Antimicrobial stewardship:
“Quick, don’t just do something! Stand there!”

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Director, Antimicrobial Stewardship Program
Geisinger Health System
It starts with a simple observation
Penicillin discovered

Penicillin mass produced
“Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever.” – **Sir William Osler**
"But I would like to sound one note of warning… It is not difficult to make microbes resistant to penicillin… Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

-- A. Fleming, 1945, Nobel Prize Acceptance Speech
1920 - Penicillin discovered

1940 - Penicillin mass produced

1960 - Methicillin replaces penicillin as drug to treat *Staphylococcus aureus*

1960 - 1st methicillin resistance reported: MRSA

1970 - 15% of all *S. aureus* is MRSA

1997-1999 - Four children die of MRSA from the community

2000 - Vancomycin resistant MRSA first reported
Vancomycin resistant *S. aureus* (VRSA)

First reported in 2002
Found on a dialysis catheter in a 40yo male from Michigan with ESRD, DM, and PVD
Case from Pennsylvania reported later the same year
Fifteen cases in the literature from the US so far
Most recently reported in Delaware this past year (February 2015)
• Existing limitations in optimizing vancomycin dosing
• Slow bacterial killing of vancomycin compared to beta-lactams
• Poor tissue penetration by vancomycin
What to use for serious MRSA infections?

Vancomycin, or…

Daptomycin
Linezolid
Tedizolid
Ceftaroline
Televancin
Dalbavancin
Oritavancin
Tigecycline

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The story is about more than just one bug
1920

Penicillin resistance first identified in pneumococcus

1940

ESBL enteric Gram negative rods first identified as nosocomial pathogens

1960

Multi-drug resistant Acinetobacter becomes endemic in hospitals worldwide

1980

First VRE identified

First carbapenem-resistant enteric Gram negative rod identified in the US

2000

First described Clostridium difficile as a cause of antibiotic associated colitis

2020

Geisinger
The superbug that doctors have been dreading just reached the U.S.

By Lena H. Sun and Brady Dennis  May 27, 2016

The Post’s Lena Sun visited Walter Reed Army Institute of Research in Silver Spring, Md., where scientists there identified a strain of bacteria resistant to the last-resort antibiotic, colistin. The bacteria was found in a Pennsylvania woman. Microbiologist Patrick McGann explains how his team identified the gene that gives the bacteria this resistance (Monica Akhtar, Lena Sun/The Washington Post).

For the first time, researchers have found a person in the United States carrying bacteria resistant to antibiotics of last resort, an alarming development that the top U.S. public health official says could mean “the end of the road” for antibiotics.

The antibiotic-resistant strain was found last month in the urine of a 49-year-old Pennsylvania woman. Defense Department researchers determined that she
'Superbug' resistant to all antibiotics killed Nevada woman

FRIDAY, Jan. 13, 2017 -- A Nevada woman in her 70s who'd recently returned from India died in September from a "superbug" infection that resisted all antibiotics, according to a report released Friday.

The case raises concern about the spread of such infections, which have become more common over past decades as germs have developed resistance to widely used antibiotics.
NATIONAL SUMMARY DATA

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses, 23,000 deaths

*bacteria and fungi included in this report

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least 250,000 illnesses, 14,000 deaths

WHERE DO INFECTIONS HAPPEN?
Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community, however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.
<table>
<thead>
<tr>
<th>Estimated annual cases</th>
<th>Infections (No.)</th>
<th>Deaths (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem-resistant enteric Gram negative rods</td>
<td>9,300</td>
<td>610</td>
</tr>
<tr>
<td>Drug-resistant Gonococci</td>
<td>2,467,000</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Multidrug resistant <em>Acinetobacter</em></td>
<td>7,300</td>
<td>500</td>
</tr>
<tr>
<td>Extended-spectrum beta-lactamase (ESBL) enteric Gram negative rods</td>
<td>26,000</td>
<td>1,700</td>
</tr>
<tr>
<td>Vancomycin resistant Enterococci (VRE)</td>
<td>20,000</td>
<td>1,300</td>
</tr>
<tr>
<td>Multi-drug resistant <em>Pseudomonas</em></td>
<td>6,700</td>
<td>440</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em> (MRSA)</td>
<td>80,000</td>
<td>11,000</td>
</tr>
</tbody>
</table>
U.S. Approvals

Source: Spellberg, CID 2004, modified

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“… the aging of the US population has shifted drug discovery efforts towards agents that treat chronic medical conditions that are more prevalent among elderly persons, such as hypercholesterolemia, hypertension, mood disorders, dementia, and arthritis. Conversely, antimicrobials are usually used for short-course therapies that cure disease and thus eliminate their own need in a given patient.” – B. Spellberg
Americans love their antibiotics
Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.
Primary care office visits and antibiotic prescriptions for acute respiratory illnesses in the United States


