Antibiotic Stewardship: Everyone’s Responsibility

Jason G. Newland MD, MEd
@JasonGNewland
@sharpsgroup
DISCLOSURES

• Grant support from Pfizer for the Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) collaborative

• Consultant for Cubist and RPSdiagnostics
Objectives

- Discuss the history of antibiotics
- List the impact of antibiotic resistance
- List effective stewardship strategies to improve the use of antibiotics.
- Discuss the impact of antimicrobial stewardship on clinical outcomes
Which of the following antibiotics was the first used to treat a child?

- Erythromycin
- Methicillin
- Penicillin
- Sulfanilamide
- Vancomycin
Sulfa Antibiotic

• Discovered by Dr. Gerhard Domagk
• Originated from research performed on red dyes
• Used in 1933 on 10 month old boy with *S. aureus* bloodstream infection
• Prontosil Rubrum used on Dr. Domagk’s own 6yo daughter with an invasive cellulitis

Spellberg B Rising Plague 2009
Impact of Sulfa Antibiotics


“For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide, and the start of the real revolution in medicine.”
Dr. Howard Florey

February 12th, 1941

- Police Officer Albert Alexander
- Horrible infection of the face and eye
- Threat of losing eye and develops pneumonia
- Penicillin given- Dose/frequency unknown
- Limited Supply

Spellberg B Rising Plague 2009
“The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicaemia or pneumonia which penicillin cannot save.”

Alexander Fleming, New York Times 1945
Antibiotic Timeline

Antibiotic deployment

Antibiotic resistance observed

Clatworthy 2007
Microbes

• $5 \times 10^{31}$ on Earth (Humans $6-7 \times 10^9$)
  • 5-10 times more microbes living on and in a human than human cells in the body
  • Comprise 60% of biomass of the planet
• Living on earth for 3.5 billion years to live and adapt (Humans not near that long)
• Replicate every 20-30 minutes (Humans 20-30 years)

Spellberg B Clin Infect Dis 2008:46
Microbes have been creating and defeating antibiotics for 20 million times longer than humans have even known antibiotics existed.

Brad Spellberg MD  5th Annual ASP conference June 2014
There are already, wide-spread in nature, resistance mechanisms to antibacterial agents we have not yet invented.

Brad Spellberg MD 5\textsuperscript{th} Annual ASP conference June 2014
“The future of humanity and microbes will likely evolve as...episodes of our wits versus their genes.”

Nobel Laureate
Joshua Lederberg
Science 2000 288:287-93
Antibiotic Use in Freestanding Children’s Hospitals

- 37 hospitals: 556,692 discharges in 2008

Gerber J et al., Pediatrics 2010; 126:1067
Antibiotic Use in Freestanding Children’s Hospitals

• 37 hospitals: 556,692 discharges in 2008
• Among the hospitals large variability
  • 38-72% receive an antibiotic
  • 368-601 days per 1000 patient days
• Positive correlation with percent receiving an antibiotic and days of therapy
  • All antibiotics
  • Broad spectrum antibiotics

Gerber J et al., Pediatrics 2010; 126:1067
Appropriateness of Antibiotics

- 50% of antimicrobial use is either unnecessary or inappropriate
  - 30% of anti-anaerobic agents inappropriate
  - 50% of vancomycin use in adult populations is inappropriate
- 35% of initial vancomycin courses inappropriate in a pediatric institution

Bolon MK et al. ICHE 2005
### Inappropriate Antibiotic Use in the NICU

Inappropriate antibiotic-days: 806 (24%) of 3,334 days

<table>
<thead>
<tr>
<th>CDC 12-Step</th>
<th>Days</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target the pathogen</td>
<td>309</td>
<td>38</td>
</tr>
<tr>
<td>Practice antimicrobial control</td>
<td>167</td>
<td>21</td>
</tr>
<tr>
<td>Treating colonization/contamination</td>
<td>130</td>
<td>16</td>
</tr>
<tr>
<td>Say ‘no’ to antibiotics</td>
<td>140</td>
<td>17</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>60</td>
<td>8</td>
</tr>
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</table>

Patel SJ, PIDJ 2009
Carbapenem-Resistant Enterobacteriaceae (CRE)

2006
Carbapenem-Resistant Enterobacteriaceae (CRE)
Carbapenem-Resistant Enterobacteriaceae (CRE)
Carbapenem-Resistant Enterobacteriaceae (CRE)

2012
Carbapenem-Resistant Enterobacteriaceae (CRE)

February 2015
Gram Negative Resistance in Children

Carbapenem-Resistant Enterobacteraceae in Children

Antimicrobial Resistance and Patient Outcomes

• Increase in mortality, morbidity, length of hospitalization, and cost of care
  - *Staphylococcus aureus*
  - *Enterococci*
  - Gram-negative bacilli

