Antimicrobial Stewardship (AMS)

June 14, 2017

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Chairperson of OhioHealth Infectious Diseases Clinical Guidance Council
I have nothing to disclose
Discussion outline

What is antimicrobial/antibiotic stewardship? (ASPs)
3 reasons for antibiotic stewardship
Regulation
Who is an Infectious Diseases Practitioner?

- Do you evaluate patients with unknown causes of inflammatory responses?
- Do you manage/assist patients with defined/presumed infections? \( \rightarrow \) RPh
- Do you order & review labs? \( \rightarrow \) RN / IP / RPh
- Do you order & review cultures? \( \rightarrow \) RN / IP / RPh
- Do you prescribe antibiotic therapy?
Up to 50% of antibiotic Rx is Inappropriate

*J of Qual Imp; Aug 2001; 27(8)*

cdc.gov

- Antibiotic Rx for treatment of syndromes not caused by bacteria
- Antibiotic Rx for treatment of culture results that represent colonization rather in infection
- Administration of broad spectrum antibiotics where narrow spectrum antibiotics are effective
- Antibiotic courses that are longer than necessary
- Antibiotic doses that are too high (toxic) or low
Antimicrobial Stewardship

A rational, systemic approach using antimicrobial agents in order to achieve optimal outcomes

Patient outcomes: treatment cure, avoidance of toxicity, & other adverse effects

Public health outcomes: avoidance of emergence or propagation of antimicrobial resistance

ASPs: improve patient outcomes, reduce the emergence of antibiotic resistance, reduce *C. difficile* infection rates, improved value: save hospitals money
85 yo female, ECF resident presents to the ED with worsening abdominal pain & diarrhea; she is currently on day #7 ciprofloxacin for a UTI; has “recurrent UTIs”

Patient is hypotensive; abdomen is tender

ED labs: WBC = 35k(left shift), cr = 2.8, UA with >180 WBCs/hpf

Rx with IV vancomycin/Zosyn?

Rx with Zosyn?

IV metronidazole?

Rx with PO vancomycin?

PO vancomycin dose?

IV & enteral vancomycin?
Why Antimicrobial Stewardship?  
3 reasons ...
#1
The Rise of MDR pathogens
(MDR = multi drug resistant)

MRSA, GISA/VISA, VRE, ESBL producing enteric gram (-) bacteria, CRE, MDR Acinetobacter baumannii, MDR Pseudomonas species, Neisseria gonorrhoea

Isolation comments …
<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Resistance/ decreased susceptibility to:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>3rd generation cephalosporins, fluoroquinolones</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3rd generation cephalosporins, carbapenems</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Methicillin (beta-lactam antibiotics) i.e. MRSA</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Penicillin</td>
</tr>
<tr>
<td>Nontyphoidal <em>Salmonella</em> (NTS)</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td><em>Shigella</em> species</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>3rd generation cephalosporins</td>
</tr>
</tbody>
</table>
## Estimates of Burden of Antibacterial Resistance

<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
<th>Deaths/Year</th>
<th>Hospital Days</th>
<th>Overall Societal Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Union</strong></td>
<td>500m</td>
<td>25,000</td>
<td>2.5m</td>
<td>€900 million – €1.5 billion</td>
</tr>
<tr>
<td><strong>Thailand</strong></td>
<td>70m</td>
<td>&gt;38,000</td>
<td>&gt;3.2m</td>
<td>US$ 84.6–202.8 mill direct – &gt;US$1.3 billion indirect</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td>300m</td>
<td>&gt;23,000</td>
<td>&gt;2.0m</td>
<td>Up to $20 billion direct – Up to $35 billion indirect</td>
</tr>
</tbody>
</table>


Global information is insufficient to show complete disease burden impact and costs.
MRSA; methicillin resistant S. aureus

