Antimicrobial Stewardship: Pediatric Applications

Jeffrey S. Gerber MD, PhD
Division of Infectious Diseases
The Children’s Hospital of Philadelphia
Agenda

• The case for Antimicrobial Stewardship

• The CHOP ASP

• Examples of Stewardship
  – Surgery
  – Primary care
Agenda

• The case for Antimicrobial Stewardship

• The CHOP ASP

• Examples of Stewardship
  – Surgery
  – Primary care
Antibiotic Use: Outpatient Children

Chai G et al. Pediatrics 2012;130:23-31
Antibiotic Use: Outpatient Children

Antibiotic Prescription Rates for Acute Respiratory Tract Infections in US Ambulatory Settings

Carlos G. Grijalva, MD, MPH
J. Pekka Nuorti, MD, DSc
Marie R. Griffin, MD, MPH

Infections caused by antibiotic-resistant microorganisms are associated with increased morbidity, mortality, and substantial economic burden. Antibiotic use creates selective pressure for the emergence of antibiotic-resistant bacteria. During the past decade, a variety of US initiatives have promoted the judicious use of antibiotics, particularly for acute respiratory tract infection (ARTI), which is a common cause of health care encounters and antibiotic prescriptions, especially in young children. In the late 1990s, antibiotic prescription rates in both children and adults decreased, but these decreases were initially accompanied by increased prescription of broad-spectrum antibiotics.

Interventions not directly targeting antibacterial use may also have reduced antibiotic prescriptions and limited the spread of antibiotic resistance. For example, routine US infant immunization with a 7-valent pneumococcal conjugate vaccine (PCV-7) resulted in decreases in rates of invasive pneumococcal disease and decreases in antibiotic use.

Context During the 1990s, antibiotic prescriptions for acute respiratory tract infection (ARTI) decreased in the United States. The sustainability of those changes is unknown.

Objective To assess trends in antibiotic prescriptions for ARTI.

Design, Setting, and Participants The National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data (1995-2006) were used to determine rates of antibiotic prescribing for ARTI.

Main Result 17
ci, 22%
ARTI rates decreased from 1000 per 1000 children and adults.

Conclusions Fewer antibiotic prescriptions for ARTI were associated with decreased antibiotic use for respiratory infections, which may have contributed to the observed decreases in antibiotic resistance.

Antibiotic Prescribing in Ambulatory Pediatrics in the United States

WHAT’S KNOWN ON THIS SUBJECT: Results of previous studies have indicated that most antibiotic prescriptions for children were for respiratory conditions, and many of them were inappropriate. Although antibiotic prescribing is declining overall, broad-spectrum antibiotic prescribing for respiratory conditions is increasing. Unnecessary antibiotic prescribing promotes resistance and adverse events.

WHAT THIS STUDY ADDS: Respiratory conditions account for more than 70% of antibiotic prescriptions in ambulatory pediatrics. Broad-spectrum antibiotics, especially macrolides, represent 50% of pediatric antibiotic use. Broad-spectrum antibiotics are frequently prescribed unnecessarily for conditions for which antibiotics are unlikely to provide benefit.
Outpatient Antibiotic Use: US and Europe, 2004

Outpatient Antibiotic Dispensing: US, 2010

Figure 1. Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.
So What?

- We use a LOT of antibiotics
- We use them variably
- But … so what?
ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
Impact of Antibiotic Resistance

Each Year in the US:

• > 2 million serious infections with antibiotic-resistant bacteria

• > 23,000 die as a direct result of antibiotic-resistant infections

• 250,000 hospitalizations for *C. difficile* infections; >14,000 deaths

• $20 billion direct healthcare costs (2008)

• Many of these infections could have been prevented
Core Actions to Combat Resistance

- preventing infections and preventing the spread of resistance
- tracking resistant bacteria
- improving the use of today’s antibiotics
- promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria

Bacteria will inevitably find ways of resisting the antibiotics we develop, which is why aggressive action is needed to keep new resistance from developing and prevent the resistance that already exists from spreading
Antibiotic use is the most important factor leading to antibiotic resistance
Resistance Aside

• 5%–25% diarrhea

• 1 in 1000 visit emergency department for adverse effect of antibiotic
  – comparable to insulin, warfarin, and digoxin

• 1 in 4000 chance that an antibiotic will prevent serious complication from URI

Shehab N. CID 2008:47; Linder JA. CID 2008:47
Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance — but permanent changes to our protective flora could have more serious consequences, says Martin Blaser.

