Antibiotic Resistance: Challenges and Solutions

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Antibiotic Defense -- www.antibioticdefense.org
Sir Alexander Fleming Discovers Penicillin

1928: A mold on a petri dish was observed to inhibit growth of *Staphylococcus* bacteria.

The active ingredient isolated from this mold was found to be a safe and effective bacteria-killing agent of enormous potency.

1945 Nobel Prize Acceptance Speech: Sir Alexander Fleming warns of the danger of resistance:

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body...”
The improbable chain of events that led Alexander Fleming to discover penicillin in 1928 is what scientific lore is made of. On a brisk London day a wind carried a mold into his lab where it took root on a culture dish and would alter forever the world's treatment of bacterial infections. *Staphylococcus* bacteria grew over this culture dish like a lawn, covering the entire plate - except for a clear area surrounding the moldy contaminant. Alexander Fleming's recognition of this halo was his "Eureka" moment, an instant of great personal insight and deductive reasoning. He correctly deduced that the mold released a substance that inhibited the growth of the bacteria. The active ingredient in that mold, which Fleming named penicillin, turned out to be a bacteria-killing agent of enormous potency, and one that could be delivered to humans safely, or so we thought.
Resistance Emerges

Penicillins

- 1960s: Resistance seen worldwide
- Between 1979 and 1987 0.02% of *S. pneumococcus* penicillin-resistant
- By 2008 ~40% *S. pneumococcus* in United States is resistant to penicillins

Notes on: Resistance Emerges

When the world finally recognized penicillin for what it was - the most efficacious life-saving drug in the world - it embraced it without question. By the middle of the century, Fleming's discovery had spawned a huge pharmaceutical industry, churning out synthetic penicillins that would treat some of mankind's most ancient scourges, including syphilis, and gangrene. Human society experienced decreased morbidity from warfare, increased food production, and increased life expectancy in large part due to the discovery of antibiotics. Although many improvements in public health and medicine and a decline in infectious disease mortality preceded the introduction of penicillin, antibiotics have made possible further reductions in deaths and disability from infectious disease. Perhaps equally important, they have facilitated the vast expansion of other medical interventions, such as kidney and heart transplants, by allowing clinicians to prevent surgical site infections and infections in immunosuppressed patients, such as organ recipients. Now, growing levels of bacterial resistance to antibiotics threaten our ability not just to treat infectious diseases but also to perform other procedures and treatments that fundamentally depend on affordable and effective antibiotics.


A Widespread Problem

Cephalosporins → Resistance [1980s]

- MRSA
- VRSA
- VRE

Vancomycin → Resistance [1996]

- HIV
- MDR-TB
- Malaria

Global spread of penicillin-resistant Pneumococcus strain 23-F.
Notes on: A Widespread Problem

No region in the world has been excluded from the inexorable spread of increasingly drug-resistant bacteria. Antimicrobial resistance (AMR) is now a serious global phenomenon. Deaths from acute respiratory infections, diarrheal diseases, measles, AIDS, malaria, and tuberculosis account for more than 85% of worldwide mortality from infectious disease. Resistance to first, second, and third-line drugs in most of the pathogens causing these diseases is increasing significantly. Associated costs of moving to second and third line therapy pose an additional economic burden. Added to this is the significant global burden of resistant hospital-acquired infections, the emerging problems of antiviral resistance and the increasing problems of drug resistance in neglected parasitic diseases of poor and marginalized populations.

MRSA: Methicillin resistant S. aureus
VRSA: Vancomycin resistant S. aureus
VRE: Vancomycin resistant Enterococcus
HIV: Human Immuno-deficiency virus
MDR-TB: Multi-drug resistant tuberculosis

Source: Cars, O., Nordberg, P. Antibiotic Resistance – The faceless threat. Published by ReAct, Sweden. 2004
The Burden of Disease

- Resistant infections increase the time patients stay in hospitals and patient mortality
  - 5.02 increase in mortality relative risk with a cephalosporin resistant *Enterobacter* infection
- Methicillin resistant vs Methicillin susceptible *S. aureus*
  - 20.1% vs 6.7% for surgical wound site mortality
- Multi-drug resistant *Pseudomonas aeruginosa*
  - 3-fold increase in mortality
  - 1.7-fold increase in hospital stay
Mortality from a resistant infection increases for multiple reasons, but, primarily, because of a delay in effective treatment of the resistant infection AMR, increased need for surgery, and other procedures. Comparing the onset of adequate treatment for susceptible versus resistant strains illustrates the how extensively delayed treatment affects patient outcomes. The median interval between obtaining a sample for culture and initiating antibiotics: 51 hours for resistant infections vs 16 hours for susceptible infections. The number of patients who receive effective treatment within 24 hours: 36% vs 68% for resistant to susceptible strains. The number of patients who receive effective treatment within 48 hours: 48% vs 90% for resistant to susceptible strains. These numbers show that within two days, less than half of the people with resistant infections receive the proper treatment. Without proper care, the infection can spread, making it even harder to eliminate (Cosgrove). -- One method to avoid misdiagnosing resistant infections is to identify patients at high risk for harboring antimicrobial resistant strains. These people include individuals in long-term care facilities and patients with a long or recent history of antimicrobial use. Patients falling into either category should alert the physician. When treating these patients, the doctor may elect to begin treatment with a stronger antimicrobial or, more ideally, perform a rapid susceptibility test to determine the resistance of the organism. In either case, being aware of the possibility of resistance may help to reduce the time to effective treatment.

Sources:
Definition: The continuation of a disease in animals that may transfer to humans under close contact and/or genetic mutation of the pathogen.

Common animal reservoirs: pigs and aquatic wildlife

Pathogens with Reservoirs: Influenza, Lyme’s Disease, Ebola Virus

How does transfer happen?

- Influenza: RNA virus with an avian reservoir
  - Influenza virus replicates in the intestinal tract of aquatic birds
  - Virus is spread in bird populations through faecal contact
- Intermediate from bird to human: swine
  - Swine serve as host for viruses from humans and birds
  - Humans contact swine infected with influenza and acquire the disease

Image: http://pigofknowledge.blogspot.com
Disease Localization

- The prevalence of resistance varies between countries

- MRSA prevalence by country
  - Japan 70%
  - USA 63%
  - Greece 49%
  - UK 45%
  - Saudi Arabia > 39%
  - Russia 36%
  - Trinidad > 29%
  - Germany 27%
  - Netherlands 1%
Many developed nations have implemented surveillance networks and monitoring systems to track the spread and increase of antimicrobial resistance in human and animal populations. Examples of these global networks include the European Antimicrobial Resistance Surveillance System (EARSS) and the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP).

MRSA incidence rates in the Netherlands are among the lowest in the world - 1.1% - in contrast to more than 25% in France, Spain, and Belgium and 43.5% in the United Kingdom. This extremely low rate is attributable to a decade-old national "search and destroy" policy to limit the spread of MRSA. The implementing guidelines are based on the premise that the best way to fight MRSA is to identify it as early as possible and to isolate infected or possibly infected patients. Patients and health care workers are categorized according to risk and screened regularly based on those risk assessments. For example, all patients treated in a foreign hospital are considered at high risk of being MRSA carriers and thus are isolated until cultures prove negative. Most importantly, the policy requires the cooperation of all health care facilities and is enforced by the Dutch government.

There are few numbers from the developing countries because monitoring resistant often requires laboratory equipment, trained personnel and financial resources, which many lower-income countries lack. It is important to strengthen the surveillance systems in these countries.

Image Source: NASA. Sources:
- Presentation by Dr. David Heyman. WHO. July 23, 2008.
Economic Burden of Resistance

• Resistance costs countries billions of dollars each year to contain and treat infections. These costs not only directly affect the healthcare sector but also the entire economy.

