A-II)
  – IV to PO conversion (if can tolerate full liquid diet, or has feeding tube): Saves costs, decrease length of stay.
  – Based on culture results.

• Dose optimization
  – Based on PK/PD parameters (B-lactams activity correlates with amount of time >MIC, and FQ and aminoglycosides are concentration dependent), including patient characteristics, causative organisms, site of infection.

• Antimicrobial Order Forms (B-II)
  – Shown to be effective component of program and can facilitate implementation of practice guidelines.
ADULT INPATIENT ANTIBiotic APPROVAL FORM

See reverse for EMPHC treatment recommendations (PRIOR to return of microbiologic data).

Latest Serum Creatinine: ____________________________

Allergies: ________________________________________

Is the patient pregnant? ☐ Yes

CLINICAL DIAGNOSES (check all that apply):

ABDOMINAL INFECTIONS
☐ Biliary tract infection - community-acquired, mild/mod. ill
☐ Biliary tract infection - severity ill and/or nosocomial
☐ Diverticulitis - community-acquired, mild/mod ill
☐ Diverticulitis - severity ill and/or nosocomial
☐ Peritonitis - mild/mod. ill
☐ Peritonitis - severity ill or immunosuppressed
☐ Spontaneous bacterial peritonitis (SBP), treatment

URINARY TRACT INFECTIONS - note criteria in guidelines
☐ Acute cystitis - uncomplicated
☐ Acute cystitis - complicated
☐ Acute pyelonephritis - not severely ill
☐ Acute pyelonephritis - severely ill or hospitalized >48
☐ Urinary catheter-associated - not severely ill
☐ Urinary catheter-associated - severely ill or hospitalized >48

FLUCONAZOLE
☐ HIV positive, esophageal candidiasis
☐ Medical oncology patient, esophageal candidiasis
☐ HIV positive, admitted on daily Fluconazole
☐ Liver/pancreas transplant, admitted on daily Fluconazole
☐ Candida urinary tract infection

CENTRAL NERVOUS SYSTEM INFECTIONS
☐ Meningitis - community-acquired
☐ Meningitis - hospital-acquired/post-operative

SKIN AND SOFT TISSUE INFECTIONS
☐ Cellulitis - mild
☐ Cellulitis - moderate/severe or nosocomial
☐ Diabetic foot infection - mild
☐ Diabetic foot infection - moderate
☐ Diabetic foot infection - severe
☐ Surgical site infection - following clean procedure
☐ Surgical site infection - following contaminated procedure

VANCOMYCIN
☐ ≥ 2 sets of blood cultures with Gram (+) cocci in clusters
☐ Severe PGN allergy & infection with MSSA or Enterococcus – culture from a sterile site or abscess within prior 72 h
☐ Proven infection with MRSA – culture from a sterile site or abscess within prior 72 h
☐ Proven infection with Ampicillin-resistant Enterococcus – culture from a sterile site or abscess within prior 72 h

PNEUMONIAS
☐ Community-acquired pneumonia – infiltrate required
☐ Healthcare-acquired pneumonia – infiltrate required
☐ Ventilator-associated pneumonia – infiltrate required

WRITE ANTIBIOTIC REGIMEN BELOW – this constitutes an approval record and MUST be accompanied by an order

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Estimated Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data/Time ____________________________  Name of Prescriber (Print legibly) ____________________________  Signature ____________________________  Prescriber #: ____________________________  Pager #: ____________________________
Not Recommended

• Antimicrobial cycling not recommended due to insufficient data.

• Combination therapy
  – Insufficient data for routine use (C-II).
  – Has role to increase coverage in empiric therapy in patients at risk for MDR.
Antibiotic Stewardship Reduces *C. difficile* Infection and Gram Negative Resistance

Rates of *C. difficile*  
Rates of Resistant Enterobacteriaceae

- A multidisciplinary antibiotic management program to minimize the inappropriate use of third-generation cephalosporins was implemented in 1991.
- Following implementation of the program, there was a 22% decrease in the use of parenteral broad-spectrum antibiotics (P < .0001) despite a 15% increase in acuity of patient care during the following 7 years.
- The program also appeared to have a favorable impact on VRE rates without a sustained impact on MRSA rates.