The average child in the United States and other developed countries has received 10–20 courses of antibiotics by the time he or she is 18 years old. In many respects, this is a life-saving development. The average US citizen born in 1940 was expected to live to the age of 65; a baby born today should reach 78, in part because of antibiotics. But the assumption that antibiotics are generally safe has fostered overuse and led to an increase in bacterial resistance to treatments.

Other, equally serious, long-term consequences of our love of antibiotics have received far less attention. Antibiotics kill the bacteria we do want, as well as those we don’t. Early evidence from my lab and others hints that, sometimes, our friendly flora never fully recover. These long-term changes to the beneficial bacteria within people’s bodies may even increase our susceptibility to infections and disease. Overuse of antibiotics could be fuelling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations (see graph).

We urgently need to investigate this possibility. And, even before we understand the full scope, there is action we should take.
Antibiotics and Obesity

- Mice fed sub-therapeutic doses of antibiotics exhibited:
  - taxonomic changes of microbiome
  - changes in copies of key genes involved in metabolism of carbohydrates to short-chain fatty acids
  - alterations in hepatic metabolism of lipids and cholesterol
  - increased adiposity

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice


The role of specific gut microbes in shaping body composition remains unclear. We transplanted fecal microbiota from adult female twin pairs discordant for obesity into germ-free mice fed low-fat mouse chow, as well as diets representing different levels of saturated fat and fruit and vegetable consumption typical of the U.S. diet. Increased total body and fat mass, as well as obesity-associated metabolic phenotypes, were transmissible with uncultured fecal communities and with their corresponding fecal bacterial culture collections. Cohousing mice harboring an obese twin’s microbiota (Ob) with mice containing the lean co-twin’s microbiota (Ln) prevented the development of increased body mass and obesity-associated metabolic phenotypes in Ob cage mates. Rescue correlated with invasion of specific members of Bacteroidetes from the Ln microbiota into Ob microbiota and was diet-dependent. These findings reveal transmissible, rapid, and modifiable effects of diet-by-microbiota interactions.
Figure 1. Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.

Percent of Obese (BMI ≥ 30) in U.S. Adults

2010

---

<previous next> play stop

---

CDC

No Data <10% 10%-14% 15%-19% 20%-24% 25%-29% ≥30%
Antibiotics and IBD

Proportion of subjects developing IBD according to age and anti-anaerobic antibiotic exposure status

Kronman MP et al. Pediatrics 2012;130
Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)
Summary: Background

- Antibiotic use is both frequent and variable

- There is a downside to antibiotic use
  - antibiotic resistance
  - patient-specific adverse drug effects
  - disruption of “healthy” flora
Agenda

• The case for Antimicrobial Stewardship

• The CHOP ASP

• Examples of Stewardship
CHOP ASP: Driver Diagram

Optimize antimicrobial use

Timely and appropriate initiation of antibiotics

Appropriate administration & de-escalation of therapy

Data monitoring and transparency

Improving ASP infrastructure, knowledge, and engagement

Outcomes:
- Adherence to guidelines
- Benchmark comparison
- Bug/drug mismatch rate
- Antibiogram shift
- Antimicrobial costs

Guideline development
Clinical pathways
Clinical decision support
Formulary restriction
Clinical pharmacy
Clinical microbiology lab
IV → PO conversion
EPIC and PHIS reports
Routine data audits
CHOP antibiogram
Clinician feedback?
Support of administration
Education and outreach
Optimize EPIC interface
Literature review, research, national ASP meetings
CHOP ASP: 2012

- 1.5 months
- 55% received intervention:
  - Stop (10%)
  - ID consult (24%)
  - ASP Advice (34%)
  - Optimize regimen (32%)
CLABSI: Tx Compliance

- **Empiric TX**
  - Compliance with Guideline for Empiric Therapy
  - Duration of TX