• Mechanisms of increased costs:
  – Additional labs and X-rays
  – Alternative, more expensive treatments
  – Longer hospital stay
  – More elaborate infection control procedures
  – Reduced quality of life
  – Increases in private insurance coverage
  – Increased overall healthcare expenditure
  – Increased cost of disease surveillance
  – Increased family burden of infected individual
  – Increased cost to firms of absentee workers
Notes on: Economic Burden of Resistance

The economic burden continues to rise as the number of resistant infections increases as well as the number of drugs to which each microorganism is resistant. As evidenced by the calculations, antimicrobial resistance is taking a financial toll not only on our hospitals but on economies, as well. Examples of costs:

- Additional hospital charges for MRSA in the USA
- Median total cost for MSSA primary nosocomial infections = $9,661
- Median cost for MRSA primary nosocomial infections = $27,083
- Approximate 3-fold increase in hospital costs from resistance

Note: this is only the increase in hospital costs from MRSA; it does not include the costs associated with other resistance infections. Also, the number of resistant bugs continues to increase, making these numbers underestimates. Treatment for resistant infections in US = $4-7 billion per year, or £500,000 to contain a 5 week outbreak of MRSA in general hospitals.

Sources:
- Image Source: West Investments Ltd.
Mechanisms of Resistance: Overview

Methods of Resistance
- Impermeability of the drug
- Alteration in the drug’s target
- Enzymatic drug modifications
- Efflux of the drug

Methods of Resistance Acquisition
- Chromosomal mutations
- Genetic transfer (ex: plasmids)

Antimicrobials Discussed
- *S. pneumoniae*
- MRSA
- VISA/VRSA
- ESBLs
- VRE
- *Neisseria gonorrhoeae*
- MDR *Salmonella Typhi*

**S. pneumoniae**

- Leading cause of serious childhood illness
- Causative agent for
  - Otitis Media
  - Pneumonia
  - Meningitis

This graph shows the number of publications each year, from 1966 to the present, under headings of Streptococcus pneumoniae, antibiotic, and resistance.

*Courtesy of Daniel M Musher, MD., Up-to-date, “Resistance of Streptococcus pneumoniae to beta-lactam antibiotics”*
Notes on: S. Pneumoniae

*S. pneumoniae* is a universal bacteria that has the distinction of being the leading cause of serious childhood illness. In fact, prior to the pneumococcal vaccine, almost 17,000 cases of invasive *S. pneumoniae* occurred annually. *S. pneumoniae* is known mainly for its ability to cause three major diseases: otitis media, pneumonia, and meningitis. Of these, meningitis is the most lethal.

As you can see in the graph, resistance to *S. pneumoniae*, as well as academic interest in this subject, has become increasing prevalent across the U.S. Fortunately most resistance of pneumococci to beta-lactams--which is the most common form of resistance--can be overcome by simply increasing the dose.

Sources:
S. pneumoniae

- Resistance strains to many antibiotics
- Penicillins (late 1970s)
  - 40% of U.S. pneumococci
  - Over 70% resistance in parts of Asia
  - Resistance mechanism:
    - Decreased drug binding
    - More common in children
- Macrolides
  - 29% of U.S. pneumococci
  - Resistance mechanisms:
    - Decreased drug binding
      - 1/3 of isolates
    - Efflux pump ejects drug
      - 2/3 of isolates

Source: Centers for Disease Control

FIGURE 1. Changes in incidence rate* of invasive pneumococcal disease (IPD) among children aged <5 years before and after introduction of 7-valent pneumococcal conjugate vaccine (PCV7), by age and year — Active Bacterial Core surveillance, eight states,† 1998–2005

* Per 100,000 population.
† California (one county); the state of Connecticut; Georgia (20 counties); Maryland (six counties); Minnesota (seven counties); New York (seven counties); Oregon (three counties); and Tennessee (four counties).

Source: Centers for Disease Control
Methicillin-resistant *S. Aureus* (MRSA)

- Up to 30-40% of people are asymptomatic *S. aureus* carriers
- 70-80% of *S. aureus* is resistant to penicillins
- Problem of disease localization:
  - HA-MRSA vs. CA-MRSA
    - e.g. quinalone-resistant HA-MRSA in adult ICUs vs. quinalone-sensitive CA-MRSA in pediatric outpatient clinics

MRSA (1)

- **Resistance:**
  - Staphylococcal cassette chromosome
    - mecA gene component
      - encodes penicillin binding protein 2
        » Binds beta-lactams with low affinity
    - beta-lactamase genes

- **Degrees of resistance**
  - Determined by antibiotic resistance testing
    - Homogenous
      - Highest degree of resistance
      - Requires fem genes
        » Interrupt peptidoglycan synthesis
    - Heterogeneous
    - Borderline

MRSA (2)

- MRSA carriage in hospitals
  - 12% in pts with risk factors
  - 1.8% in pts without risk factors
- Patients colonized with MRSA
  - 10-30% rate of developing MRSA infection
    - either in-hospital or after discharge
- Active surveillance for MRSA
  - Can reduce incidence of HA-MRSA by up to 50%

HA-MRSA most commonly transmitted by the hands of healthcare workers

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>MRSA (N=249)</th>
<th>Other Bacteria (N=135)</th>
<th>Odds Ratio (95% CI)&lt;br&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abcess</td>
<td>203/243 (84)</td>
<td>97/131 (74)</td>
<td>1.8 (1.0-3.1)&lt;br&gt;</td>
</tr>
<tr>
<td>Taken any antibiotic in past mo</td>
<td>84/245 (34)</td>
<td>24/134 (18)</td>
<td>2.4 (1.4-4.1)&lt;br&gt;</td>
</tr>
<tr>
<td>Close contact with person with similar infection</td>
<td>43/245 (18)</td>
<td>8/135 (6)</td>
<td>3.4 (1.5-8.1)&lt;br&gt;</td>
</tr>
<tr>
<td>Reported spider bite</td>
<td>71/248 (29)</td>
<td>17/135 (13)</td>
<td>2.8 (1.5-5.3)&lt;br&gt;</td>
</tr>
<tr>
<td>Underlying illness</td>
<td>25/249 (10)</td>
<td>34/135 (25)</td>
<td>0.3 (0.2-0.6)&lt;br&gt;</td>
</tr>
<tr>
<td>HIV infection</td>
<td>11/249 (4)</td>
<td>4/135 (3)</td>
<td>1.5 (0.5-4.9)&lt;br&gt;</td>
</tr>
<tr>
<td>History of MRSA infection</td>
<td>28/242 (12)</td>
<td>5/132 (4)</td>
<td>3.3 (1.2-10.1)&lt;br&gt;</td>
</tr>
</tbody>
</table>


**Treatment: Vancomycin**
- Daptomycin or linezolid if vancomycin is not an option
- Hand hygiene, minimizing patient contact, wearing a gown, etc.
**Enterococcus**

- Gram-positive, facultative anaerobic cocci
- Two species are common commensal organisms in the intestines of humans: *E. faecalis* (90-95%) and *E. faecium* (5-10%).
- Important clinical infections include urinary tract infections, bacteremia, bacterial endocarditis, diverticulitis, and meningitis
- High level of endemic antibiotic resistance:
  - Some *Enterococci* are intrinsically resistant to β-lactam-based antibiotics (some penicillins and virtually all cephalosporins) as well as many aminoglycosides
  - In the last two decades, particularly virulent strains of *Enterococcus* which are resistant to vancomycin (vancomycin–resistant enterococcus or VRE) have emerged

Source: [http://www.biologie.uni-hamburg.de/b-online/library/onlinebio/BioBookDiversity_2.html](http://www.biologie.uni-hamburg.de/b-online/library/onlinebio/BioBookDiversity_2.html)
Notes on: Enterococcus

*Enterococci* are the leading cause of nosocomial infection (or secondary infection acquired while in a hospital). They are responsible for approximately 110,000 cases of urinary tract infection, 25,000 cases of bacteremia, 40,000 wound infections, and 1,100 cases of endocarditis yearly in the United States. To infect hosts enterococci primarily colonize mucosal surfaces. They also must evade host defenses although little is known about the actual mechanism of evasion. The pathogenicity of the organism is believed to be closely associated with its ability to produce cytolysin, a toxin that causes rupture of a variety of target membranes, including bacterial cells, erythrocytes, and other mammalian cells.