Benefits of an Antimicrobial Stewardship Program: Beyond Pharmacy Costs (Univ Pennsylvania)

- Main target of program is to improve patient safety through active interventions and healthcare provider education

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HUP Program (n=96)</th>
<th>Usual Practice (n=95)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial appropriate</td>
<td>86 (90%)</td>
<td>30 (32%)</td>
<td>2.8 (2.1 – 3.8)</td>
</tr>
<tr>
<td>Cure</td>
<td>52/57 (91%)</td>
<td>34/62 (55%)</td>
<td>1.7 (1.3 – 2.1)</td>
</tr>
<tr>
<td>Failure</td>
<td>5 (5%)</td>
<td>29 (31%)</td>
<td>0.2 (0.1 – 0.4)</td>
</tr>
<tr>
<td>Clinical</td>
<td>0</td>
<td>10 (11%)</td>
<td>--</td>
</tr>
<tr>
<td>Microbiologic</td>
<td>0</td>
<td>8 (8%)</td>
<td>--</td>
</tr>
<tr>
<td>Superinfection</td>
<td>0</td>
<td>8 (8%)</td>
<td>--</td>
</tr>
<tr>
<td>Adverse drug effect</td>
<td>0</td>
<td>2 (2%)</td>
<td>--</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>--</td>
</tr>
<tr>
<td>Resistance</td>
<td>1 (1%)</td>
<td>9 (9%)</td>
<td>0.13 (0.02 – 1.0)</td>
</tr>
</tbody>
</table>

- Annual savings (600 interventions/month) amounted to $302,400 for antibiotic costs, $533,000 for infection-related costs, and $4.25 million in total hospital costs
- The majority of the cost savings were attributable to a decreased length of stay in the intensive care unit (ICU), although the total hospital length of stay in the study was unchanged

Nine Factors to Consider When Selecting an Antibiotic

I. Spectrum of coverage
II. Patterns of resistance
III. Evidence or track record for the specified infection
IV. Achievable serum, tissue, or body fluid concentration (e.g. cerebrospinal fluid, urine)
V. Allergy
VI. Toxicity
VII. Formulation (IV vs. PO); if PO assess bioavailability
VIII. Adherence/convenience (e.g. 2x/day vs. 6x/day)
IX. Cost
# Principles of Antibiotic Therapy

<table>
<thead>
<tr>
<th>Empiric Therapy (85%)</th>
<th>Directed Therapy (15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection not well defined (“best guess”)</td>
<td>• Infection well defined</td>
</tr>
<tr>
<td>• Broad spectrum</td>
<td>• Narrow spectrum</td>
</tr>
<tr>
<td>• Multiple drugs</td>
<td>• One, seldom two drugs</td>
</tr>
<tr>
<td>• Evidence usually only 2 randomized controlled trials</td>
<td>• Evidence usually stronger</td>
</tr>
<tr>
<td>• More adverse reactions</td>
<td>• Less adverse reactions</td>
</tr>
<tr>
<td>• More expensive</td>
<td>• Less expensive</td>
</tr>
</tbody>
</table>
Why So Much Empiric Therapy?

• Need for prompt therapy with certain infections
  – Life or limb threatening infection
  – Delay in antimicrobials increases mortality
• Cultures to identify the organism are difficult to (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 use of Directed Therapy for Outpatients:

• **Define the infection 3 ways:**
  – Anatomically, microbiologically, pathophysiologically

• **Obtain cultures** before starting antibiotics.
  – Often difficult, esp. in outpatient setting (acute otitis media, sinusitis, community-acquired pneumonia).

