Antimicrobial Use and Stewardship in the Pediatric Outpatient Setting

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NIAA Antibiotic Symposium 2014
Overview

• Definitions and Scope of Problem
• Antibiotic Use in Outpatient Pediatrics
• Antibiotic Stewardship
• Antibiotics and the Microbiome
Definition

Commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case = antibiotic stewardship
Framing the Issue

• Although antibiotics have saved countless lives, their use is not benign
• Antibiotic resistance is occurring in populations and individual patients
• At least 5% of hospitalized patients experience an adverse reaction
  – Rash, nephrotoxicity, *C. difficile* infection
• 50% are prescribed for people who do not need them or are not prescribed appropriately
• Very few antibiotics are being developed
Antibiotic Resistance

- CDC described antibiotic resistance as "one of the world's most pressing health problems"

- WHO has identified antibiotic resistance as "one of the three greatest threats to human health."

Impact of Antibiotic Resistance

• Patients with resistant infections are at higher risk for disability and death
• $20 billion in excess direct healthcare costs with additional costs to society of $35 billion
• Loss of effective antibiotics
• Increased number of immunosuppressed patients
• Drug development is not sufficient to deal with this threat
Dearth of New Drugs...

The number of new antibiotics approved for sale in the United States has dwindled.

20 antibiotics approved for sale

...For Hardier Germs

Acinetobacter germs in U.S. hospitals that are resistant to a powerful antibiotic often used as a last line of treatment.

30% Acinetobacter germs resistant to imipenem

Sources: Infectious Diseases Society of America; Resources for the Future
“Don’t forget to take a handful of our complimentary antibiotics on your way out.”
Pediatric Antibiotic Use in the Community
Top 1 through 6 drug markets according to the total estimated number of outpatient prescriptions dispensed to the US pediatric population (ages 0–17 years) from US retail pharmacies, 2002 through 2010. *Statistically significant linear trend at P value = .05.

Chai G et al. Pediatrics 2012;130:23-31
Antibiotic Prescribing in Ambulatory Pediatrics in US

- Nationally representative sample
- National ambulatory Medical Care Survey – 2006-2008
- Antibiotics prescribed during 21% pediatric ambulatory visits
- 50% were broad-spectrum, mostly macrolides
- Respiratory infections accounted for 70% of use

Frequency of narrow- and broad-spectrum antibiotic use according to class for all pediatric ambulatory visits, 2006–2008.

Hersh A L et al. Pediatrics 2011;128:1053-1061
# Antibiotic-Prescribing Patterns

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Annual No. of visits for Condition, Millions</th>
<th>N. Of visits Antibiotics were prescribed, Millions (%)</th>
<th>No. of Visits Broad Spectrum Antibiotics were prescribed, Millions (% of antibiotics that were broad-spectrum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ARTIs for which antibiotics are indicated</td>
<td>65.6</td>
<td>31.7 (48.4)</td>
<td>16.9 (53.1)</td>
</tr>
<tr>
<td>• ARTIs for which antibiotics are not indicated</td>
<td>29.9</td>
<td>21.5 (71.7)</td>
<td>10.3 (48.0)</td>
</tr>
<tr>
<td>• Other respiratory conditions for which antibiotics are not definitely indicated</td>
<td>19.5</td>
<td>2.8 (29.6)</td>
<td>3.6 (62.5)</td>
</tr>
<tr>
<td>• Other respiratory conditions for which antibiotics are not definitely indicated</td>
<td>16.2</td>
<td>4.5 (27.8)</td>
<td>2.9 (64.5)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Skin/cutaneous/mucosal</td>
<td>158.6</td>
<td>12.2 (7.7)</td>
<td>5.1 (41.9)</td>
</tr>
<tr>
<td>• Urinary tract infections</td>
<td>28.2</td>
<td>5.2 (18.6)</td>
<td>2.1 (37.8)</td>
</tr>
<tr>
<td>• Gastrointestinal infections</td>
<td>1.4</td>
<td>0.9 (59.3)</td>
<td>0.3 (39.3)</td>
</tr>
<tr>
<td>• Miscellaneous infections</td>
<td>2.3</td>
<td>0.1 (5.7)</td>
<td>0.1 (54.1)</td>
</tr>
<tr>
<td>• Other</td>
<td>8.7</td>
<td>0.8 (9.6)</td>
<td>0.2 (29.0)</td>
</tr>
<tr>
<td>• Other</td>
<td>117.9</td>
<td>5.1 (4.3)</td>
<td>2.5 (48.3)</td>
</tr>
<tr>
<td>Total</td>
<td>224.2</td>
<td>5.2 (18.6)</td>
<td>22.0 (50.1)</td>
</tr>
</tbody>
</table>

Hersh A L et al. Pediatrics 2011;128:1053-1061
Rates of antibiotic dispensing per person-year of enrollment for children aged as follows: A, 3 to 24 months; B, 2 to <4 years; C, 4 to <6 years; D, 6 to <12 years; and E, 12 to <18 years.