*Enterococci* inhabit the gastrointestinal tract, the oral cavity, and the vagina in humans as normal commensals. A potential reason for the emergence of *E. faecalis* as a causative agent of nosocomial infection is the robust nature of this organism. *E. faecalis* has an intrinsic ability to grow in hypotonic, hypertonic, acidic, or alkaline conditions and to withstand detergents, oxidative stress, and desiccation.

Fischetti VA et al. (editors) *Gram-Positive Pathogens*. ASM Press 2000

http://www.cdc.gov/ncidod/dhqp/ar_vre.html

Murray, BE. The life and times of the Enterococcus. *Clinical Microbiology Reviews*. 1990; 3, 46-65
Vancomycin Resistant *Enterococcus* (VRE)

- Vancomycin normally complexes with D-alanyl-D-alanine termini of normal peptidoglycan cell wall precursors, inhibiting cell wall synthesis.
- The genes associated with VRE encode a ligase responsible for the synthesis of the D-alanyl-D-lactate which is incorporated into the terminal portion of the peptidoglycan cell wall precursor:
  - limits vancomycin-peptidoglycan precursor binding
- 6 glycopeptide-resistant enterococcal phenotypes have been described:
  - VanA and VanB are most clinically relevant
  - VanA is the most widely-distributed

Source: [http://www.nature.com/nrg/journal/v4/n6/fig_tab/nrg1084_F1.html](http://www.nature.com/nrg/journal/v4/n6/fig_tab/nrg1084_F1.html)
Notes on: Vancomycin Resistant *Enterococcus* (VRE)

Of the six phenotypes for VRE resistance that have been reported, VanA and VanB are most clinically relevant: VanA phenotype, induces high level resistance to both vancomycin and teicoplanin while VanB induces variable levels of resistance to vancomycin but is sensitive to teicoplanin. Van A and Van B are usually associated with *E. faecalis* and *E. faecium*, but Van A is more widely distributed and thus the predominant type of resistance reported. Moreover, vancomycin resistance has appeared preferentially in *E. faecium*, which is inherently more resistant to multiple drugs making therapy extremely problematic.

- http://www.hopkinsmedicine.org/heic/ID/vre/
Clinical Significance of VRE

**Hospital Related Risk Factors**
- ICU Admission
- Proximity to a patient with VRE
- Length of hospitalization
- Multiple unit stays
- Enteral feedings

**Medication Related Risk Factors**
- Number, type, and duration of antibiotic therapy
- Vancomycin use
- 3rd Generation Cephalosporin utilization
- Anti-anaerobic antibiotics (such as clindamycin)
- Fluoroquinolones (such as ciprofloxacin)
- Preoperative bowel preparations

Most VRE infections can be treated with antibiotics other than vancomycin.

People who are colonized (bacteria are present, but have no symptoms of an infection) with VRE do not usually need treatment.
Notes on: *Clinical Significance of VRE*

*Enterococci* are very tolerant organisms and can survive easily on the hands of health care personnel. Patient-to-patient spread by health care personnel has been documented. Strict observance of hand-washing policies would then be a key element in controlling the spread of epidemic strains of enterococci or any other organism. Cohorting of infected and colonized patients with poor hygiene has been used to prevent the spread of this organism. Proper barriers such as gloves and gowns when soiling is likely are important in preventing dissemination. Each health care facility through collaboration of its quality improvement and infection control programs such as pharmacy, reference microbiology laboratory, nursing, physicians, housekeeping services should develop a comprehensive, institutional-specific strategic plan to detect, prevent and control infection and colonization with VRE.

Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC) Centers for Disease Control and Prevention. MMWR (1995); 44 (RR-12):1-13

Noskins, GA. Recovery of vancomycin-resistant enterococci on fingertips and environmental surfaces. *Infection Control Hospital Epidemiology*. 1995: 16; 577-581
VISA/VRSA (1)

- Vancomycin resistance and susceptibility
  - **VISA**
    - "vancomycin intermediate"
    - AKA glycopeptide-intermediate (GISA)
    - Reduced vancomycin susceptibility
    - First noted in 1996
  - **VRSA**
    - Vancomycin resistance
    - First noted in 2002
- Epidemiology
  - RARE!
    - ≤0.3% of *S. Aureus* infections
    - Only 7 cases of VRSA in the US from 2002-2006
      - 5 of 7 had a history of MRSA or VRE, or previous exposure to vancomycin
    - Thought to originate from transfer of vanA resistance genes from VRE to MRSA
VISA/VRSA (2)

- **VISA**
  - Exact mechanism of resistance is unknown
  - Abnormal increased thickening of D-ala D-ala cell wall dipeptides
    - Decreased penetrance of antibiotics
  - Lacks the vanA gene

- **VRSA**
  - vanA gene cluster
    - Plasmid-mediated transfer
      - Mobile genetic element Tn1546 from VRE
    - Results in production of D-alal D-lac cell wall dipeptide
      - Decreased binding to vancomycin

Figures from Applebaum PC. Clin Microbiol Infect 2006(12):16-23
β-lactam antibiotics and β-lactamase

- β-lactam antibiotics are a broad class of antibiotics that include penicillin derivatives, cephalosporins, monobactams, and carbapenems.

- Production of plasma encoded β-lactamases (e.g., TEM-1, TEM-2, and SHV-1) by gram negative bacteria is the main mechanism of bacterial resistance to β-lactam antibiotics.

- Inactivated by hydrolysis of the amide bond of the β-lactam ring.

- Resistance is NOT conferred to expanded-spectrum cephalosporins.

Source: http://www.cic.klte.hu/~gundat/betalaca.htm
Notes on: β-lactam antibiotics and β-lactamase

β-lactam antibiotics are a broad class of antibiotics that include penicillin derivatives, cephalosporins, monobactams, and carbapenems. These antibiotics are bactericidal and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. β-lactam antibiotics are analogues of D-alanyl-D-alanine - the terminal amino acid residues on the peptide subunits of the nascent peptidoglycan layer. The structural similarity between β-lactam antibiotics and D-alanyl-D-alanine facilitates their binding to the active site of penicillin-binding proteins (PBPs), transpeptidases that facilitate the final step in the synthesis of the peptidoglycan. This irreversible inhibition of the PBPs prevents the final crosslinking of the nascent peptidoglycan layer, disrupting cell wall synthesis.

Unfortunately, many gram-negative bacteria have found a way to resist the effects of β-lactam antibiotics. The most common mechanism of β-lactam resistance is due to enzymatic hydrolysis of the β-lactam ring. If the bacteria produces β-lactamase, the enzymes will break open the β-lactam ring of the antibiotic, rendering the antibiotic ineffective. The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer.


Extended Spectrum β-lactamase Producing (ESBL) Gram negatives

- ESBLs confer resistance to expanded-spectrum cephalosporins (e.g. ceftriaxone, cefotaxime, and ceftazidime), aztreonam, and related oxyimino-beta lactams.