- **Definitive TX**
  - Compliance with Guideline for Definitive Therapy

- **Duration of TX**
  - Compliance with Guideline for Duration of Therapy

- **Pathogen Targeted**
  - Appropriate Coverage of Culture Positive CLABSI with Empiric Treatment

Legend:
- Green = at or above target
- Yellow = within 15% of Target
- Red = >15% from Target
Cost savings: $714,463
Benchmarking

Gerber et al. Pediatrics 2010
Where should we focus stewardship efforts?
Antibiotic Use at Children’s Hospitals, by Service Line

Percent of Total Abx Use
(524,364 discharges from 32 hospitals in 2010)

- Surgery: 40.8%
- Infectious Diseases: 22.3%
- Pulmonary: 9.2%
- Neonatology: 5.9%
- Hematology: 4.2%
- Oncology: 3.7%
- Gastroenterology: 2.8%
- Other: 2.7%
- Bone Marrow Transplant: 2.6%
- Neurology: 1.5%
- Cardiology: 1.0%
- Orthopedics/Rheumatology: 0.6%
- Urology/Nephrology: 0.6%
- Dermatology: 0.5%
- Endocrine/Metabolism: 0.4%
- ENT: 0.4%
- Dental: 0.3%
- Psychiatry: 0.3%
- Ophthalmology: 0.2%
- Rehab: 0.2%
- HIV: 0.0%
- OBGYN: 0.0%
Variability of Antibiotic Use Across Hospitals, Top Four APR-DRGs

Each circle represents one hospital. Size of circles corresponds to number of discharges with diagnosis receiving antibiotics. Red lines represent median values.

Broad-spectrum anti-MRSA coverage: vancomycin, linezolid, tigecycline, daptomycin

Broad-spectrum anti-pseudomonal coverage: imipenem, meropenem, cefepime, piperacillin, ticarcillin, piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime
Agenda

- The case for Antimicrobial Stewardship
- The CHOP ASP
- Examples of Stewardship
  - Surgery: prophylaxis and treatment
Antibiotic Use at Children’s Hospitals, by Service Line

Percent of Total Abx Use
(524,364 discharges from 32 hospitals in 2010)

- Surgery: 40.8%
- Infectious Diseases: 22.3%
- Pulmonary: 9.2%
- Neonatology: 5.9%
- Hematology: 4.2%
- Oncology: 3.7%
- Gastroenterology: 2.8%
- Other: 2.7%
- Bone Marrow Transplant: 2.6%
- Neurology: 1.5%
- Cardiology: 1.0%
- Orthopedics/Rheumatology: 0.6%
- Urology/Nephrology: 0.6%
- Dermatology: 0.5%
- Endocrine/Metabolism: 0.4%
- ENT: 0.4%
- Dental: 0.3%
- Psychiatry: 0.3%
- Ophthalmology: 0.2%
- Rehab: 0.2%
- HIV: 0.0%
- OBGYN: 0.0%
Surgical Antimicrobial Prophylaxis

- surgical AMP is used to reduce the microbial burden of skin colonization that may contribute to intraoperative contamination = SSI
- most common Healthcare Associated Infection (HAI)
- SSIs cause harm, prolong hospitalizations, can cause readmissions, and can increases mortality rate

- Prophylaxis; not treatment

When appropriately used, AMP reduces SSI rate by 50-70%
Surgical Wound Classes

I. **Clean**: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered.

II. **Clean-Contaminated**: Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.

III. **Contaminated**: Open, fresh, accidental wounds; operations with major breaks in sterile technique or gross spillage from GI tract, and incisions in which acute, nonpurulent inflammation is encountered.

IV. **Dirty or Infected**: Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.
Antimicrobial Prophylaxis: Timing

Goal is to have peak antibiotic serum/tissue levels at the time of incision.

Therefore, complete antibiotic infusion 0 - 60 minutes prior to incision

- Start 0-60 minutes prior to incision for agents with brief infusion times
- Start 60-120 minutes prior to incision for vancomycin and fluoroquinolones
cal-wound infections in 2847 patients undergoing elective clean or "clean-contaminated" surgical procedures at a large community hospital. The administration of antibiotics 2 to 24 hours before the surgical incision was defined as early; that during the 2 hours before the incision, as preoperative; that during the 3 hours after the incision, as perioperative; and that more than 3 but less than 24 hours after the incision, as postoperative.