Vaz L E et al. Pediatrics 2014;133:375-385
Distribution of antibiotic classes among health plans, 2000–2001 and 2009–2010, for children aged as follows: A, 3 to <24 months; B, 2 to <4 years; C, 4 to <6 years; D, 6 to <12 years; and E, 12 to <18 years.

Vaz L E et al. Pediatrics 2014;133:375-385
Variability in Pediatric Antibiotic Use in the Community
Total outpatient antibacterial use in the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy).


© 2007 Infectious Diseases Society of America
Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.

Antimicrobial prescription rates in outpatient ARTI visits using restrictive definitions, both individually and in aggregate, by year.

# Antimicrobial Prescriptions for ARTI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Visits in Thousands (% of all Outpatient Visits)</th>
<th>Visits With Antimicrobial Prescription in Thousands (%)</th>
<th>Visits With Expected Bacterial Pathogen in Thousands (%)</th>
<th>Potentially Preventable Antimicrobial Prescriptions in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM</td>
<td>12 141 (8.5)</td>
<td>10 428 (85.9)</td>
<td>7859 (64.7)</td>
<td>2569</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>789 (0.6)</td>
<td>701 (88.8)</td>
<td>616 (78)</td>
<td>85</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10 534 (7.3)</td>
<td>5991 (56.9)</td>
<td>2124 (20.2)</td>
<td>3867</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2512 (1.8)</td>
<td>1795 (71.5)</td>
<td>0 (0)</td>
<td>1795</td>
</tr>
<tr>
<td>URI</td>
<td>12 715 (8.9)</td>
<td>3108 (24.4)</td>
<td>0 (0)</td>
<td>3108</td>
</tr>
<tr>
<td><strong>All ARTI</strong></td>
<td>38 692 (27.0)</td>
<td>22 027 (56.9)</td>
<td>10 598 (27.4)</td>
<td>11 429</td>
</tr>
<tr>
<td><strong>Children &lt; 2 y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM</td>
<td>5165 (11.5)</td>
<td>4314 (83.5)</td>
<td>3343 (64.7)</td>
<td>971</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>59 (0.1)</td>
<td>51 (87.0)</td>
<td>46 (78)</td>
<td>5</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1023 (2.3)</td>
<td>554 (54.1)</td>
<td>206 (20.2)</td>
<td>348</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>608 (1.4)</td>
<td>331 (54.4)</td>
<td>0 (0)</td>
<td>331</td>
</tr>
<tr>
<td>URI</td>
<td>4656 (10.3)</td>
<td>871 (18.7)</td>
<td>0 (0)</td>
<td>871</td>
</tr>
<tr>
<td><strong>All ARTI</strong></td>
<td>11 511 (25.5)</td>
<td>6119 (53.2)</td>
<td>3153 (27.4)</td>
<td>2966</td>
</tr>
<tr>
<td><strong>Children 2 - 17 y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM</td>
<td>6960 (7.1)</td>
<td>6121 (88.0)</td>
<td>4505 (64.7)</td>
<td>1616</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>728 (0.7)</td>
<td>641 (88.0)</td>
<td>568 (78)</td>
<td>73</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9500 (9.7)</td>
<td>5409 (56.9)</td>
<td>1915 (20.2)</td>
<td>3494</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1910 (1.9)</td>
<td>1474 (77.2)</td>
<td>0 (0)</td>
<td>1474</td>
</tr>
<tr>
<td>URI</td>
<td>8072 (8.2)</td>
<td>2242 (27.8)</td>
<td>0 (0)</td>
<td>2242</td>
</tr>
<tr>
<td><strong>All ARTI</strong></td>
<td>27 161 (27.6)</td>
<td>15 894 (58.5)</td>
<td>7439 (27.4)</td>
<td>8455</td>
</tr>
</tbody>
</table>
Core Actions to Combat Resistance