• Delays in therapy or severity of illness likely contribute to worse outcomes

Inadequate Antibiotic Therapy Increases Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Inadequate Therapy</th>
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</thead>
<tbody>
<tr>
<td>Ibrahim et al.</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Leibovici et al.</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>Luna et al.</td>
<td>1997</td>
<td></td>
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<tr>
<td>Alvarez-Lerma et al.</td>
<td>1996</td>
<td></td>
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<tr>
<td>Rello et al.</td>
<td>1997</td>
<td></td>
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</tbody>
</table>

**Bloodstream Infections**


**Nosocomial Pneumonia/VAP**

CDC Threat Report

- 23,000 Americans die annually from an antibiotic resistant infection
- 2 million Americans are infected annually with an antibiotic resistant infection
- 250,000 Americans suffer from *C. difficile* infection
  - 19,000 die from *C. difficile* infection

http://www.cdc.gov/drugresistance/threat-report-2013/
Deaths Attributable to AMR

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Measles: 130,000
- Diarrhoeal disease: 1.4 million
- Cholera: 100,000–120,000
- Cancer: 8.2 million
- Diabetes: 1.5 million
- AMR now: 700,000 (low estimate)

AMR in 2050: 10 million

Amr-review.org accessed 10-20-2015
Antibiotic-Associated Adverse Events

*Clostridium difficile*

- Increasing in hospitalized children
- 10 fold increase in community-onset
- Hospital-Onset C. difficile infections associated
  - Increased risk of mortality OR 6.73 (3.77-12.02)
  - Increased length of stay - 5.5 days (4.5-6.5 days)
  - Increased hospital costs - $93K (80-107,200)

Antibiotic-Associated Adverse Events

- Trimethoprim-Sulfamethoxazole ADRs requiring hospitalization have significantly increased at CMH
  - 2000-2004: 5
  - 2005-2009: 104
- Nationally they have almost tripled
  - 5 cases per 100,000 admissions in 2000
  - 13 cases per 100,000 admissions in 2009

Goldman JL et al. Pediatrics 2013
Potential Solutions

• New Antimicrobial Development
• Antimicrobial Stewardship Programs
• Better Diagnostics
• Know best lengths of therapy
• Reduction of Hospital Acquired Infections
• Vaccines
• Decrease Antimicrobial Use in Agriculture
Children’s Mercy ASP

Children’s Mercy Hospital-Kansas City
• 354 bed tertiary care free-standing hospital
• 40 bed PICU, 70 bed NICU
• 2 campuses
• All Pediatric Subspecialties
• Average daily census of 250
Children’s Mercy ASP

ASP strategies

• Prospective-audit with feedback
• Prior-approval
• Clinical practice guideline(s)
  • Community-acquired pneumonia
  • Febrile infant < 60 days of age
• Empiric antibiotic guideline
Impact of CAP Guideline

- Implemented in July of 2008
- Guideline recommendations were
  - Ampicillin for hospitalized uncomplicated CAP
  - Blood cultures on all hospitalized children
  - Duration of therapy of 7 days
- National Guideline published 2011
  - Similar recs except duration of therapy 10 days
Impact of CAP Guideline

Impact of CAP Guideline

% of Pneumonia Cases

- Amoxicillin
- Amox/CA
- Cefdinir

Impact of CAP Guideline

Median LOT - 9.5 days

Johnson M et al PAS 2015
Children’s Mercy ASP

Prospective-Audit with Feedback

• All inpatients 6 days a week
• Review patients on monitored antibiotic two calendar days after initiation
• Appropriateness and duration determined
• Discuss with teams and physicians about recommendations of ASP
• Recommendations agreed upon provided in patient chart
Monitored Antibiotics

- Ceftazidime
- Cefepime
- Ceftriaxone
- Cefotaxime
- Meropenem
- Aztreonam
- Vancomycin
- Linezolid*
- Daptomycin*
- Amoxicillin/Clavulanate
- Ampicillin/Sulbactam
- Piperacillin/Tazobactam
- Ticarcillin/Clavulanate
- Ciprofloxacin
- Moxifloxacin
- Levofloxacin*
- Amikacin
- Tobramycin

*Require Prior Approval
CMH ASP

Data from 3/3/08- 3/2/13

• 14,402 Patient Reviews performed
• Recommendations- 2317
  • Stop therapy- 45%
  • Modify therapy- 26%
  • Optimize therapy- 19%
  • Consult Infectious Diseases- 10%
• 22% Disagreement with recommendations