- 1983: First documentation of plasmid-encoded β-lactamases capable of hydrolyzing the extended-spectrum cephalosporins with an oxyimino side chain, collectively termed the extended spectrum beta-lactamases

- Derived from mutations in plasmid-encoded genes for TEM-1, TEM-2, or SHV-1 that extends the spectrum of β-lactam antibiotics susceptible to hydrolysis by these enzymes.

Notes on: Extended Spectrum β-lactamase Producing (ESBL) Gram negatives

Gram negatives commonly express plasmid-encoded β-lactamases (e.g., TEM-1, TEM-2, and SHV-1) which confer resistance to penicillins but not to expanded-spectrum cephalosporins. However, in Germany in 1983, the extended-spectrum β-lactamases (ESBLs) were detected. ESBLs are beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These cephalosporins include cefotaxime, ceftriaxone, and ceftazidime, as well as the oxyimino-monobactam aztreonam. Typically, they derive from genes for TEM-1, TEM-2, or SHV-1 by mutations that alter the amino acid configuration around the active site of these β-lactamases. This extends the spectrum of β-lactam antibiotics susceptible to hydrolysis by these enzymes.

ESBL Clinical Significance

- ESBLs are commonly found in *Klebsiella, E.Coli, Enterobacter, Proteus, Citrobacter, Pseudomonas*.

- Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides)
  - Treatment is limited

- Risk factors
  - Critically ill patients
  - Long hospitalization (median 11-67 d)
  - Invasive medical devices
  - Heavy antibiotic treatment

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Infections due to ESBL *K. pneumoniae*

*Hospital de Bellvitge (1993-1995), 145 Patients*

<table>
<thead>
<tr>
<th>Infections</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>40</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>13</td>
</tr>
<tr>
<td>Ventilator associated pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Tracheobronquitis</td>
<td>8</td>
</tr>
<tr>
<td>Surgical wound infections</td>
<td>28</td>
</tr>
<tr>
<td>Intrabdominal abscesses</td>
<td>23</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>25</td>
</tr>
</tbody>
</table>

Notes on: ESBL Clinical Significance

The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported. ESBL-producing organisms may appear susceptible to some extended-spectrum cephalosporins. However, treatment with such antibiotics has been associated with high failure rates.

Known risk factors for colonization and/or infection with organisms harboring ESBLs include admission to an intensive care unit, recent surgery, instrumentation, prolonged hospital stay and antibiotic exposure, especially to extended-spectrum beta-lactam antibiotics. Use of extended-spectrum antibiotics exerts a selective pressure for emergence of ESBL producing gram negatives. The resistance plasmids can then be transferred to other bacteria of a variety of species.


Yang, K. Diagnosis and Treatment of Extended-Spectrum and AmpC ß-Lactamase-Producing Organisms. The Annals of Pharmacotherapy 2007; 41: 1427-1435

Neisseria gonorrhoeae

- Gram-negative bacteria responsible for the sexually transmitted disease gonorrhea
- Infections are acquired by sexual contact or direct content (in the context of neonates) and usually affect the mucous membranes of the urethra in males and the endocervix and urethra in females
- Symptoms include purulent discharge from the genitals which may be foul smelling and a burning sensation during urination and conjunctivitis in neonates
- Patients with *N. gonorrhoeae* should also be tested for *Chlamydia* infections, since co-infection is frequent

Source: [http://www.textbookofbacteriology.net/neisseria.html](http://www.textbookofbacteriology.net/neisseria.html)
Antimicrobial resistance in *N. gonorrhoeae* occurs as:

- Plasmid-mediated resistance to
  - Penicillin
  - Tetracycline
- Chromosomally mediated resistance to
  - Penicillins
  - Tetracyclines
  - Spectinomycin
  - Fluoroquinolones
- Cephalosporins are the treatment of choice. As a precaution, treatment for Chlamydia is usually included as well.
Salmonella Typhi and Typhoid Fever

- Strain of Salmonella enterica and the cause of the disease typhoid fever
- Transmitted by the fecal-oral route-- excreted by humans in feces and may be transmitted by contaminated water, food, or by person-to-person contact
- Symptoms usually develop 1–3 weeks after exposure; include high fever, malaise, headache, constipation or diarrhea, rose-colored spots on the chest, and enlarged spleen and liver.
- Healthy carrier state may follow acute illness.
- Can be treated with antibiotics-- BUT resistance to common antimicrobials is widespread.
Notes on: *Salmonella Typhi* and Typhoid Fever

Typhoid fever is a bacterial infection of the intestinal tract and bloodstream. Symptoms can be mild or severe and include sustained fever as high as 39°-40° C, malaise, anorexia, headache, constipation or diarrhoea, rose-colored spots on the chest area and enlarged spleen and liver. Most people show symptoms 1-3 weeks after exposure.

Typhoid is caused by the bacteria *S. typhi*. Typhoid germs are passed in the feces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the bacteria. Once the bacteria enter the person’s body they multiply and spread from the intestines, into the bloodstream.

Even after recovery from typhoid, a small number of individuals (called carriers) continue to carry the bacteria. These people can be a source of infection for others. The transmission of typhoid in less-industrialized countries may be due to contaminated food or water. Where water quality is high, and chlorinated water piped into the house is widely available, transmission is more likely to occur via food contaminated by carriers handling food.

- [http://www.cdc.gov/ncidod/dbmd/diseaseinfo/typhoidfever_g.htm](http://www.cdc.gov/ncidod/dbmd/diseaseinfo/typhoidfever_g.htm)
Multi-Drug Resistant *Salmonella Typhi*

- Resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and streptomycin is common-- these agents have not been used as first line treatment now for almost 20 years
- Typhoid that is resistant to these agents is known as multidrug-resistant typhoid (MDR typhoid)
- Ciprofloxacin resistance is an increasing problem, especially in the Indian subcontinent and Southeast Asia

In geographic areas where MDR *S. typhi* is common, the recommended first line treatment is **ciprofloxacin or ceftriaxone**. There is also a **vaccine** available for travelers to these areas.
Multidrug-resistant (MDR) strains of *Salmonella* are encountered frequently and the rates of multidrug-resistance have increased considerably in recent years. Even worse, some variants of *Salmonella* have developed multidrug-resistance as an integral part of the genetic material of the organism, and are therefore likely to retain their drug-resistant genes even when antimicrobial drugs are no longer used, a situation where other resistant strains would typically lose their resistance.

Drug-resistant *Salmonella* emerge in response to antimicrobial usage in food animals. Selective pressure from the use of antimicrobials is a major driving force behind the emergence of resistance, but other factors also need to be taken into consideration.

The fluoroquinolones - ofloxacin and ciprofloxacin, the third generation cephalosporins - ceftriazone and cefixime, and azithromycin, a macrolide antibiotic, are the drugs of choice for MDR typhoid fever. Fluoroquinolones achieve excellent penetration in macrophages and bile, important sites of infection. However, resistance to fluoroquinolones has also developed and represents a significant threat to the treatment of typhoid fever. The presence of ciprofloxacin resistance is a marker for decreased susceptibility to fluoroquinolones and should be tested for when dealing with MDR strains. Switching to ceftriaxone or azithromycin may be preferable in these patients. These agents should be given for at least 7 days.

There are also vaccines that are available for typhoid fever. The oral vaccine (Vivotif) contains a live but weakened strain of *Salmonella typhi*. The single-dose injectable vaccine (Typhim Vi) contains capsular polysaccharide antigen.