Results. Of the 1708 patients who received the prophylactic antibiotics preoperatively, 10 (0.6 percent) subsequently had surgical-wound infections. Of the 282 patients who received the antibiotics during the perioperative period, 36 (12.8 percent) had infections. Stepwise logistic-regression analysis confirmed that the administration of antibiotics was associated with the lowest risk of surgical-wound infection.

Conclusions. In surgical practice there is considerable variation in the timing of the prophylactic administration of antibiotics, and administration in the two hours before surgery reduces the risk of wound infection. (N Engl J Med 1992;326:281-6.)

The widespread use of antimicrobial agents for prophylaxis has altered surgical practice markedly in the past 20 years and now represents one of the most frequent uses of antibiotics in hospitals, accounting for as many as half of all antibiotics prescribed.1-3 Surgical antimicrobial prophylaxis has been shown variations in the timing of prophylaxis affect the occurrence of surgical-wound infections in actual clinical practice.

It is increasingly recognized that to assess the quality of care, investigators must examine the linkage between the processes of care and patients' outcomes.
Staphylococcus aureus is most common cause of SSI

Cefazolin has activity against most strains of S. aureus; therefore, Cefazolin is the empiric choice for most procedures

However, Cefazolin may not always be the appropriate choice…

1. procedures involving organs with alternate or additional colonizing bacteria (e.g. GI tract)
2. patients with cephalosporin allergy
3. patients known to be colonized with resistant bacteria
Antimicrobial Selection: Using CHOP Guidelines

1) procedures involving organs with alternate or additional colonizing bacteria

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Antibiotic</th>
<th>Alternative for Penicillin and/or Cephalosporin allergy</th>
<th>MRSA History of colonization or infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiothoracic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants</td>
<td>vancomycin + cefazolin</td>
<td>vancomycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>(pacemaker, ICD, LVAD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung transplant</td>
<td>targeted therapy&lt;sup&gt;2&lt;/sup&gt;</td>
<td>targeted therapy&lt;sup&gt;2&lt;/sup&gt;</td>
<td>vancomycin + targeted therapy&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ceftriaxone + metronidazole</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Esophageal, gastroduodenal,</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>jejunal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ceftriaxone + metronidazole</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>piperacillin/tazobactam</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + piperacillin/tazobactam</td>
</tr>
<tr>
<td>NEC</td>
<td>piperacillin/tazobactam</td>
<td>none</td>
<td>vancomycin + piperacillin/tazobactam</td>
</tr>
<tr>
<td><strong>Biliary tract</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open and laparoscopic</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Head and Neck</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>With implant</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td><strong>Obstetric or Gynecologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>cefazolin or cefoxitin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td><strong>Orthopedic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants</td>
<td>vancomycin + cefazolin (+/- gentamicin)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>vancomycin + gentamicin</td>
<td>Vancomycin + cefazolin (+/- gentamicin)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>(spinal rods, VEPTR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurosurgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cefazolin</td>
<td>vancomycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td><strong>Urologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Cystourethroscopy</td>
<td>targeted therapy&lt;sup&gt;5&lt;/sup&gt;</td>
<td>targeted therapy&lt;sup&gt;5&lt;/sup&gt;</td>
<td>vancomycin + targeted therapy&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> History of colonization or infection

