Antibiotic Resistance
End of Antibiotic Era
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Recent Consultation

- 56 y nurse works in VA seen for urinary tract complaints
- Started in January and went to Loyola University where she was treated for UTI with ciprofloxacin and then underwent cystoscopy in February.
- Recurrent symptoms and saw her primary care in May and started on Cipro again with pan sensitive E. Coli
- 3 More courses with Cipro, Bactrim and Urinary antiseptic
- Latest urine culture in June 26 with CRE Klebsiella only sensitive to gentamicin

NDM-1
Nightmare Bacterium

Antibiotic Era’s

- Fleming 1928 discovered Penicillin
- 1940’s widespread use and resistance
- 1960’s- Methicillin introduced- Soon MRSA followed in Boston city hospitals
- 1980’s- Gram Negative Era
- 1990’s- Return of Blue Bugs-VRE/MRSA/VRSA
- 2000- Fungi, and Gram negative Bacteria
- 2010- Pan resistance becomes wide spread. End of Antibiotics
Complex Interactions of Microbes

- Microbes have acquired resistance genes for Eons
- Kluyvera and Shewanella isolates found in environment have CTX-M β-Lactamase and qnr genes respectively
- Fosberg et al. Science 2012 Showed by using a new technique PARFuMS, exchange of resistance to proteobacteria in soil to all 12 antibiotic classes that were tested
- Soil is the natural habitat for Actinomycete genus and Streptomycetes which account for majority of all naturally produced antibiotics

Soil and Microbes

- Soil resistome is an important reservoir for exchange of resistance genes
- Nosocomial resistance infections with Acinetobacter is an example
- Ochrobactrum and Pseudomonas isolates originating from farmland soils have resistome cassettes which are mobile and transferable
- One lineage of Staphylococcus aureus (STS) spread from human to poultry and another (CC398) to pigs. Hundred others are shared between livestock and humans

Pathways to Resistance
Antibiotic and animal weight

<table>
<thead>
<tr>
<th>Week</th>
<th>Animal Weight Increase (kg)</th>
<th>Protein (grams) Increase</th>
<th>Fat (grams) Increase</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.001 (1)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>1</td>
<td>0.012 (2)</td>
<td>0.012</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>2</td>
<td>0.010 (1)</td>
<td>0.010</td>
<td>0.010</td>
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<tr>
<td>3</td>
<td>0.007 (1)</td>
<td>0.007</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>4</td>
<td>0.008 (1)</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Antimicrobials in Animals

- First used in 1946 for bovine mastitis – penicillin
- Moore et al 1946 reported increase in weight of chicks when streptomycin was added to feed
- 1949- Stokstad reported use of chlortetracycline and increase in weight and decrease in need for feed for chicks
- Later applied to swine and Bovine animals
- Resistance occurred quickly to all these classes approaching 94% of E. Coli with tetracycline resistance

Antibiotics and Animals

- Activity against gram positive flora seems important
- Antibiotics used prophylactically to prevent “shipping fever” caused by pasturella Multocida or hemolytica has a ROI of 3 times
- Emergence of VRE and resistant strains PRIOR to release of antibiotics for human use- Avoparcin in animal feed
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Is Mo betta?

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Too little too late

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What Is MRSA?

- MRSA = "Methicillin Resistant Staphylococcus aureus"
- Is a bacteria that is resistant to a synthetic penicillin, methicillin.
- MRSA causes a variety of disseminated, lethal infections in humans.
- Has the ability to easily transfer resistant genes to other species directly and indirectly.
- Overuse of antibiotics imposes selective pressures which mediates the acquisition of resistance.
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Common Mechanisms of Resistance in Methicillin-Resistant S. aureus

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Original Article
Methicillin-Resistant S. aureus Infections among Patients in the Emergency Department
Gregory J. Moran, M.D., Anusha Krishnadasan, Ph.D., Rachel J. Gorwitz, M.D., M.P.H., Gregory E. Fosheim, M.P.H., Linda K. McDougal, M.S., Roberta B. Carey, Ph.D., David A. Talan, M.D., for the EMERGEncy ID Net Study Group

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Study Overview
• The rapid emergence of methicillin-resistant S. aureus (MRSA) as a community pathogen threatens to change the practice of outpatient medicine
• In this report, investigators from emergency departments in 11 cities throughout the United States show that S. aureus accounts for 76 percent of culturable skin and soft-tissue infections, of which 59 percent are MRSA
**Conclusion**

- MRSA is the most common identifiable cause of skin and soft-tissue infections among patients presenting to emergency departments in 11 U.S. cities.
- When antimicrobial therapy is indicated for the treatment of skin and soft-tissue infections, clinicians should consider obtaining cultures and modifying empirical therapy to provide MRSA coverage.