Epidemiology of Multi-Drug Resistant *Salmonella Typhi*

With an estimated 16-33 million cases of MDR S. Typhi annually resulting in 500,000 to 600,000 deaths in endemic areas, the World Health Organization identifies typhoid as a serious public health problem. Its incidence is highest in children between 5 and 19 years old.

http://www.who.int/vaccine_research/diseases/diarrhoeal/en/index7.html
Factors affecting the development and spread of resistance

- Rapid urbanization
- Pollution and environmental degradation
- Demographic changes
- AIDS epidemic
- Growth of global trade and travel
- Role of poverty
- Easy access w/o Rx
- Animal feed
- Antibacterial Cleaning Products
- Counterfeit medications

Rapid Urbanization

• Asia and Africa are expected to double their urban populations to roughly 3.4 billion by 2030
• When a population grows beyond its resources, overcrowding and poor hygiene and sanitation result
• Poor hygiene and sanitation increase disease prevalence

• Isolates from *E. coli* strains in urban Nigeria (Lagos) showed significantly more antimicrobial resistance than ones in rural/suburban SW Nigeria
Africa now has 350 million urban dwellers, more than the populations of Canada and the United States combined, and in 2008, for the first time in history, half of the earth’s population will live in urban areas. This rapid urbanization is often not accompanied by a rapid increase in resources, especially in developing countries.

Complicating this situation is the negative impact of poverty, which also plagues many developing country urban dwellers. These factors create settings that encourage the spread of infection. For instance, more than 1/3 of the world’s population lacks access to proper excreta disposal, which is discouraging since proper sanitation has been shown to prevent disease, especially diarrhea, trachoma and intestinal diseases. Improper sewage disposal, on the other hand, encourages AMR transmission and exchange of AMR genes among bacteria. It is not difficult to see why disease and AMR transmit so easily in situations with improper sewage systems, such as the case in Nairobi's slums, where plastic bags, or "floating toilets," are commonly used as containers for excreta disposal and then thrown into the street.

Sources:
Pollution

Fecal contamination of water supply

- Contamination can occur from leaking septic tanks, run-off of manure from fields
- Feces in the water brings human or animal pathogens in contact with potentially resistant bacteria
- This water is used for drinking or irrigation for agriculture

Increased levels of ozone air pollution

- Hastened by warmer temperature
- More micro-organisms enter drinking water from associated increase in rainfall and run-off
- Higher risk for resistance transfer
Notes on: Pollution

Applying manure to crops has the potential for runoff into surrounding water supplies. Antibiotics present in the manure, therefore, also end up in the water. A study of rivers across the US found that 50% of surface water was contaminated with antibiotics. Year-long monitoring of manure runoff from fields showed that small quantities (>5%) of dissolved antibiotics (chlorotetracycline, tylosin, and monensin) were lost through leaching and runoff. This study also concluded that the majority of runoff occurred during the fall. A simple strategy to minimize the runoff is spring manure application instead of fall.

Sources:

Image: feww.wordpress.com
AIDS Epidemic and Demographic Changes

People living with HIV/AIDS (PLWHA), the young, and the elderly have a diminished natural ability to fight off infection.

More immunocompromised patients in a population

Infections are more easily caught and spread

Resistance is more likely to occur and spread
Notes on: AIDS Epidemic and Demographic Changes

The AIDS epidemic is a strong risk factor for the formation of AMR. Because HIV diminishes a body’s ability to fight infections, many PLWHA frequently use antimicrobials prophalactically and to treat infections. Indeed, it is likely that HIV is impacting the state of AMR. An Italian study found that individual exposure to beta-lactams, multiple hospitalizations, and low CD4+ cell number were all independent risk factors for MRSA infections in PLWHA. Since CD4+ cells are used by the body to fight infection, the lower the CD4+ number, the more immunocompromised one is. Notably, once highly active antiretroviral therapy (HAART) usage increased, the prevalence of MRSA bacteraemia in PLWHA decreased, indicating that bolstering a PLWHA’s immune system could correlate with a lower prevalence of AMR infections.

A frequently overlooked social factor that can exacerbate AMR is the effect of a high concentration of very young and old patients in a health care system. Since it is easier for infection to take root in these populations, the effects of the shifting patient population on the spread of infection should be examined.

Sources:


Globalization of Trade and Travel

- Globalization has enabled microbes to travel fast and far, leaving no region unaffected
- AMR is more pronounced in developing countries
  - AMR commensal organisms are often part of the normal gut flora in developing country residents
  - Urban migration, inadequate sewage disposal and overcrowding encourage AMR dissemination
- Most strains of multi-drug resistant typhoid in the US come from 6 developing countries

Direct cargo flights leaving from Vancouver, Canada go to four continents. Source: Vancouver Airport Authority
Notes on: Globalization of Trade and Travel

Globalization requires that efforts be made on an international, coordinated level. National initiatives will be ineffective if neighboring countries do not engage in similar measures. To date, no country has fully implemented the WHO's 2001 Global Strategy for Containment of AMR, with varying levels of commitment in different nations.

In addition to MDR-typhoid in the US, many other instances of resistant infections spreading globally exist. Two examples include MRSA outbreaks in Canada that originated in an Indian village and genetically-identical strains of resistant S. pneumoniae that have been found in Iceland, Europe, and Latin America.

Source:


Sub-clinical doses of antibiotics in animal feed select for resistance microorganisms, including *Campylobacter*, *Salmonella*, *E.coli* and *E. faecium*.

Use of antibiotics in animals creates reservoirs of resistance.

Humans eat meat or poultry contaminated with resistant organisms.

Ingesting AMR bacteria changes the normal intestinal microbiota.

Potentially acquisition of a resistant infection.

**ANTIBIOTIC RESISTANCE**
Aquaculture

• Similar to antibiotics in animal feed, antibiotics are frequently given to prevent infection in aquaculture, commercial farms of seafood.

• Mechanisms that spread antibiotic resistant organisms:
  – Transporting fish and consequently the antibiotic bacteria they carry between environments
  – Uneaten fish food and fish faeces, both containing antibiotics, settle with the natural sediment at the bottom of the pen; antibiotics leach from the sediment and travel to distant sites
  – Contamination of fisheries with untreated sewage containing normal intestinal flora and pathogens
**Antibacterial Cleaning Products**

- Antibacterial soaps commonly contain triclosan
  - Have not shown any added infection protection
  - Effect on resistance is unknown

- Antibacterial cleaning products commonly contain quaternary ammonium products
  - Have been used for decades
  - Households with high use have shown increased resistance

- More research is needed on these compounds: it is likely that common usage encourages AMR
Notes on: Antibacterial Cleaning Products

Antibacterial soaps containing the common ingredients triclosan or trilocarban have not been shown to offer any added infection protection and their effects on resistance are unknown. Their potential harm should be further researched: although no increase in AMR was shown in three community settings, these soaps increased *in vitro* resistance in ten of eleven studies.

The usage of antibacterial cleaning products containing quaternary ammonium compounds, such as benzalkonium chloride, has also correlated with increased resistance. Little literature on this subject exists, however, and more is needed to definitively determine the impact on resistance.

Image source:
http://www.flickr.com/photos/pbouchard/2807076457/

Sources:

Over-the-counter access to pharmaceuticals

• In many developing countries, antibiotics are readily available from hospitals, pharmacies, patent medicine stalls, roadside stalls and hawkers.