<sup>2</sup> Targeted therapy

<sup>3</sup> Appendectomy, esophageal, gastroduodenal, jejunal

<sup>4</sup> High-risk implants: spinal rods, VEPTR

<sup>5</sup> Cystourethroscopy
<table>
<thead>
<tr>
<th>Surgery</th>
<th>Antibiotic</th>
<th>Alternative for Penicillin and/or Cephalosporin allergy</th>
<th>MRSA History of colonization or infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiothoracic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants (pacemaker, ICD, LVAD)</td>
<td>vancomycin + cefazolin</td>
<td>vancomycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>targeted therapy$^a$</td>
<td>targeted therapy$^a$</td>
<td>vancomycin + targeted therapy$^a$</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy$^b$</td>
<td>ceftriaxone + metronidazole</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Esophageal, gastroduodenal, jejunal</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Colorectal$^c$</td>
<td>ceftriaxone and metronidazole</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>piperacillin/tazobactam</td>
<td>ciprofloxacin + metronidazole</td>
<td>vancomycin + piperacillin/tazobactam</td>
</tr>
<tr>
<td>NEC</td>
<td>piperacillin/tazobactam</td>
<td>none</td>
<td>vancomycin + piperacillin/tazobactam</td>
</tr>
<tr>
<td>Biliary tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open and laparoscopic procedures</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Head and Neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>With implant</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Obstetric or Gynecologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>cefazolin or cefoxin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants (spinal rods, VEPTR)</td>
<td>vancomycin + cefazolin (+/- gentamicin)$^d$</td>
<td>vancomycin + gentamicin</td>
<td>Vancomycin + cefazolin (+/- gentamicin)$^d$</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cefazolin</td>
<td>vancomycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Cystourethroscopy</td>
<td>targeted therapy$^a$</td>
<td>targeted therapy$^a$</td>
<td>vancomycin + targeted therapy$^a$</td>
</tr>
</tbody>
</table>

1) procedures involving organs with alternate or additional colonizing bacteria
Antimicrobial Selection: Using CHOP Guidelines

1) procedures involving organs with alternate or additional colonizing bacteria
2) patients with cephalosporin allergy
3) colonization with resistant bacteria
   ✷ specific procedures
   ✷ MRSA colonization

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Antibiotic</th>
<th>Alternative for Penicillin and/or Cephalosporin allergy</th>
<th>MRSA History of colonization or infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiothoracic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants (pacemaker, ICD, LVAD)</td>
<td>vancomycin + cefazolin</td>
<td>vancomycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>targeted therapy²</td>
<td>targeted therapy²</td>
<td>vancomycin + targeted therapy²</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy²</td>
<td>ceftriaxone + metronidazole</td>
<td>ceftriaxone + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Esophageal, gastroduodenal, jejunal</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Colorectal³</td>
<td>ceftriaxone + metronidazole</td>
<td>ceftriaxone + metronidazole</td>
<td>vancomycin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>pipercillin/tazobactam</td>
<td>pipercillin/tazobactam</td>
<td>vancomycin + pipercillin/tazobactam</td>
</tr>
<tr>
<td>NEC</td>
<td>pipercillin/tazobactam</td>
<td>none</td>
<td>vancomycin + pipercillin/tazobactam</td>
</tr>
<tr>
<td>Biliary tract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open and laparoscopic procedures</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Head and Neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>With implant</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Clean-contaminated</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Obstetric or Gynecologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>cefazolin or cefoxitin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>High-risk implants (spinal rods, VEPTR)</td>
<td>vancomycin + cefazolin</td>
<td>vancomycin + gentamicin</td>
<td>Vancomycin + cefazolin (+/- gentamicin)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefazolin</td>
<td>vancomycin</td>
<td>vancomycin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>cefazolin</td>
<td>clindamycin + gentamicin</td>
<td>vancomycin + cefazolin</td>
</tr>
<tr>
<td>Cystourethroscopy</td>
<td>targeted therapy²</td>
<td>targeted therapy²</td>
<td>vancomycin + targeted therapy²</td>
</tr>
</tbody>
</table>
Antimicrobial Selection: Using CHOP Guidelines

1) procedures involving organs with alternate or additional colonizing bacteria
2) patients with cephalosporin allergy
3) colonization with resistant bacteria
   ✧ specific procedures
   ✧ MRSA colonization
Clinical practice guidelines for antimicrobial prophylaxis in surgery


Am J Health-Syst Pharm. 2013; 70:195-283
How do we do at CHOP?