J. Clin. Microbiol. June 2012 vol. 50 no. 6
US Pharm. 2014; (39):6

- MRSA: improved trends, but related to infection control measures, hand hygiene and “bundles”
- Healthcare associated community onset
- Hospital onset: 1.2 million annual hospital acquired invasive MRSA infections while inpatients (20% of all hospital infections)
- Community associated onset: CDC report, 2007, 14% of people with MRSA infections contracted the infection outside of a healthcare setting
MRSA Infections

Across Epidemiologic Categories

Rate per 100,000 population

2005: 21.49 (9.89 + 5.9)
2006: 20.87 (9.1 + 6.2)
2007: 19.22 (8.4 + 5.23)
2008: 18.52 (7.1 + 5.2)
2009: 17.1 (6.2 + 5.1)
2010: 16.1 (5.1 + 4.5)
2011: 15.0 (4.5 + 5.2)
ESBL producing *Enterobacteriaceae*

ESBL (extended spectrum β-lactamase) producing *Enterobacteriaceae* are among the most multidrug-resistant pathogens in hospitals and are spreading worldwide.

Infections caused by ESBL–producing organisms have resulted in poor outcomes, reduced rates of clinical and microbiological responses, longer hospital stays, and greater hospital expenses.

Risk factors for ESBL infection: antibiotic use, LTACH / ECF exposure, multiple hospitalizations
Many published studies provide evidence that previous antibiotic Rx is a risk factor for acquiring ESBL-producing bacterial colonization → infection. 

AM J of Infect Cont; 2015 Jul 1;43(7):719-23

Antimicrobial Resistance and Infection Control 2014 3:9
ESBL producers: now becoming a Community Pathogen

Clin Infect Dis 2013 Mar 1. Foxman B.

5 American medical centers (including: Pittsburg, Detroit, Iowa)
Prospective observational studies; 9/2009 → 9/2010
13,279 E. coli isolates
523 / 3.9 % were ESBL producers
56%: community onset
37%: no healthcare association
Carbapenem resistant *Enterobacteriaceae*

CRE: return to pre-antibiotic era?

The next step of evolution for β-lactamase: carbapenemase

Clinical dilemma? What is the clinical relevance of this non-sterile body culture (that isolates an ESBL isolate)?

Most CRE are associated with health-care exposures

**LTACHs** Clin Infect Dis; ePub 2017 May 3

Invasive infections (e.g., bloodstream infections) with CRE are associated with mortality rates exceeding 40%

**Treatment?** Optimal treatment is unknown

Infect Control Hosp Epidemiol 2008;29:1099–106

www.cdc.gov/mmwr/preview/mmwrhtml/mm6209a3.htm
Urine is not sterile

*J. Clin Microbiol.* April 2012 50; 1376-83
*Am Fam Physician.* 2006 Sep 15;74(6):985-990

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, premenopausal women</td>
<td>1.0–5.0</td>
<td>[31]</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>1.9–5.5</td>
<td>[31]</td>
</tr>
<tr>
<td>Postmenopausal women aged 50–70 years</td>
<td>2.8–8.6</td>
<td>[31]</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>9.0–27</td>
<td>[32]</td>
</tr>
<tr>
<td>Men</td>
<td>0.7–11</td>
<td>[32]</td>
</tr>
<tr>
<td>Elderly persons in the community*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>10.8–16</td>
<td>[31]</td>
</tr>
<tr>
<td>Men</td>
<td>3.6–19</td>
<td>[31]</td>
</tr>
<tr>
<td>Elderly persons in a long-term care facility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>25–50</td>
<td>[27]</td>
</tr>
<tr>
<td>Men</td>
<td>15–40</td>
<td>[27]</td>
</tr>
<tr>
<td>Patients with spinal cord injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent catheter use</td>
<td>23–89</td>
<td>[33]</td>
</tr>
<tr>
<td>Sphincterotomy and condom catheter in place</td>
<td>57</td>
<td>[34]</td>
</tr>
<tr>
<td>Patients undergoing hemodialysis</td>
<td>28</td>
<td>[28]</td>
</tr>
<tr>
<td>Patients with indwelling catheter use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>9–23</td>
<td>[35]</td>
</tr>
<tr>
<td>Long-term</td>
<td>100</td>
<td>[22]</td>
</tr>
</tbody>
</table>

* Age, ≥70 years.
#2
Clostridium difficile infection (CDI)
Pathogenesis of CDI

1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.