• **Narrow therapy** with good supporting evidence:
  – Amoxicillin or amoxicillin/clavulanate for AOM, sinusitis and CAP
  – Penicillin for Group A Streptococcal pharyngitis
  – 1st generation cephalosporin or clindamycin for simple cellulitis
  – Trim/sulfa or cipro/levofloxacin for cystitis
Tenets of Appropriate Antibiotic Use

- **Tenet 1:** Treat bacterial infection, not colonization:
  - i.e. asymptomatic bacteriuria, foley catheter colonization, tracheostomy colonization, chronic wounds, lower extremity stasis ulcers, chronic bronchitis

- **Tenet 2:** Do not treat sterile inflammation or abnormal imaging without infection:
  - i.e. CAP often difficult to diagnose. Infiltrates may be due to atelectasis, malignancy, hemorrhage, pulmonary edema
  - Do not treat unless systemic evidence of inflammation (fever, WBC, sputum production)

- **Tenet 3:** Do not treat viral infections with antibiotics:
  - i.e. acute bronchitis, common colds, sinusitis with symptoms <7 days, sinusitis not localized to maxillary sinuses, pharyngitis not due to GAS

- **Tenet 4:** Limit duration of antibiotic therapy.
Other Tenets of Antibiotic Stewardship

• Re-evaluate, de-escalate or stop therapy:
  — At 48-72 hours based on diagnosis and microbiologic results
  — 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*).
• 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.
Asymptomatic Bacteriuria: Points

• $\geq 10^5$ colony forming units/mL urine, 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.
• Multiple RCTs have shown no benefit in treatment of asymptomatic bacteriuria in elderly (survival, urinary incontinence, mental status, recurrent UTIs) – but antibiotics can cause harm.
• Difficult to obtain clean catches of urine from elderly patients sometimes.
## Prevalence of Asymptomatic Bacteriuria

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>70</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;70 + long-term care</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>(with intermittent catheterization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic urinary catheter</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ileal loop conduit</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Fever of >37.9°C (100°F) or 1.5°C (2.4°F) increase above baseline on at least two occasions over last 12 hours?**

- Yes
  - 2 or more symptoms or signs of non-urinary tract infection*
    - Yes: Do not order urine culture
    - No: Order urine culture for one or more of following:
      - Dysuria
      - Urinary catheter
      - Urgency
      - Flank pain
      - Shaking chills
      - Urinary incontinence
      - Frequency
      - Gross haematuria
      - Suprapubic pain
  - No: Urinary catheter?
    - Yes: Order urine culture for new onset burning urination or for two or more of following:
      - Urgency
      - Flank pain
      - Shaking chills
      - Urinary incontinence
      - Frequency
      - Gross haematuria
      - Suprapubic pain
    - No: Order urine culture for one or more of following:
      - New costovertebral tenderness
      - Rigors
      - New onset of delirium

* Respiratory symptoms include increased shortness of breath, increased cough, increased sputum production, new pleuritic chest pain.
* Gastrointestinal symptoms include nausea or vomiting, new abdominal pain, new onset of diarrhoea
* Skin and soft tissue symptoms include new redness, warmth, swelling, purulent drainage

*Loeb M et al. BMJ. 2005 Sep 24;331(7518):669*
Suspected SSTI: SBAR

A – Assessment (check boxes and determine recommendation)

Minimum Criteria for Initiating an Antibiotic

☐ New or increasing purulent drainage at a wound, skin, or soft-tissue site

☐ At least two of the following:

☐ Fever of 100°F (38°C) or repeated temperatures of 99°F (37°C)*

☐ redness

☐ tenderness

☐ warmth

☐ swelling that is new or increasing
### Antibiotic Prescribing and Use in Doctor’s Offices

**Adult Treatment Recommendations**

The table below summarizes the most recent recommendations for appropriate antibiotic prescribing for adults seeking care in an outpatient setting. Antibiotic prescribing guidelines establish standards of care and focus quality improvement efforts.