**VRE-The Cockroach of bacteria**

*Vancomycin-resistant enterococci*

Enterococci is a bacteria. It is present in intestines and female genital tract normally and can live without causing harm.

When the bacteria seeds elsewhere, it can cause infections including urinary tract, blood, and wound infections.

**Characteristics of phenotypes of glycopeptide-resistant enterococci in the majority of reported isolates.**

How is VRE spread?

VRE is usually passed to others by direct contact with stool, urine or blood containing VRE. It can also be spread indirectly via the hands or on contaminated environmental surfaces. VRE usually is not spread through casual contact such as touching or hugging. VRE is not spread through the air by coughing or sneezing.

The Inanimate Environment Can Facilitate Transmission

Contaminated surfaces increase cross-transmission.


People at increased Risk

Individuals who have been treated in the past with vancomycin and combinations of other antibiotics.

People in hospitals, esp. on antibiotics for long durations.

People with weak immune systems or who have had surgical procedures.

People with indwelling percutaneous medical devices and catheters.
### Survival of Pathogens

**On Environmental Surfaces**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>&gt;5 months</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>7 months</td>
</tr>
<tr>
<td>VRE</td>
<td>4 months</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>5 months</td>
</tr>
<tr>
<td>Norovirus</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>3 months</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3 months</td>
</tr>
<tr>
<td>SARS, HIV etc.</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>

### Treatment

Most VRE infections can be treated with antibiotics other than vancomycin. The treatment of VRE is determined by laboratory testing to determine which antibiotics are effective.

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

### Antibiotics as a Paradigm

- Microbiome is dynamic and disturbances occur due to many factors - example personal oral hygiene
- 1-3% of people in developed world are on antibiotics
- Unintended consequences include selection of resistance; killing of flora which is not intended target.
- Most microbiota return to normal taxa within several weeks but resistant strains persisted
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Antibiotics and Microbiota

- C. Difficile bloom due to loss of ecological niche
- Short courses of antibiotics result in rapid recovery of flora
- Repeated courses and extended courses of antibiotics result in a longer period of reassembly via filtering of existing population.
- Microbiome is highly vulnerable to invasion by pathogens at this time

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Clostridium Difficile

- Spore-forming bacteria - resists drying and most agents except bleach solution when in spore form
- Causes colitis and is a major source of morbidity and mortality in hospitalized and ill patients
- Antibiotic use predisposes for infection due to disruption of bowel microbiota
- Environment as well as hands are major modes of transmission

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Clostridium difficile

- Spore-forming, anaerobic, gram-positive bacterium
- Causes gastrointestinal infections resulting in diarrhea and colitis
  - Severity ranges from mild colitis to toxic megacolon and death
- Leading cause of healthcare-associated infectious diarrhea in US
- Rivals methicillin-resistant Staphylococcus aureus (MRSA) as the most common organism to cause healthcare-associated infections in US

CDC. Fact Sheet, August 2004 (updated 7/22/05).
CDI Epidemiology

- Incidence of CDI appears to be increasing in the US

Healthcare Cost and Utilization Project (HCUP).

138,954
348,950

CDI Pathophysiology

- Primary virulence factors:
  - Toxin A (TcdA)
  - Toxin B (TcdB)
  - Toxins A and B are potent cytotoxic enzymes that damage the human colonic mucosa
  - Binary toxin (CDT) was previously identified in ~6% of C. difficile isolates, but is present in all isolates of the hypervirulent strain
  - May potentiate toxicity of TcdA and TcdB and lead to more severe disease


Pathogenesis of CDI

Risk Factors for Initial CDI

- Classic risk factors:
  - Antibiotic therapy
  - Advanced age
  - Prolonged stay in healthcare facility
  - High severity of illness
- Additional risk factors:
  - Inflammatory bowel disease
  - Gastrointestinal surgery
  - Gastric acid suppression (PPIs)
  - Immunosuppression

Elderly

- Risk related to transmission of C. difficile spores
  - Primary source from healthcare workers
    - Staff may carry C. difficile spores on their hands (not likely fecal carriers)
  - Environmental contamination important secondary source
  - Up to 50% of LTCF residents and 40% of hospitalized patients have been found to be colonized with C. difficile or its toxin
  - Infection control and prevention strategies (e.g., hand hygiene, isolation precautions) can reduce this risk

References:
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Clostridium Difficile

- Now with NAP-1 strain
- Hyper producer of toxin and associated with higher mortality
- Treatment is with metronidazole/oral vancomycin
- Stool transplantation or fecal microbiota transplant- Dr. Hines is the expert
- Prevention is key. Short courses of antibiotics and only when needed

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Mechanisms of Resistance in Gram-Negative Bacteria, and the Antibiotics Affected


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Carbapenemases- What are they?