1. Preventing Infections, Spread of Resistance
   – Immunization, infection control, handwashing, safe food preparation

2. Tracking

3. Improving Antibiotic Use/Stewardship
   – Perhaps most important action needed

4. Development of drugs and diagnostic tests
Improving Antibiotic Use/Stewardship

• The use of antibiotics is the single most important factor leading to antibiotic resistance and the single most important action needed to greatly slow the development and spread of resistance
Leading Infectious Diseases Experts Call For Increased Focus On Protecting Antibiotics

SHEA, IDSA, PIDS position paper outlines a national approach to antimicrobial stewardship

Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS)

Study Setting: CHOP Care Network

- 5 urban, academic
- 24 “private” practices
  - urban, suburban, rural
- common EHR
Antibiotic Prescribing for Sick Visits

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

- **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 CAP varies.
Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial

Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE:

*JAMA. 2013 Jun 12;309(22):2345-52*
Three clinicians in the intervention group and 5 in the control group did not attend acute-care encounters during the study period.
1. Guideline development
2. Education
3. Prescribing audit and feedback
ICD9 codes for common infections
(+/- GAS testing, antibiotic use)
verified by chart review and provider feedback

Excluding:
- antibiotic allergy
- visit within prior 3 months with antibiotic
- concurrent bacterial infection
  - AOM, SSTI, UTI, lyme, acne, chronic sinusitis,
    mycoplasma, scarlet fever, animal bite, proph, oral
    infections, pertussis, STD, bone/joint
- children with complex chronic diseases
Outcomes

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

**BACTERIAL**
- acute sinusitis
- Strep pharyngitis
- pneumonia

**Outcomes**
- no antibiotics
- penicillin/amoxicillin
Intervention: Timeline

- Site presentation
- Feedback reports
- 12 months baseline data
- 12 months of audit/feedback
- 12 months after feedback ends
Broad Spectrum Antibiotics for Acute Sinusitis
(amoxicillin-clavulanate, 2nd/3rd cephalosporins, or azithromycin)

<table>
<thead>
<tr>
<th></th>
<th>YOU</th>
<th>Your Practice</th>
<th>Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (1/1/10-5/31/10)</td>
<td>25.9</td>
<td>16.9</td>
<td>27.7</td>
</tr>
<tr>
<td>Q1 (6/1/10-9/30/10)</td>
<td>34.1</td>
<td>23.9</td>
<td>35.5</td>
</tr>
<tr>
<td>Q2 (10/1/10-1/31/11)</td>
<td>49.5</td>
<td></td>
<td>42.5</td>
</tr>
</tbody>
</table>
Figure Legend:
The estimate of interest (and associated P value) is the treatment \times time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.
The estimate of interest (and associated P value) is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs. Y-axis in blue indicates range 0% to 30%.
Figure Legend:
Standardized Rates of Broad-Spectrum Antibiotic Prescribing Before, During, and After Audit and Feedback
The estimate of interest is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.
Perceptions of the intervention

• Qualitative study using semi-structured interview
  – 24 pediatricians from 6 primary care practices
  – All interviews were transcribed and analyzed using a modified grounded theory approach.

• Results
  – Deep skepticism of the audit and feedback reports
  – Respondents ignored reports or expressed distrust about them.
  – One respondent admitted to gaming behavior.
  – Recognized it as a problem, but believed it was driven by the behaviors of non-pediatric physicians.
  – Parent pressure for antibiotics was identified by all respondents as a major barrier to the more judicious use of antibiotics
  – Respondents reported that they sometimes “caved” to parent pressure for social reasons

Szymcak J et al. ICHE in press
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 63; 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 fueling 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.
Fig. 1. Representation of the impact of antibiotic administration on the bacterial community of the colon.

Jernberg C et al. Microbiology 2010;156:3216-3223
A, Proportion of subjects developing IBD according to age and antianaerobic antibiotic exposure status.


©2012 by American Academy of Pediatrics
Could Antibiotics Be A Factor In Childhood Obesity?

- National Public Radio 2012

Antibiotics Could Be Driving Up Obesity

- ABC News November 2012

Early use of antibiotics linked to obesity, research finds

- Washington Post, August 22, 2012
Weight and body composition of control and STAT mice

Antibiotics in early life alter the murine colonic microbiome and adiposity

- Mice fed subtherapeutic doses of antibiotics exhibited:
  - Increased adiposity
  - Increased hormone levels related to metabolism
  - 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
  - Increase in colonic levels of short chain fatty acids

Summary

1. Antibiotic resistance is critical public health issue
2. Antimicrobial stewardship is key to reducing resistance
3. Antibiotic prescribing variable and often inappropriate in community
4. Develop community antimicrobial stewardship programs
5. Opening Pandora’s box by altering the microbiome