Goldman J et al. ICHE 2015 36:673-80
<table>
<thead>
<tr>
<th>Table 2. Diagnostic Categories for CommonlyReviewed Antimicrobial Indications</th>
</tr>
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<tbody>
<tr>
<td><strong>ENT (%)</strong></td>
</tr>
<tr>
<td>Tracheitis (40)</td>
</tr>
<tr>
<td>Otitis media (19)</td>
</tr>
<tr>
<td>Pharyngitis (12)</td>
</tr>
<tr>
<td>Orbital cellulitis (9)</td>
</tr>
<tr>
<td>Adenitis (9)</td>
</tr>
<tr>
<td>Mastoiditis (6)</td>
</tr>
<tr>
<td>Tonsillitis (3)</td>
</tr>
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Goldman J et al. ICHE 2015 36:673-80
CMH ASP

Goldman J et al. ICHE 2015 36:673-80
CMH ASP

• 22% Disagreement with recommendations
• Most common antibiotics
  • Linezolid: OR 7.2 (95% CI 2.1-24.6)
  • Carbapenem: OR 2.8 (95% CI 1.4-5.3)
• Most common indications
  • ENT: OR 4.2 (95% CI 2.4-7.2)
  • CAP: OR 4.1 (95% CI 2.4-7.0)

Goldman J et al. ICHE 2015 36:673-80
Results: Select Antibiotics

Newland JG et al. JPIDS 2012;1:179
Clinician Survey

Agreed vs. Disagreed: LOS

Newland JG et al. IDweek 2014
Agreed vs. Disagreed: Readmission

Newland JG et al. IDweek 2014
Results: All Antibiotics

Newland JG et al. JPIDS 2012;1:179
### TABLE 2. Comparison of Antimicrobial Management Strategies between Hospitals with and without Antimicrobial Stewardship Programs (ASPs)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without ASP (n = 22)</th>
<th>With ASP (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective audit and feedback alone</td>
<td>2 (9)</td>
<td>2 (13)</td>
<td>.524</td>
</tr>
<tr>
<td>Formulary restriction alone</td>
<td>9 (41)</td>
<td>3 (19)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Both</td>
<td>7 (32)</td>
<td>10 (63)</td>
<td>.311</td>
</tr>
<tr>
<td>Neither specified</td>
<td>4 (18)</td>
<td>1 (6)</td>
<td>Reference</td>
</tr>
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# Children’s Hospitals ASPs

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<th>With ASP (n = 16)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>15 (68)</td>
<td>16 (100)</td>
<td>.014</td>
</tr>
<tr>
<td>Antimicrobial use</td>
<td>7 (32)</td>
<td>12 (75)</td>
<td>.02</td>
</tr>
<tr>
<td>Antimicrobial costs</td>
<td>5 (23)</td>
<td>10 (63)</td>
<td>.02</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>7 (32)</td>
<td>6 (38)</td>
<td>.742</td>
</tr>
<tr>
<td>Compliance with ASP recommendations</td>
<td>NA</td>
<td>12 (75)</td>
<td>NA</td>
</tr>
<tr>
<td>Rate of <em>Clostridium difficile</em> infection</td>
<td>16 (73)</td>
<td>6 (38)</td>
<td>.047</td>
</tr>
</tbody>
</table>
Impact of a Formal ASP

SHARPS Collaborative

• SHaring Antimicrobial Reports for Pediatric Stewardship
• Quality improvement collaborative of 40 children’s hospitals
• Utilizing PHIS reports on antibiotic use to help determine best interventions
• Social media presence: @Sharpsgroup and http://sharpsgroup.tumblr.com/
Summary

• Microbes have been developing ways to survive for billions of years
• Antimicrobial resistance will continue to impact clinical care and patient safety
• Antimicrobial Stewardship Programs are beneficial
• More work is needed to describe the clinical benefits of ASPs
Acknowledgements

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• Angie Myers, MD MPH
• Mary Anne Jackson MD
SHARPS Collaborative

FTE Allocated to ASP

- Pharmacist
- Physician
- Analyst
CDC Vital Signs

• Estimated the impact of a coordinated approach to reduce antibiotic resistant infections and *C. difficile* infections

• Modeled in 10 and 102 facility healthcare systems

• Impact modeled after UK and Israel which saw 30-50% reduction in infections

Slayton RB et al. MMWR 2015;64.
Impact of National Effort

10% increase of HAIs by 2016

Slayton RB et al. MMWR 2015;64.
Impact of National Effort

- Implementation of infection control and antibiotic stewardship will in 5 years:
  - Reduce MDR HAIs or CDI deaths by 37,000
  - Reduce MDR HAIs or CDI infections by 619,000