The table also offers information related to over-the-counter medication for symptomatic therapy. Over-the-counter medications can provide symptom relief, but have not been shown to shorten the duration of illness. They also have a low incidence of minor adverse effects. Providers and patients should weigh the potential for benefits and minor adverse effects when considering symptomatic therapy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Acute rhinosinusitis**<sup>1,2</sup> | • About 1 out of 8 adults (12%) in 2012 reported receiving a diagnosis of rhinosinusitis in the previous 12 months, resulting in more than 30 million diagnoses  
• Ninety-98% of rhinosinusitis cases are | • Diagnose acute bacterial rhinosinusitis based on symptoms that are:  
  - **Severe** (>3-4 days), such as a fever ≥39°C (102°F) and purulent nasal discharge or facial pain;  
  - **Persistent** (>10 days) **without improvement**, such as nasal discharge or daytime cough; or  
  - **Worsening** (3-4 days) such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper | If a bacterial infection is established:  
  - Watchful waiting is encouraged for uncomplicated cases for which reliable follow-up is available.  
  - Amoxicillin or amoxicillin/clavulanate is the recommended first-line treatment. |

---


<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
</table>
| Acute rhinosinusitis¹,² | • About 1 out of 8 adults (12%) in 2012 reported receiving a diagnosis of rhinosinusitis in the previous 12 months, resulting in more than 30 million diagnoses  
• Ninety–98% of rhinosinusitis cases are viral, and antibiotics are not guaranteed to help even if the causative agent is bacterial. | • Diagnose acute bacterial rhinosinusitis based on symptoms that are:  
  ○ **Severe (>3–4 days)**, such as a fever ≥39°C (102°F) and purulent nasal discharge or facial pain;  
  ○ **Persistent (>10 days) without improvement**, such as nasal discharge or daytime cough; or  
  ○ **Worsening (3–4 days)** such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper respiratory infections (URI) lasting 5–6 days.  
• Sinus radiographs are not routinely recommended. | If a bacterial infection is established:  
• Watchful waiting is encouraged for uncomplicated cases for which reliable follow-up is available.  
• Amoxicillin or amoxicillin/clavulanate is the recommended first-line therapy.  
• Macrolides such as azithromycin are not recommended due to high levels of *Streptococcus pneumoniae* antibiotic resistance (~40%).  
• For penicillin-allergic patients, doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) are recommended as alternative agents. |
Acute uncomplicated bronchitis

- Cough is the most common symptom for which adult patients visit their primary care provider, and acute bronchitis is the most common diagnosis in these patients.
- Evaluation should focus on ruling out pneumonia, which is rare among otherwise healthy adults in the absence of abnormal vital signs (heart rate ≥ 100 beats/min, respiratory rate ≥ 24 breaths/min, or oral temperature ≥ 38 °C) and abnormal lung examination findings (focal consolidation, egophony, fremitus).
- Colored sputum does not indicate bacterial infection.
- For most cases, chest radiography is not indicated.

Routine treatment of uncomplicated acute bronchitis with antibiotics is not recommended, regardless of cough duration.
Options for symptomatic therapy include:
- Cough suppressants (codeine, dextromethorphan);
- First-generation antihistamines (diphenhydramine);
- Decongestants (phenylephrine).

Evidence supporting specific symptomatic therapies is limited.
<table>
<thead>
<tr>
<th>Pharyngitis(^\text{8,2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Group A beta-hemolytic streptococcal (GAS) infection is the only common indication for antibiotic therapy for sore throat cases.</td>
</tr>
<tr>
<td>- Only 5–10% of adult sore throat cases are caused by GAS.</td>
</tr>
<tr>
<td>- Clinical features alone do not distinguish between GAS and viral pharyngitis; a rapid antigen detection test (RADT) is necessary to establish a GAS pharyngitis diagnosis.</td>
</tr>
<tr>
<td>- Those who meet two or more Centor criteria (e.g., fever, tonsillar exudates, tender cervical lymphadenopathy, absence of cough) should receive a RADT. Throat cultures are not routinely recommended for adults.</td>
</tr>
<tr>
<td>- Antibiotic treatment is NOT recommended for patients with negative RADT results.</td>
</tr>
<tr>
<td>- Amoxicillin and penicillin V remain first-line therapy due to their reliable antibiotic activity against GAS.</td>
</tr>
<tr>
<td>- For penicillin-allergic patients, cephalexin, cefadroxil, clindamycin, or macrolides are recommended.</td>
</tr>
<tr>
<td>- GAS antibiotic resistance to azithromycin and clindamycin are increasingly common.</td>
</tr>
<tr>
<td>- Recommended treatment course for all oral beta lactams is 10 days.</td>
</tr>
<tr>
<td>Acute uncomplicated cystitis</td>
</tr>
</tbody>
</table>
Antibiotic Prescribing and Use in Doctor's Offices

CDC > Antibiotic Use > Appropriate Antibiotic Use: Community

For Patients

Common infections, whether caused by bacteria or viruses, are often painful and can get in the way of our well-being and everyday lives. Many infections do not require antibiotics, but there are other actions you can take to lessen symptoms.