• Common issues with OTC drugs that contribute to AMR:
  – Substandard quality
  – Sub-therapeutic doses
  – Improper self-medication

• Internet/mail-order pharmacies present a new, easy way to obtain OTC antibiotics
  – Few regulations monitor internet drug sales
  – Difficult to impose restrictions on the sale of these drugs given the nature of the internet and international sales
Counterfeit and Substandard Medicines

- Antimicrobials appear to be the most counterfeited product in developing countries
  - TB, malaria, and HIV drugs are the most common
  - 'Old' antibiotics are also targeted: penicillin, tetracycline, cotrimoxazole, chloramphenicol
- 20-90% of antimalarials were found to be counterfeit in a WHO survey of 7 African nations
- Many laws in developing countries are ineffective, which more easily enable the sale of counterfeit drugs
- Many storage and transport conditions in developing countries lead to the degradation of medication and a loss of efficacy

While it seems logical that a high prevalence of sub-therapeutic medications will increase the selective pressure for resistance to form, and thus add to the problem of AMR, evidence proving this series of events is lacking. The lack of studies examining this link should not be mistaken for a lack of causation, however. Several studies do cite cases of resistance likely hastened by a high presence of substandard medications. For instance, Kelesidis et al. concludes that the high prevalence of substandard chloramphenicol and co-trimoxazole in Burma could have contributed to the high rate of typhoid antibiotic resistance in the region. The lack of direct evidence speaks to the need for further studies on the extent of the effects of counterfeit and substandard drugs on AMR.

Sources:
Poverty impairs infection prevention and control

**FACTORS THAT CHALLENGE INFECTION PREVENTION:**
- Decreased caloric and nutrient intake
- Poor hygiene and sanitation
- Crowded conditions

**FACTORS THAT CHALLENGE INFECTION CONTROL:**
- Inaccessible health facilities
- Inaccessible drugs
- Lack of education about antimicrobials
- Lack of money to buy full courses of drugs

*The more infections, the more chances that AMR can emerge and spread*
Notes on: Poverty

These co-factors affect infection prevention and control in the following ways:

- **Malnutrition** and **starvation** affect the body’s natural ability to fight infection.
- **Poor hygiene and sanitation** significantly increase the risk of infection (see Rapid Urbanization slide).

**Crowded conditions** that outgrow resources can lead to poor sanitation and increase the probability of coming in contact with infections due to increased close contact with others. **Inaccessible health facilities** decrease one’s ability to get an accurate diagnosis and treat their infection. In developing countries rural communities are especially affected, like in Uganda where only 49% of the population lives within 5 km of a health care facility.

When **drugs are inaccessible**, infection is allowed to continue and spread.

Having **insufficient funds** to buy drugs can lead to the sharing of prescriptions among families or not buying the full course of antimicrobials, and both of these actions can increase AMR.

Sources:

Global Action Areas for Containing AMR

Adapted from WHO, Alliance for Patient Safety, departmental report, 2007
## What Can We Do?

### INDIVIDUALS
- Personal hygiene
- Educate others about the problem

### DOCTORS
- Judicious use of drugs
- Educate patients about the proper use of antibiotics
- Collect more data on the extent of resistance

### HOSPITALS
- Improve hospital infection control
- Enforce regulations by patient safety oversight committees

### GOVERNMENTS
- Increase worldwide access to the appropriate drugs
- Revive R&D on antibiotic innovation
- Revive innovation of rapid diagnostic technologies
- Revive R&D for vaccines that target AMR organisms

Adapted from WHO, Alliance for Patient Safety, departmental report, 2007
Quiz

• We regret that this website cannot accommodate the 24-question quiz that was developed for this module. In time we hope it will be possible to include the quiz.
Credits

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Antibiotic Defense
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Notes on *S. pneumoniae*

Fortunately, most resistance of pneumococci to beta-lactams--which is the most common form of resistance--can be overcome by simply increasing the dose. Unfortunately, meningitis caused by *S. pneumoniae* does not, and so all meningitis is treated urgently with vancomycin.

That said, resistance among *S. pneumoniae* is common and widespread. Some resistance is seen to many of the main classes of antibiotics: penicillins, macrolides, tetracyclines, fluoroquinolones, etc. Each of these has a distinct mechanism of resistance. Pencillins show decreased binding to the peptidyl transferase molecules in the bacterial cell wall, whereas macrolide resistance relates to the presence of either the *erm(B)* gene, which prevents macrolide binding through methylation of the 23S rRNA subunit, or the *mef(A)*, which encodes an efflux pump that ejects the drug from the cell. The *erm(B)* gene also conveys resistance to clindamycin, which operates in a similar manner to macrolides.

Globally, the threat of *S. pneumoniae* can be greatly reduced by vaccinated children with the multivalent pneumococcal vaccine. This vaccine contains the 7 most common serotypes: 4 6B, 9V, 14, 18C, 19F, 23F, although many developing countries harbor a varying cast of serotypes and require a modified combination. Employment of this vaccine has led to a 30-50% reduction in penicillin-resistant isolates. However, the vaccine is also selecting for other resistant serotypes of *S. pneumoniae*, such as 19A. That said, these remain a minor fraction of the total *S. pneumoniae* infections seen.

Image: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5706a2.htm

Sources:


Shortridge VD, Doern GV, Brueggemann AB, Beyer JM, Flamm RK. Prevalence of macrolide


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Notes on: Methicillin-resistant *S. Aureus* (MRSA)

Perhaps the most epidemiologically important of all the antibiotic-resistant bacteria. With up to 40-60% of *S. aureus* carriers having a form resistant to penicillins (depending on the country), it medical problem of truly global proportions. In the U.S. alone, there are an estimated 90,000 cases of invasive *S. aureus* a year, contributing to the cause of death in an estimated 18,000 people. In fact, nearly 7% of patients coming into the hospital test positive for MRSA on admission--with the anterior nares being the most common site for MRSA inhabitance. This raises the point of community-acquired MRSA with hospital-acquired MRSA. In contrast to earlier years, in which clinical distinction was made between these diseases, they are now consider to be one and the same. While they may differ in exposure and etiology, they are the same clinical disease, and may present in the same fashion--most often as small, red skin lesions that progress to ulceration. Moreover, they are defined by the same criteria: namely, the *S. aureus* strain must have an oxacillin minimum inhibitory concentration of greater than or equal to 4 mcg/mL. Nevertheless, differing local resistance patterns continues to cause problems with MRSA. Examples of localized resistance have lead to reports to quinalone resistance in MRSA from inpatients when outpatients display quinalone-sensitivity. Such examples demonstrate the complexity of antibiotic resistance patterns (especially when considered on a national and international scale).

Sources:

Notes on: MRSA (1)

The genetics behind MRSA have been well studied. All MRSA isolates have a mobile chromosomal element called the staphylococcal cassette chromosome, which contains the mec gene. The mec gene contains the structural component, mecA, and two regulatory components, the beta-lactamase genes and the negative regulators of mecA transcription. There are actually several different forms of the regulators and beta-lactamases, which correlate somewhat with CA-MRSA vs HA-MRSA, but these differences have only nominal impact on MRSA as a clinical entity. While these regulatory genes do contribute to MRSA virulence--indeed, the beta-lactamase genes assist in cleaving the functional component of penicillins, it is the mecA gene that is most prominent. It encodes penicillin binding protein 2a (PBP2a). The penicillin binding proteins are peptidase enzymes in the bacterial membrane. Typically, these catalyze cell wall synthesis, and it is these molecules that penicillin will bind in order to disarm bacteria. However, PBP2a has low affinity for penicillins, allowing \textit{S. aureus} isolates with the mecA gene to gain penicillin resistance.

The degrees of MRSA resistance are defined as the homogenous, heterogenous, and borderline phenotypes. Borderline is exactly what it sounds like: \textit{S. aureus} isolates that have very mild resistance (oxacillin MIC of 4-8 mg/mL). Heterogenous and homogenous phenotypes refer to the fem genes, which also function to disrupt cell wall synthesis. Isolates that are homogenous for the fem genes tend to have the greatest level of resistance, whereas heterogenous isolates are less resistant.