2. Spores germinate within the intestine.

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of C. difficile in colon.

4. Toxin A & B Production leads to colon damage pseudomembrane.
Exposure to antimicrobial is the single most important risk factor for CDI

Chang; In Con Hosp Epi 2007; 28(8); Hansgens; J Anti Chemo 2012;67(3); Hsu; Am J Gast 2010;105(11)

- Antibiotic exposure has lasting impact on the microbiome.
  - Risk of CDI is elevated (7-10 fold) during and in the 3 months following antimicrobial therapy
  - 85-90% of CDI occurs within 30 days of antimicrobial exposure

- Target high risk antibiotics for CDI prevention
  - Fluoroquinolones
  - 3rd/4th generation cephalosporins, carbapenems
Modifiable Risk Factors

Exposure to antibiotics
High Risk:
• Fluoroquinolones¹
• 3rd and 4th generation cephalosporins, clindamycin, carbapenems²

Exposure to C. difficile spores
• Spores can remain viable for months³
• Contamination is increased in rooms of patients with active CDI ⁴,⁵
• Hands of patients and personnel are easily contaminated⁵

Gastric acid suppression
• Data, though inconsistent, implicate proton pump inhibitor (PPI) use¹,⁴,⁶,⁷
• More study is needed to link restriction of PPIs with decreased CDI incidence⁸

2. J Antimicrob Chemother 2012; 67(3)
3. Infect Control Hosp Epidemiol 2011; 32
5. Infect Control Hosp Epidemiol 2011; 32
The ultimate battle against MRSA

Published September 13, 2016
The Wall Street Journal

This colorized scanning electron micrograph (SEM) depicts numerous clusters of methicillin-resistant Staphylococcus aureus (MRSA) bacteria. It is especially dangerous because it is resistant to many antibiotics. (CDC.gov)

If you are admitted to one of the 320 intensive-care units at HCA Inc.'s hospitals, you will be bathed with germ-killing soap and administered an antibiotic nose ointment.

Outbreaks

Drug-resistant bladder bug raises growing concerns

By JoNeil Alexcia

msnbc.com

A nasty bug that appears to be disarming the top drugs used to treat bladder infections is raising concerns for the 6 million to 8 million sufferers, mostly women, who develop the painful, annoying conditions each year.

A rare but aggressive strain of multi-drug-resistant E. coli bacteria, dubbed E. coli ST131, could be responsible for up to 1 million bladder infections and for more than 3,000 deaths a year from infections that started out in the urinary tract, estimated Dr. James R. Johnson, an infectious disease expert at the Veterans Affairs Medical Center in Minneapolis.

"I think it's high time to worry," said Johnson, who adds that the new strain is one resistance gene away from being untreatable. "Before, resistant strains were wimpy. Now, we have a winner."

#3
Back to the Pre-antibiotic Era?
Resistance is Futile...

In both Gram (+) & Gram (-) bacteria, resistance will occur

<table>
<thead>
<tr>
<th>Year</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940</td>
<td>Penicillin</td>
</tr>
<tr>
<td>1950</td>
<td>Penicillin resistance</td>
</tr>
<tr>
<td>1960</td>
<td>Methicillin</td>
</tr>
<tr>
<td>1961</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>1970</td>
<td>Vancomycin resistance</td>
</tr>
<tr>
<td>1990</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>1999</td>
<td>Daptomycin</td>
</tr>
<tr>
<td>2000</td>
<td>Linezolid</td>
</tr>
<tr>
<td>2001</td>
<td>Quinupristin/dalfopristin</td>
</tr>
<tr>
<td>2005</td>
<td>Methicillin resistance (MRSA)</td>
</tr>
</tbody>
</table>