Orhtopedic Surgery
n=175 for antibiotics

- Appropriate Abx Admin 97%
- Abx Not Administered 3%

Cardiac Surgery
n = 48 for antibiotic

- Appropriate Abx Admin 100%
Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America


Clinical Infectious Diseases 2010; 50:133–64
Intra-abdominal Infections

Intra-abdominal infection

Community-acquired

- Mild-moderate: Ceftriaxone + metronidazole

Severe

- Healthcare-acquired: Piperacillin & tazobactam

Any severity

ALT: Ciprofloxacin + metronidazole
Intra-abdominal Infections: duration

- antimicrobial tx of established infection should be **limited to 4–7 days**, unless difficult to achieve adequate source control
• acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens; treatment should be discontinued within 24h
Agenda

• The case for Antimicrobial Stewardship

• The CHOP ASP

• Examples of Stewardship
  – Surgery
  – Primary care
Study Setting: CHOP Care Network

- 5 urban, academic
- 24 “private” practices
  - urban, suburban, rural
  - >200 clinicians
  - >200,000 patients
- common EHR
Case Definitions

• ICD9 codes for common infections
  – AOM, sinusitis, strep throat, pneumonia
  – (+/- GAS testing, antibiotic use)

• Excluding:
  – concurrent bacterial infection
    • AOM, SSTI, UTI, lyme, acne, chronic sinusitis, mycoplasma, scarlet fever, animal bite, proph, oral infections, pertussis, STD, bone/joint
  – complex chronic conditions (Feudtner, Pediatrics 2000)
  – antibiotic allergy
  – visit within prior 3 months with antibiotic
1,296,517 encounters

630,502 office visits

399,793 sick visits

363,049 sick visits

102,102 antibiotic Rx

51,421 narrow ABX

29,635 broad ABX

8,204 prior ABX

36,744 visits w/ CCC

666,015 phone, refills

230,709 preventive

260,947 no antibiotics

14,298 ABX allergy
Antibiotic Prescribing for Sick Visits

Excluding: preventive visits, CCC
Standardized by: age, sex, race, Medicaid
Broad-Spectrum Antibiotics

- amoxicillin-clavulanate
- cephalosporins
- azithromycin*

*not considered broad-spectrum therapy for pneumonia
Excluding: preventive visits, CCC, antibiotic allergy, prior antibiotics
Standardized by: age, sex, race, Medicaid
Diagnosis rate of AOM

Excluding: preventive visits, CCC, prior antibiotics
Standardized by: age, sex, race, Medicaid
Diagnosis Rate of Sinusitis

Excluding: preventive visits, CCC, prior antibiotics
Standardized by: age, sex, race, Medicaid
Summary of Across-Practice Analyses

- **antibiotic prescribing** at sick visits varies significantly across practice sites
- **broad-spectrum antibiotic prescribing** at sick visits varies significantly across practice sites
- **the rate of diagnosis** of ARTIs varies significantly across practice sites
- **adherence to prescribing guidelines** for AOM, sinusitis, GAS pharyngitis, and pneumonia varies significantly across practice sites
Antimicrobial Stewardship

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


• Antimicrobial Stewardship Programs recommended for hospitals
• most antibiotic use (and misuse) occurs in the outpatient setting
• is outpatient “stewardship” achievable?
Specific Aim

• To determine the impact of an outpatient antimicrobial stewardship bundle within a pediatric primary care network on antibiotic prescribing for common ARTI:

1. Antibiotic prescribing for viral infections

1. Broad-spectrum antibiotic prescribing for conditions for which narrow-spectrum antibiotics are indicated
Antimicrobial Stewardship

- Core strategies
  - Prior authorization
  - Prospective audit & feedback
  - Formulary restriction

- Supplemental Strategies
  - Education
  - Clinical guidelines
  - IV to PO conversion
  - Dose optimization
  - Antimicrobial order forms
Antimicrobial Stewardship

• Core strategies
  – Prior authorization
  – **Prospective audit & feedback**
  – Formulary restriction

• Supplemental Strategies
  – **Education**
  – **Clinical guidelines**
  – IV to PO conversion
  – Dose optimization
  – Antimicrobial order forms
Study Design

- cluster-randomized controlled trial
- bundled intervention vs. no intervention
- unit of observation will be the practitioner but randomized at practice level
  - natural distribution of physicians
  - avoids intra-practice contamination
Intervention

1. guideline development
2. education
3. audit and feedback
Hypotheses

1. clinicians have **incomplete knowledge** of the data regarding the effectiveness of antibiotics for ARTIs
   - GAS and broad spectrum antibiotics
   - antibiotic activity against pneumococcus
   - prevention of bacterial superinfection
   - role of *moraxella* and *Hflu* in disease