Sources:


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Notes on: MRSA (2)

As previously mentioned, over 6% of patients have MRSA isolates already upon admission. In the hospital, that risk only increases. In fact, the percent of patients with MRSA isolates may double to a full 12%—with 10 - 30% of these patients likely to develop an MRSA infection—especially if these patients qualify as having several different risk factors. Risk factors include antibiotic usage in the last 3 months, hospitalization in the past 12 months, diagnosis of skin or soft tissue infections on presentation (which is often the first sign of MRSA), or a known HIV infection. By contrast, less than 2% of patients who lack these risk factors will test positive for MRSA isolates.

With such prominence in the healthcare system, MRSA treatment is crucial. Medically, vancomycin is the drug of choice, although linezolid or daptomycin may be used if vancomycin is not an option. Otherwise, the most important precautions are astounding simple, and really ought to be a part of all clinical care. Most importantly, hand washing: HA-MRSA has been proven to be directly related to the hand hygiene of medical professionals. In addition, minimizing patient contact, wearing a gown and gloves, and other similar common-sense measures are critical. Using these standards, the incidence of HA-MRSA can be reduced by up to 50%.

Sources:


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Notes on: VISA/VRSA (1)

Recently, newer, more deadly forms of *S. aureus* infections have been surfacing around the world. Termed vancomycin-intermediate and vancomycin-resistant, these bacteria are frequently also methicillin-resistant, as vancomycin resistance is often discovered when MRSA isolates are unresponsive to vancomycin. VISA and VRSA associated with rapid death, with nearly 100% mortality occurring within 6 months of infection, although death in these cases can not be attributed to *S. aureus* alone. As with MRSA, vancomycin resistance is determined by evaluating the responsiveness of a strain to increasing concentrations of vancomycin. In certain cases, colonies of vancomycin-sensitive *S. aureus* may contain subpopulations of resistant *S. aureus*, a phenomenon termed “heteroresistance”. Heteroresistant isolates should be considered vancomycin-resistant for treatment purposes.

Vancomycin resistance in *S. aureus* is thought to have originated from horizontal gene transfer of the vanA resistance cluster from Vancomycin-Resistant enterococci to MRSA. In 1992, scientists showed that, in fact, conjugal transfer of the vanA gene cluster from VRE to MRSA could create VRSA in laboratory mice.

Thankfully, vancomycin resistance is exceedingly rare, with only a handful of cases reported. In fact, only 0.3% of *S. aureus* isolates demonstrate vancomycin resistance, with only some of these displaying total vancomycin resistance. From 2002-2006, only 7 cases of VRSA were recorded in the US, most of which occurred in patients with a previous history of vancomycin exposure as well as MRSA or VRE colonization.

Sources:


Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. *J Antimicrob*
Notes on: VISA/VRSA (2)

As with MRSA, the genetics behind vancomycin resistance have been well studied. VRSA, like MRSA, contains a prominent gene cluster--known as vanA--that is not active in normal S. aureus isolates. vanA is harbored in a mobile genetic element originally found in vancomycin-resistant enterococci (VRE). This mobile genetic element finds its way to S. aureus via a plasmid-mediated transfer from VRE. Once inside the S. aureus bacteria, vanA encodes for an alternative cell wall dipeptide composed of D-ala D-lac, rather than the normal D-ala D-ala. This D-ala D-lac dipeptide prevents vancomycin from binding to S. aureus, thereby granting the bacteria resistance.

It would be logical to think that VISA shared a similar mechanism of resistance. Interestingly, it does not. VISA, in fact, has a resistance signature distinct from not only VRSA but also MRSA and VRE as well. Whereas the other three contain a vanA gene, VISA does not. Rather, VISA resistance is not well understood, but it seems to rely on increased synthesis of normal D-ala D-ala dipeptides, resulting in an abnormally thickened cell wall. This increased synthesis may be due to a polymorphism in the accessory gene regulator, agr, but this is not universal among VISA isolates.

Given that vancomycin is one of the most powerful antibiotics at our disposal, the question of treatment for VISA/VRSA is still a great debate. Unfortunately, there is no easy treatment, and no existing treatment has been particularly effective. Chloramphenicol, rifampin, TMX-SMX, and ciprofloxacin, among many other options, have been tried with varying degrees of success.

Sources:


Notes on: *Neisseria gonorrhoeae*

The family *Neisseriaceae* consists of Gram-negative aerobic bacteria from fourteen genera, including *Neisseria, Chromobacterium, Kingella*, and *Aquaspirillum*. The genus *Neisseria* contains two important human pathogens, *N. gonorrhoeae* and *N. meningitidis*. *N. gonorrhoeae* causes gonorrhea, an infection with a high prevalence and low mortality.

The disease gonorrhea is a specific type of urethritis that practically always involves mucous membranes of the urethra, resulting in a copious discharge of pus, more apparent in the male than in the female. Gonorrheal infection is generally limited to superficial mucosal surfaces lined with columnar epithelium. The areas most frequently involved are the urethra, cervix, rectum, pharynx, and conjunctiva.

Uncomplicated gonorrhea in the adult male is an inflammatory and pyogenic infection of the mucous membranes of the anterior urethra. The most common symptom is a discharge that may range from a scanty, clear or cloudy fluid to one that is copious and purulent. Dysuria (difficulty in urination) is often present. Inflammation of the urethral tissues results in the characteristic redness, swelling, heat, and pain in the region. There is intense burning and pain upon urination.

Endocervical infection is the most common form of uncomplicated gonorrhea in women. Such infections are usually characterized by vaginal discharge and sometimes by dysuria. About 50% of women with cervical infections are asymptomatic. Asymptomatic infections occur in males, as well. Males with asymptomatic urethritis are an important reservoir for transmission and are at increased risk for developing complications. Asymptomatic males and females are a major problem as unrecognized carriers of the disease, which occurs in the U.S. at an estimated rate of over one million cases per year.

Ocular infections by *N. gonorrhoeae* can have serious consequences of corneal scarring or perforation. Ocular infections (ophthalmia neonatorum) occur most commonly in newborns who are exposed to infected secretions in the birth canal. Part of the intent in adding silver nitrate or an antibiotic to the eyes of the newborn is to prevent ocular infection by *N. gonorrhoeae*.

http://www.cdc.gov/std/gonorrhea/arg/


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Notes on: *Resistance in Neisseria gonorrhoeae*

*N. Gonorrhoeae*, originally highly susceptible to antibiotics can adapt to adverse conditions. A hostile environment in which antibiotics are present may select for the multiple changes which result in resistance and treatment failure.

Mechanisms of antibiotic resistance in *N. Gonorrhoeae* may be conveniently grouped as those that involve reduced access of the antibiotic to the target site and those that involve alteration of the target site itself. Access of antibiotics to the target site may be limited by: reduced permeability of the cell envelope caused by changes in porin proteins; active export of antibiotics from the cell by means of efflux pumps; and destruction of the antibiotic before it can interact with the target. Alteration or deletion of the target site of the antibiotic results in a reduction of its affinity for the antibiotic.

Genetically, these changes may be mediated by either chromosomal or extra-chromosomal elements (plasmids). Multiple resistance determinants may coexist in a single organism so that the level of resistance can increase incrementally and a single strain can be resistant to a number of different antibiotics. In gonococci, chromosomally mediated resistance is generally slow to emerge and disseminate. While genetic transformation, the mechanism of acquisition of these determinants, is common in *N. gonorrhoeae*, clinically relevant resistance requires multiple gene transfers. Plasmid-mediated resistance, at present limited to penicillins and tetracyclines, is transmitted by means of conjugation. This process requires the presence of a conjugative plasmid to mobilize the plasmid carrying the resistance determinants. Since not all strains possess conjugative plasmids, the rate of spread of resistance may be limited to some extent. However, conjugative plasmids are also transferable during conjugation, so that some recipient strains then become donors themselves. Different rates of dissemination of extrachromosomally mediated resistance have thus been observed.


http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5316a1.htm


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Notes on: Animal Husbandry

To prevent infection in animals, many farms add antibiotics to animal feed at sub-clinical doses, selecting for resistat bacteria. Once bacteria are resistant, they have the potential of spreading this resistant to a variety of other bacteria living in a diverse range of environments, including the human digestive tract. When an individual ingests exogenous bacteria containing AMR genes, AMR genes transfer to bacteria that comprise the microbiota of the intestine and to other foreign microorganisms with which it comes in contact.