No antibiotic pipeline …
No new novel compounds

1928: Penicillins
1932: Sulfonamides
1945: Tetracyclines
1947: Polymyxins, Phenicols
1948: Cephalosporins
1950: Pleuromutilins
1952: Macrolides
1953: Glycopeptides, Nitroimidazoles, Streptogramins
1955: Cycloserine, Novobiocin
1957: Rifamycins
1961: Trimethoprim
1962: Quinolones, Lincosamides, Fusidic acid
1969: Fosfomycin
1971: Mupirocin
1976: Carbapenems
1978: Oxazolidinones
1979: Monobactams
1987: Lipopeptides

© ReAct Group 2015

DISCOVERY VOID
No antibiotic pipeline ... 
CID. 2011;52(suppl 5) s397-428
Oh no!...

*Nature* 2011 472:32

**A PERFECT STORM**

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

- **Companies researching antibiotics:**
  - MRSA: 18
  - VRE: 4

*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQR, fluoroquinolone-resistant *Pseudomonas aeruginosa.*
Filling the Void? Big Pharma?

- Big pharma has shown lack of interest/investment in antimicrobial research
- High risk / low return
- More lucrative options; not defined antibiotic Rx
- Inevitable resistance
- Limited lifespan of drug / patent protection
- “low hanging fruit” already captured
Where are we now?
Where are we going?
2020 Goals:
* Establishment of antibiotic stewardship programs in all acute care hospitals and improved antibiotic 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 important multidrug resistant organisms

obamawhitehouse.archives.gov
Antibiotic Stewardship Programs (ASP)

Implementing an ASP; CID; 2016; 62:51-77
First practice guidelines published by IDSA in 2007
Percent of Hospitals With Antibiotic Stewardship Programs, by State (2015)

Nationally, 48.1% of all hospitals have stewardship programs (2,199 of 4,549); the national goal is 100% of hospitals by 2020.

*A hospital stewardship program is defined as a program following all 7 of CDC’s Core Elements of Hospital Antibiotic Stewardship Programs.

Source: CDC’s National Healthcare Safety Network (NHSN) Survey
June, 2016: CMS releases proposed rule change to its Conditions of Participation; require hospitals to implement antibiotic stewardship programs in order to participate in Medicare and Medicaid; approved: New Antimicrobial Stewardship Standard

July, 2016: Joint Commission recently announced a new Medication Management (MM) standard for hospitals, critical access hospitals, and nursing care centers; addresses antimicrobial stewardship and becomes effective January 1, 2017; see jointcommission.org.
Seven Core Elements of Antimicrobial Stewardship

1. Leadership Commitment
   *Dedicating necessary human, financial, technological resources*

2. Accountability
   *Appointing a single leader (physician or pharmacist) responsible for program outcomes*

3. Drug Expertise
   *A single dedicated (physician or pharmacist) with responsibility to improve antibiotic use*

4. Tracking
   *Monitoring antibiotic prescribing and resistance patterns*

5. Reporting
   *Feedback of information on antibiotic use and resistance to frontline providers*

6. Education
   *Ongoing education of clinicians about resistance and optimal prescribing*

7. Action
   *Implementing at least one recommended action*
Get Smart About Antibiotics Week
Nov. 12-18, 2017

1. Antibiotics are LIFE-SAVING drugs
2. Antibiotics only treat BACTERIAL infections
3. Some ear infections DO NOT require an antibiotic
4. Most sore throats DO NOT require an antibiotic
5. Green colored mucus is NOT a sign that an antibiotic is needed
6. There are potential RISKS when taking any prescription drug

Talk to your clinician about when and how to safely use antibiotics
www.cdc.gov/getsmart
Candida auris MMWR; 5/19/2017