- Large diverse family of microbial enzymes which hydrolyze Carbapenems and frequently other β-lactamases with the exception on occasion of Aztreonam
- Classified- function or Structure
- Ambler Classification- structure A, B or D
- A and D are serine Carbapenemases with serine at active site like ESBL's and B is a Metallo-β-lactamase with zinc as cofactor
Klebsiella Pneumonia Carbapenemase (KPC) - Why Should we care?

- Now called CRE (Carbapenemase Producing Enterobacteriaceae)
- Class A
- First isolated in 1996 in US
- ST-258 accounts for 70%
- Now found throughout the globe
- Linked to intercontinental travel

CRE

- Further Classified basis of single amino acid substitutions – KPC1 thru 10
- Widely disseminated in other enteric organisms including E. Coli, Enterobacter species, Serratia, Morganella Citrobacter, Salmonella and Non Fermenters such as Pseudomonas.
- KPC genes - Transposon Tn 4401 - Facilitates transfer between plasmids and across bacterial species.

Tn4401

- TEM and SHV class ESBL have been detected with Tn4401
- KPC producers carry multiple additional B Lactamases
- Tn4401 associated with genes conferring resistant to non B lactams such as plasmid mediated resistance to aminoglycosides and quinolones
Perfect Storm

- New resistance to Tigecycline and Colistin
- Increased mortality vs. Non KPC Klebsiella 48% vs. 26%
- No New antibiotics in pipeline for next 10 years to treat this class

(Patel G et al. Outcomes of Carbapenems-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 2008; 29)

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study - Lancet - Kumarsamy et al.

- NDM-1: Described an outbreak of Enterobacteriaceae with Metallo-
  β-lactamase resistant to all classes of antibiotics except Colistin and monobactams from 2003-2009 from India, Pakistan, U.K, and Bangladesh
- Plasmid mediated conferring resistance to many species
- Clonal outbreak in Haryana

NDM-1

- Non Clonal in Chennai and elsewhere
- Importation to UK from patients from Indian subcontinent
- Many cases in India were community acquired
- Typing did not identify common strains between UK and Indian Subcontinent
- Netherlands starts screening all patients from Indian subcontinent for KPC- colonization detected without contact with healthcare facility from returned traveler
End of Antibiotic Era

- Plasmids are diverse and confer resistance to all classes of antibiotics.
- More than 1 type of plasmid carries blaNDM-1
- Community antibiotic pressure by unregulated antibiotic prescriptions may be a factor
- Average age of patient in India was 36
- Found throughout India
- Infection Control only proven method to control spread
Renewed Respect for Role of the Environment: Who’s Been in the Room Before or With You?

- Huang SS (2006); Drees M (2008); Zhou Q (2008); Moore C (2008); Hamel M (2010)

- All documented increased risk of acquisition of VRE, MRSA, &/or CDI when admitted to room where prior occupant had one of these or if in multi-occupancy room

- So what’s the answer?

CDC Perspectives on MDROs & Environmental Surfaces

- MDROs, e.g. VRE and MRSA, are no more resistant to inactivation by recommended use dilution of EPA-registered disinfectants than susceptible organisms.

- “The use of stronger solutions of disinfectants for inactivation of either VRE, MRSA, or VISA is not recommended based on the organisms’ resistance to antibiotics.”

- Key Message: Resistance to Antibiotics Does Not Mean Resistance to Disinfectants

- Do not conduct random, undirected microbiologic sampling of air, water, and environmental surfaces in health care facilities

Strategies to combat resistance

- Prevent transmission- Proven methods
- Hand hygiene
- Diagnostic improvements- Rapid diagnosis using proteomics
- Antibiotic stewardship- 6 D’s
  - Diagnosis
  - Drug
  - Dose
  - Duration
  - De-escalation
  - Documentation
New Strategies
Application of Ecological Strategy

- Body as a battle ground approach vs management of ecological system
- Understanding ecosystem providers (ESP’s) in disease states such as Faecalibacterium prausnitzii, Inflammatory bowel disease association as this may be an ESP.

Adaptive Management of Human Body

- Transition from body as a battleground to human as habitat perspective
- Use principles of plant and animal management strategies known as “adaptive management”
- Uses system management to bring the system back to homeostasis
- This will require continuous monitoring of the human microbiome during health
Adaptive management

- Establish a baseline and more intensive monitoring during illness and treatment
- Bring back to baseline
- Recent examples fecal transplantation
- Require development of new diagnostic tests to allow real time decision making
- Identification of more ESP's for disease states