Spanish: Para los pacientes

COMMON ILLNESSES
Antibiotics are not always needed for sinus infections, sore throats, ear infections...

SYMPTOM RELIEF
There are often things you can do to feel better even if antibiotics won't treat your illness...
Why does taking antibiotics lead to antibiotic resistance?

Any time antibiotics are used, they can cause side effects and lead to antibiotic resistance. Antibiotic resistance is one of the most urgent threats to the public’s health. Always remember:

1. Antibiotic resistance does not mean the body is becoming resistant to antibiotics; it is that bacteria have become resistant to the antibiotics designed to kill them.
2. When bacteria become resistant, antibiotics cannot fight them, and the bacteria multiply.
3. Some resistant bacteria can be harder to treat and can spread to other people.

What is the right way to take antibiotics?

If you need antibiotics, take them exactly as prescribed.

Improving the way healthcare professionals prescribe antibiotics, and the way we take antibiotics, helps keep us healthy now, helps fight antibiotic resistance, and ensures that these life-saving drugs will be available for future generations.

Talk with your doctor if you have any questions about your antibiotics, or if you develop any side effects, especially diarrhea, since that could be *Clostridium difficile* infection (also called *C. difficile* or *C. diff*), which needs to be treated. *C. diff* can lead to severe colon damage and death.

What are the side effects?

Common side effects range from minor to very severe health problems and can include:

- Rash
- Dizziness
- Nausea
- Diarrhea
- Yeast infections

More serious side effects can include:

- *Clostridium difficile* infection
- Severe and life-threatening allergic reactions

To learn more about antibiotic prescribing and use, visit [www.cdc.gov/antibiotic-use](http://www.cdc.gov/antibiotic-use).
**Viruses or Bacteria: What's got you sick?**

Antibiotics are only needed for treating certain infections caused by bacteria. Viral illnesses cannot be treated with antibiotics. When an antibiotic is not prescribed, ask your healthcare professional for tips on how to relieve symptoms and feel better.

<table>
<thead>
<tr>
<th>Common Condition</th>
<th>Common Cause</th>
<th>Are Antibiotics Needed?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteria</td>
<td>Bacteria or Virus</td>
</tr>
<tr>
<td>Strep throat</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Sinus infection</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Middle ear infection</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Bronchitis (in otherwise healthy children and adults)*</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Common cold/runny nose</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Sore throat (except strep)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Flu</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

* Studies show that in otherwise healthy children and adults, antibiotics for bronchitis won't help you feel better.

Plenty of others at: [https://www.cdc.gov/antibiotic-use/community/materials-references/print-materials/index.html](https://www.cdc.gov/antibiotic-use/community/materials-references/print-materials/index.html)
Conclusion

• 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, and thoughtful antibiotic prescribing, is important for preserving existing antibiotics and improving patient outcomes.
References

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- Core Elements of Hospital Antibiotic Stewardship Programs. Finding what fits. Loria Pollack, MD, MPH. Division of Healthcare Quality Promotion. Centers for Disease Control and Prevention
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- Ohl CA, Luther VP. J. Hosp. Med. 2011;6:S4
- Newland & Hersh/PIDJ/2010
- Barlam et al CID 2016 IDSA Guidelines
- Understanding antimicrobial stewardship. Vanthida Huang, Pharm D, Midwestern University College of Pharmacy.
- SHEA Antimicrobial Stewardship page: http://www.shea-online.org/GuidelinesResources/FeaturedTopicsinHAIPrevention/AntimicrobialStewardship.aspx
- CDC’s Get Smart for Healthcare - comprehensive website on the appropriate use of antibiotics and antibiotic resistance. www.cdc.gov/getsmart/healthcare