© 2001 by the Infectious Diseases Society of America
Almost 60% of patients who get hospitalized are put on antibiotics.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DOT/1000 PDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2006</td>
</tr>
<tr>
<td>Antibiotic class</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>732.5</td>
</tr>
<tr>
<td>Teaching</td>
<td>713.8</td>
</tr>
<tr>
<td>Nonteaching</td>
<td>752.9</td>
</tr>
<tr>
<td>No. of beds, &lt;300</td>
<td>739.0</td>
</tr>
<tr>
<td>No. of beds, ≥300</td>
<td>726.7</td>
</tr>
<tr>
<td>Large, urban teaching hospital</td>
<td>713.6</td>
</tr>
<tr>
<td>Hospitals other than large, urban, teaching</td>
<td>744.2</td>
</tr>
</tbody>
</table>

As a general rule, we are not always very good at picking the right antibiotics.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients treated for UTI present on admission, without indwelling catheter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine culture was not ordered, although standard practice before treatment</td>
<td>111</td>
<td>—</td>
</tr>
<tr>
<td>Urine culture was positive, but no documented symptoms were present</td>
<td>18</td>
<td>(16.2)</td>
</tr>
<tr>
<td>Urine culture was negative, and no documented symptoms were present</td>
<td>23</td>
<td>(20.7)</td>
</tr>
<tr>
<td>No. of patients with potential for improvement in prescribing</td>
<td>3</td>
<td>(2.7)</td>
</tr>
<tr>
<td>No. of patients with potential for improvement in prescribing</td>
<td>44</td>
<td>(39.6)</td>
</tr>
<tr>
<td><strong>Patients treated with intravenous vancomycin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diagnostic culture obtained around antibiotic initiation, although standard practice with most infections</td>
<td>185</td>
<td>(9.2)</td>
</tr>
<tr>
<td>Diagnostic culture showed no Gram-positive bacterial growth, but patient still treated for long duration (&gt;3 days) (excludes presumed SSTI, which often can be culture negative)</td>
<td>40</td>
<td>(21.6)</td>
</tr>
<tr>
<td>Diagnostic culture grew only oxacillin-susceptible Staphylococcus aureus, but patient still treated for long duration (&gt;3 days) (likely missed opportunity to switch antibiotic based on culture result)</td>
<td>9</td>
<td>(4.9)</td>
</tr>
<tr>
<td>No. of patients with potential for improvement in prescribing</td>
<td>66</td>
<td>(35.7)</td>
</tr>
<tr>
<td><strong>Combined UTI or vancomycin prescribing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients with potential for improvement in prescribing</td>
<td>296</td>
<td>—</td>
</tr>
<tr>
<td>Total no. of patients with potential for improvement in prescribing</td>
<td>110</td>
<td>(37.2)</td>
</tr>
</tbody>
</table>

Abbreviation: SSTI = skin and soft tissue infection.
Review of 255 meropenem orders
6 month period
Only 36% of meropenem orders were for generally appropriate indications:
- Patients with a history of ESBL, or having documented ESBL enteric Gram negative rod infection
- History of, or documented *Pseudomonas* infections
- *Acinetobacter* infections
- Empiric use for meningitis in patients with penicillin/cephalosporin allergies
ID service consulted in less than half of cases
## Review of Fluoroquinolone use at Geisinger

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented infection present</td>
<td>53 (55.2%)</td>
<td>43 (44.8%)</td>
<td>--</td>
</tr>
<tr>
<td>Alternative oral option available</td>
<td>39 (40.6%)</td>
<td>57 (58.3%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Duration of therapy appropriate</td>
<td>59 (61.5%)</td>
<td>37 (38.5%)</td>
<td>--</td>
</tr>
</tbody>
</table>
C diff. C diff run. Run, diff, run!
• Estimated number of cases of C diff infection in the United States: **453,000 annually**
• Associated with **29,000 deaths**
• Female slightly more affected than male: **256,000 cases vs. 197,000 cases**
• Age group >65 years disproportionately affected: **259,800 cases**

*Figure 1. Estimated U.S. Burden of Clostridium difficile Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.*

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure. CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.

Hospital-acquired C. difficile Rates

# of cases/10,000 pt-days

GMC  GWV  G-CMC

2014  2015  2016

Geisinger
Consequences of C diff

- Longer length of stay (13.2 vs 8.5 days)
- Higher rates of inpatient mortality (OR 1.13, 95%CI 1.09-1.17)
- Higher cost of care (39.3% higher on avg)
- Higher 30-day, 60-day, and 90-day readmission rates (OR 1.77-1.83 with 95%CI 1.73-1.87)

*P* value <0.01

What can antimicrobial stewardship hope to accomplish?
### Table 1  Clinical outcomes in a randomized controlled trial comparing the Hospital of the University of Pennsylvania (HUP)* program to usual practice

<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>4 (4%)</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>Service changed antibiotic</td>
<td>0</td>
<td>5 (5%)</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>

CI = confidence interval.

*Philadelphia, PA.