A study showed the transfer of vanA resistance gene (VRE) from \textit{E. faecium} strain of animal origin to an \textit{E. faecium} strain of human origin in the human intestine. Since no selective antimicrobial pressure was applied during the study, colonization with resistant bacteria was transient. However, it is reasonable to assume that if a selective pressure of antimicrobials is introduced, colonization with resistant bacteria would have persisted. Since enterococci are typically found in meat and milk products ranging from 10^2 to 10^5 per gram (30), the potential AMR transfer is high. This poses increased risk for immunocompromised patients, who are more susceptible (22).

Fortunately, studies show that removing antimicrobials from animal feed decreases the rate of antimicrobial resistance. Denmark, like the rest of Europe, has banned the use of certain growth promoting antimicrobials, avoparcin in 1995, virginiamycin in 1998 and in 1999 producers voluntarily stopped the use of all antimicrobial growth promoters. Because the Danish surveillance system is well-developed, many trends seen around the EU have been quantified by the Danish. After stopping the use of antimicrobial growth promoters, there has been a decrease in the amount of resistance to all antibiotics. For instance, the erythromycin resistant \textit{E. faecium} reached a peak among broilers in 1997 at 76.3%. However, after restricting use of virginiamycin, resistance decreased to 12.7% in 2000 (27). Similar resistance trends are seen for vancomycin and avilamycin. Similar results have been seen throughout Europe; resistance prevalence has declined rapidly following the removal of growth promoters in pigs and chickens, suggesting that in the absence of selective pressure, a susceptible population begins to replace resistant strains (26).

Extensive guidelines in this area have been made in the past year by a joint commission of the FAO/WHO/OIE. The interventions that the commission recommends are continued monitoring of AMR in foodborne pathogens as well as risk management measures, including the use of guidelines, vaccinations policies, and development of alternative treatments. Other possible interventions consist of standardizing international methods, namely the MIC, frequently updating risk assessments, and employing resources to help developing countries contain and monitor AMR.

Sources:


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Notes on: Aquaculture

In the past 20 years, industrial aquaculture has quadrupled in size, and a faster rate of growth in the industry has been predicted for the future. However, responsible practices in aquaculture have not evolved like the industry itself. Developing countries around the globe currently use prophylactic antibiotics indiscriminately, selecting for not only resistant fish pathogens but human pathogens, as well.

The main concern with prophylactic antibiotics in aquaculture is the spread of resistance from fish pathogens to human pathogens. Several cases have been well documented, strongly suggesting that this transfer has taken place. The drug-resistant outbreaks of Salmonella enterica serotype Typhimurium DT104 in the United States and Europe was traced to the Far East (Angulo). The plasmid in Salmonella enterica contained genes for tetracycline and fluoroquinolone resistance, which were traced to the fish pathogens Vibrio damsela and Vibrio anduillarum. Not an isolated case, other fish pathogens have been shown to transfer resistance to human pathogens, as well. Aeromonas salmonicida through the plasmid IncU, containing resistance to sulfonamides, trimethoprim, and tetracycline, have transferred resistance to the human pathogens around the globe, including Aeromonas hydrophila, Aeromonas caviae and E. coli (Rhodes). The use of antibiotics in aquaculture increase rates of AMR in human pathogens, posing a threat to our current treatment of human infections.

Several techniques have been suggested to decrease the dependence on antimicrobial agents, including vaccines and improved water sanitation. Vaccines exist for more than 15 fish pathogens. Vaccines are not a substantial upfront cost, and the economic impact of the vaccine favors the investment, to the extent that only a marginal improvement in survival is necessary to pay for the investment of the vaccine. When choosing between vaccines, minor differences in the overall vaccine efficacy produce substantially greater profits (Ragnar). Sanitation measures aim to eliminate or reduce the number of fish pathogens present in the water. Current techniques include UV light radiation, chemicals such as hypochlorous acid and ozone. Furthermore, new technologies continue to be developed to improve the quality and sanitation of industry water in economical manners.

Sources:


Notes on: Over-the-counter access to pharmaceuticals

In many situations legal and illegal over-the-counter access to antimicrobials leads to injudicious drug use. Often antimicrobials are frequently obtained without the guidance of a physician or other knowledgeable prescriber in developing countries. This may cause consumers to erroneously determine their need for antimicrobials, as well as the optimal dose and length of treatment. Even if they seek outside advice on using antimicrobials for their symptoms, like from a pharmacist or untrained drug seller, this information can easily be inaccurate.

Inappropriate over-the-counter drug use is not restricted to indigent people in developing countries. Larson and Grullon-Figueroa found that in Manhattan, New York, 34 of 34 pharmacies in a Hispanic neighbourhood sold OTC antibiotics, even though antibiotic sales require a prescription in the US. Additionally, antibiotics for fish, which have the same active ingredients as the ones that humans use, are widely sold OTC in pet stores across the US. Recently, a new method of drug acquisition has been created through internet pharmacies. While some online pharmacies obey the laws of their place of residence, many do not. Online pharmacies are capable of selling substandard or counterfeit drugs, as well as good quality drugs for which the consumer has no legitimate use for. Effective regulation of these pharmacies is still a new and relatively untested field. Some interventions, such as a seal of pharmaceutical quality issued by the national pharmaceutical licensing board, are in progress and provide consumers with a stronger security that they will receive quality medications. In general, though, internet pharmacies will be difficult to effectively regulate due to their non-physical nature and international reach.

Sources:


Notes on: Global Action Areas for Containing AMR

Currently, there is a lack of data on AMR. An international coalition of stakeholders (policy makers, epidemiologists and economists) -- already begun at WHO -- should assemble to outline a strategy to collect national surveillance data, collect national and global burden of disease data, and national and global economic burden data.

A paradigm shift is needed in how we view antibiotics. The working group should develop a strategy:

- that builds public perception of antibiotic effectiveness as a natural resource and global public good
- that changes the public's perception of antibiotics from "magic bullets" or "miracle drugs" to dangerous blunt instruments with indiscriminate targets like healthy bowel flora
- that emphasizes rather than war, disarmament, equilibrium, and coexistence with bacteria

Major contributors to the irrational use of antibiotics are doctors, the public, and industry. The working group should utilize the WHO Rational Drug Use strategy to revive new actions:

- that encourages doctors to use antibiotics responsibly, including behavior modification surrounding administration of broad spectrum and prophylactic antibiotics
- that educates the public about the dangers of indiscriminate antibiotic use, over the counter use, and animal use
- that eliminates direct-to-consumer marketing in nations that currently allow it

There is a lack of new technologies to rapidly diagnose resistant infections. (see pg.14) The working group should develop a strategy:

- that encourages governments to provide incentives for industry to develop rapid diagnostic technologies
- that creates incentives for doctors to fine tune prescription habits to narrower spectrum regimens

The antibiotic pipeline has dried up (see pg.14). The working group should develop a strategy:

- that helps governments to treat antibiotics as a natural resource, like oil, fisheries, and
clean water

- that encourages governments to pull antibiotics out of the private sector and into the public domain

- that encourages governments to provide incentives for industry to revive R&D on antibiotic vaccines and new antibiotic drugs

- that encourages innovative infection control practices