Antimicrobial Resistance

The Case for Diagnostics to Better Direct Therapy
Objectives

- Explain the medical significance of antibiotic resistance
- Assess the medical impact of disease, such as pneumonia and C. *difficile*
- Describe the diagnostic option available for pneumonia and C. *difficile*
What do you think are the top 7 threats to the human race?
One of the top 7 issues that threatens the human race

**Global Drivers**

- Changed C/N cycles and rising atmospheric GHG concentration
- Increasing antibiotic resistance
- Increasing connectivity (economic, social, ecological)
- Rising human numbers and urbanization
- Increasing per capita resource use
- Nuclear proliferation
- International terrorism

**Unwanted Outcomes**

- CLIMATE
- ECOSYSTEM
- HUMAN HEALTH
- ECONOMIC

Source adapted from: Science, Vol 325, September 2009
Available at: http://www.sciencemag.org/content/325/5948/cover-expansion
Infectious Disease in the US

1970: William Stewart, the Surgeon General of the United States declared the U.S. was “ready to close the book on infectious disease as a major health threat”; modern antibiotics, vaccination, and sanitation methods had done the job.

1995: Infectious disease had again become the third leading cause of death, and its incidence is still growing!
The Problem – Drug Resistance Rates Can Occur Quickly

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1928</td>
<td>Alexander Fleming announces the discovery of Penicillin</td>
</tr>
<tr>
<td>1947</td>
<td>Antibiotic resistance was first seen – only 4 years after the drug started being mass produced</td>
</tr>
<tr>
<td>1945</td>
<td>(17 years later) Fleming wrote:</td>
</tr>
</tbody>
</table>
The time may come when penicillin can be bought by anyone in the shops. 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, educate them to resist penicillin.

Nobel lecture, 1945
How it was

Penicillin cures gonorrhea in 4 hours. See your doctor today.

Syphilis is a dangerous disease but it can be cured.
Drug store in Mexico
The Costs of Antibiotic Resistance

- Antibiotic resistance increases the economic burden on the entire US healthcare system
  - Resistant infections cost more to treat and can prolong healthcare use

- More than $1.1 billion is spent annually on unnecessary antibiotic prescriptions for respiratory infections in adults

- In total, antibiotic resistance is responsible for:
  - $20 billion in excess healthcare costs
  - $35 billion in societal costs
  - 8 million additional hospital days
Inpatient Settings

One in every three patients will receive two or more antibiotics in the course of their hospital stay.

Of the patients receiving antibiotics, three out of every four will receive unnecessary or redundant therapy, resulting in excessive use of antibiotics.

CDC – Get Smart Campaign
Outpatient Settings

Each year, tens of millions of antibiotics are prescribed unnecessarily for upper viral respiratory infections.

Antibiotic use in primary care is associated with antibiotic resistance at the individual patient level.

The presence of antibiotic-resistant bacteria is greatest during the month following a patient’s antibiotics use and may persist for up to 1 year.

CDC – Get Smart Campaign


FOR INTERNAL USE ONLY. NOT FOR PRINT OR DISTRIBUTION
New drugs vs. Resistant organisms

Death of New Drugs...
The number of new antibiotics approved for sale in the United States has dwindled.

20 antibiotics approved for sale

...For Hardier Germs
Acinetobacter germs in U.S. hospitals that are resistant to a powerful antibiotic often used as a last line of treatment.

30% Acinetobacter germs resistant to imipenem

Potential Reasons to Shift Focus of Drug Discovery from Antibiotics to Other Types

- Other types of drugs are more profitable
- Antibiotics become auto-obsolete
- Thought leaders advocating conservative use
- Increasing standards for efficacy and safety evaluation
- Increasingly complex patients in clinical trials
- Significantly increased costs in clinical trials

Edwards J, ICAAC, 2003
Slide from Ebbing Lautenback, University of Pennsylvania
“A post-antibiotic era means, in effect, and end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill.”

Margaret Chan, WHO Director General
Penicillin Resistance in Pneumococci

- Correlation between the use of antibiotics and resistance
Test Target Treat model
Why do providers give antibiotics when not certain?