†Sum may be >100% because individuals can fail for multiple reasons.
**Table 2. Appropriateness of Antibiotic Use in Randomized Controlled Trial of Impact of Antimicrobial Utilization Teams**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportion (%) of prescriptions</th>
<th>Risk ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use deemed appropriate Initial (&lt;72 hours)</td>
<td>305/390 (78)</td>
<td>229/394 (58)</td>
<td>1.35 (1.22–1.49)</td>
</tr>
<tr>
<td>Empirical</td>
<td>242/294 (82)</td>
<td>211/291 (73)</td>
<td>1.14 (1.04–1.24)</td>
</tr>
<tr>
<td>Definitive</td>
<td>92/112 (82)</td>
<td>60/138 (43)</td>
<td>1.89 (1.53–2.33)</td>
</tr>
<tr>
<td>Appropriate cultures obtained</td>
<td>188/270 (70)</td>
<td>193/286 (67)</td>
<td>1.03 (0.92–1.15)</td>
</tr>
<tr>
<td>Changed to recommended antibiotics</td>
<td>168/186 (90)</td>
<td>85/199 (43)</td>
<td>2.11 (1.79–2.50)</td>
</tr>
<tr>
<td>Appropriate end antimicrobial usage</td>
<td>367/390 (94)</td>
<td>277/394 (70)</td>
<td>1.34 (1.25–1.43)</td>
</tr>
</tbody>
</table>

**Note.** CI, confidence interval.

* In the control group, a blinded assessment of the appropriateness of the antimicrobial therapy was still made by the medical director of the antimicrobial utilization program. However, any recommendations for optimization of therapy were only recorded and never conveyed to the control group physicians.
Where do we go from here?
CMS mandates that all hospitals have an Antimicrobial Stewardship Program by 2017

WHO declares antibiotic resistance a worldwide threat to public health

The White House crafts a National Action Plan for combating antibiotic resistance

Joint Commission mandates that Antimicrobial Stewardship Programs are necessary for accreditation
# TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria

By 2020, the United States will:

**For CDC Recognized Urgent Threats:**
- Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
- Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
- Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.

**For CDC Recognized Serious Threats:**
- Reduce by 35% multidrug-resistant *Pseudomonas* spp. infections acquired during hospitalization compared to estimates from 2011.
- Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011.*
- Reduce by 25% multidrug-resistant non-typhoidal *Salmonella* infections compared to estimates from 2010-2012.
- Reduce by 15% the number of multidrug-resistant TB infections.¹
- Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008.
- Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008.

* This target is consistent with the reduction goal for MRSA bloodstream infections (BSI) in the *National Action Plan to Prevent Healthcare-Associated Infections (HAI): Road Map to Elimination*, which calls for a 75% decline in MRSA BSI from the 2007-2008 baseline by 2020. Additional information is available at [http://www.health.gov/hai/prevent_hai.asp#hai_plan](http://www.health.gov/hai/prevent_hai.asp#hai_plan).
• Immediate nationwide infection control and antibiotic stewardship interventions, over 5 years, could avert an estimated 619,000 HAIs resulting from CRE, multidrug-resistant *Pseudomonas aeruginosa*, invasive methicillin-resistant *Staphylococcus aureus* (MRSA), or *C. difficile*

• A coordinated response to prevent CRE spread across a group of inter-connected health care facilities resulted in a cumulative 55-74% reduction in acquisitions

Slayton RB, et al. MMWR 2015;64:1
What should an antimicrobial stewardship program consist of?

- Prospective monitoring of antibiotic use with intervention and feedback
- Formulary restriction and preauthorization
- Education
- Guidelines and clinical pathways
- Streamlining or de-escalation of therapy
- Dose optimization
- IV to PO switch

Clin Infect Dis 2007;44:159-177
Antimicrobial Stewardship at Geisinger

Use of restricted antimicrobials and reviewing them for appropriateness within 2-3 days
Help ensure clearly documented approved indications for antibiotics
Review antimicrobial sensitivity patterns and develop evidence-based treatment guidelines with input from local susceptibility patterns
Formal Infectious Diseases consultation in the following situations:
  – Continued use of restricted Antimicrobials
  – Severe Complicated Clostridium difficile Disease
  – All patients receiving simultaneously ≥ 3 antimicrobials
  – Any documented Staphylococcus aureus bacteremia
  – Any patients expected to be discharged on intravenous antimicrobial therapy
IV to PO conversion when appropriate
Automatic stop dates of 5 days
Daily review for “drug/bug” mismatches
Don’t Just Do Something…Stand There!
The need for a cultural change

The concept of an “Antibiotic time out”:
- What bacterial infectious syndrome are we actually treating?
- What diagnostic studies need to be done/have been done? What are the results?
- Is this drug really the one needed?
- Is this drug being dosed and administered properly?
- Are there any side effects from this antibiotic we should be monitoring for?
Emphasis should be on the patient

Historically the emphasis of antimicrobial stewardship was on cost savings. The primary purpose of any Antimicrobial Stewardship Program should be to optimize clinical outcomes and minimize unintended consequences of antimicrobial use:

- Improve patient outcomes
- Toxicity
- Selection of antimicrobial resistance
- Clostridium difficile
- Appropriate monitoring and follow-up
Thank you for your attention. Now please, wash your hands!