2. clinicians might be influenced by presentation of their prescribing habits relative to **peer benchmarking data**
Study Setting: CHOP Care Network

- 5 urban, academic
- 24 non-academic practices
- common EHR
Outcomes

VIRAL
- common cold
- URI
- acute bronchitis
- tonsillitis
- pharyngitis (non-strep)

no antibiotics

BACTERIAL
- acute sinusitis
- Strep pharyngitis
- pneumonia

penicillin/amoxicillin
25 Clinician practice groups assessed for eligibility

7 Practices excluded
- 5 Academic practices
- 2 Refused participation

18 Practices (170 clinicians) randomized

9 Practices (84 clinicians) randomized to receive intervention
- 9 Received intervention as assigned

9 Practices (86 clinicians) randomized to receive no intervention (control condition)
- 9 Received no intervention as assigned

9 Practices (81 clinicians) included in analysis\textsuperscript{a}

9 Practices (81 clinicians) included in analysis\textsuperscript{a}
Intervention: Timeline

- Site presentation
- Feedback reports
- 20 months baseline data
- 12 months of audit/feedback
- 12 months after feedback ends

Over 32 month study period (so far):
- 185,212 patients
- 1,435,605 encounters
Broad Spectrum Antibiotics for Acute Sinusitis
(amoxicillin-clavulanate, 2nd/3rd cephalosporins, or azithromycin)

% Antibiotics Rx

<table>
<thead>
<tr>
<th></th>
<th>Baseline (1/1/10-5/31/10)</th>
<th>Q1 (6/1/10-9/30/10)</th>
<th>Q2 (10/1/10-1/31/11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YOU</td>
<td>49.5</td>
<td>34.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Your Practice</td>
<td>47.9</td>
<td>23.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Network</td>
<td>42.5</td>
<td>35.5</td>
<td>27.7</td>
</tr>
</tbody>
</table>
Antibiotics for Viral Infection

Excluding: preventive visits, CCC, antibiotic allergy, prior antibiotics
Standardized by: age, sex, race, Medicaid

Antibiotic use for viral diagnoses
Rate of prescribing before and during intervention

- Control Practices
- Intervention Practices

$p=0.093$
Broad-Spectrum per Sick Visit

Excluding: preventive visits, CCC, antibiotic allergy, prior antibiotics
Standardized by: age, sex, race, Medicaid
Broad-Spectrum: by condition

SINUSITIS ➔

GAS PHARYNGITIS
Summary/Future Directions

• clinician education coupled with audit & feedback significantly improved guideline adherence for the treatment of common ARTI

• this was most pronounced for pneumonia

• need to measure outcomes
Why did it work?  
Can we do better?
Qualitative Analyses

- semi-structured interviews of 21 clinicians in the intervention group
- 6/21 ignored or did not remember reports
- 9/15 reported considerable skepticism and distrust of auditing data
- most did not believe that their prescribing behavior contributed to antibiotic overuse
“I did not read my audit reports because honestly, I didn’t really care. To me, it was just another piece of paper. It didn’t impress me at all. They [the study team] gave you a number describing your behavior but they had no deeper understanding of what was really going on.”
Qualitative Analyses

- reported frequently confronting parental pressure, sometimes acquiescing to:
  - appear competent
  - avoid losing patients to other practices that would “give them what they want”
  - provide comfort to anxious parents
  - help with upcoming travel, family celebrations, parent work schedules
“We have lots of parents who come in and they know what they want. They don’t care what we have to say. They want the antibiotic that they want because they know what is wrong with their child.”
Study Team

- **Primary Care Pediatrics**
  Bob Grundmeier, Alex Fiks, Mort Wasserman
- **General Pediatrics**
  Lou Bell, Ron Keren
- **Pediatric Infectious Diseases**
  Theo Zaoutis, Priya Prasad
- **Biostatistics/data management**
  Russell Localio, Lihai Song
- **PeRC Administrator**
  Jim Massey
- **Sociology**
  Julie Szymczak

*supported by US Agency for Health Care Research and Quality*
I think I need antibiotics for my col...

IT'S A VIRUS!