Medscape survey

- 53% - Prescriptions written when “certain enough”
- 42% - Worry that it could be bacterial
- 31% - Lab work takes too long
- 30% - Infection didn’t appear to be bacteria or viral
- 19% - Patient didn’t want or couldn’t afford test
- 15% - Malpractice concerns
How Resistance Is Transmitted

How Antibiot
ANTIBIOTIC RESISTANCE

Initiation of antibiotic therapy

Antibiotic resistance of bacterial population measured by \( \mu g/ml \) of antibiotic needed to control growth

Bacteria count

Days

0 1 2 3 4 5 6 7 8 9 10 11

Bacteria (number/ml)

Antibiotic resistance (\( \mu g/ml \))

10^3 10^4 10^5 10^6 10^7 10^8

50,000 40,000 30,000 20,000 10,000 0
EMERGENCE OF ANTIMICROBIAL RESISTANCE

Susceptible Bacteria

Resistant Bacteria

Resistance Gene Transfer

Mutations

New Resistant Bacteria
ANTIBIOTIC SELECTION FOR RESISTANT BACTERIA
ANTIMICROBIAL RESISTANCE:
KEY PREVENTION STRATEGIES

Susceptible Pathogen

Prevent Transmission

Prevent Infection

Antimicrobial Resistance

Optimize Use

Antimicrobial Use

Effective Diagnosis and Treatment

Infection
Antibiotic Resistance Mechanisms

Bacteria can inactivate the antibiotic
- B-lactamase can cleave molecule, rendering it inactive

The bacteria can modify the target the antibiotic binds to
- Penicillin binding protein in MRSA

The bacteria can actively pump the antibiotic outside of the cell
- Eflux pumps keep the antibiotic level below what would kill cell

Bacterial pathways can be inhibited, such as metabolic pathway
- Alternative pathway can be used
Problems of Multidrug-Resistant Bacteria

Hospital

**Gram-negative**
- Acinetobacter sp.
- Citrobacter sp.
- Enterobacter sp.
- Klebsiella sp.
- Pseudomonas aeruginosa

**Gram-positive**
- Clostridium difficile
- Enterococcus sp.: VRE
- Coagulase-negative Staphylococcus
- Staphylococcus aureus: MRSA/VRSA

Community

**Gram-negative**
- Escherichia coli
- Neisseria gonorrhoeae
- Salmonella typhi
- Salmonella typhimurium

**Gram-positive**
- Enterococcus sp.: VRE
- Mycobacterium tuberculosis
- Staphylococcus aureus: MRSA
- Streptococcus pneumoniae
- Streptococcus pyogenes
What percent of antibiotics made in this country goes into animal feed?
What percent of antibiotics made in this country goes into animal feed?

80%
“Poster children” for antibiotic resistance
Gram-Positive

MRSA
MRSA

Most invasive organism that we face today

Attacks all groups regardless of age

Community-acquired and hospital-acquired

About 19,000 deaths from MRSA in US in 2005 alone
Gram-Negative

CRKP
Carbapenem-Resistant Enterobacteriaceae

*Klebsiella* are normally found in intestines

May cause pneumonia, bloodstream infections, wound or surgical site infections, and meningitis

Mortality rates can be as high as 40%-50%

National Healthcare Safety Network found in 2009-2010 that 13% of *Klebsiella* species from catheter-associated UTI’s and central line associated bloodstream infections were resistant
Gram-Positive Anaerobe

C. diff
Clostridium difficile

- Gram positive spore former – the most common cause of healthcare-associated diarrhea
- Spread by health care workers - spores difficult to eradicate
- Causes 25% of antibiotic associated diarrhea and 90-99% of pseudomembranous colitis
- Disease is caused by the toxins the organism produces
Treating Respiratory Diseases in the Emergency Department

Is the pathogen bacterial or viral?

Influenza and pneumonia symptoms can overlap dramatically.

Who do you test?

If it is flu season, do you test for other pathogens?

What do you test them for?

Different age groups are linked to different pathogens.

Can treatment be impacted if the appropriate testing is done?

Stop indiscriminate use broad spectrum antibiotics.
Importance of FQ Resistance

One of the most commonly used antibiotic classes\(^1,2\)

Most common antibiotic used in nursing homes\(^3\)

Broad spectrum

Oral bioavailability

Long half-life

Well tolerated


Slide from Ebbing Lautenback, University of Pennsylvania
FQ Resistance vs. FQ Use

Neuhauser MM, JAMA 2003;289:885

Slide from Ebbing Lautenback, University of Pennsylvania
Implications: Addressing FQ Overuse/Misuse

On whom/Where are they being used?
- Inpatient
- Outpatient
- Emergency Departments

Why/How are they being used?
- Indications
- Dose/duration

Slide from Ebbing Lautenback, University of Pennsylvania
Appropriateness of ED FQ Use

81% of courses inappropriate

- **Other Agent First Line** (n=43) 53%
- **No Infection** (n=27) 33%
- **Insufficient Information** (n=11) 14%


Slide from Ebbing Lautenback, University of Pennsylvania
Appropriateness of FQ Use: EDs

19/100 (19%) patients received appropriate FQ therapy (judged by indication)

- 14 received both an incorrect dose & duration
- 4 received either an incorrect dose or duration
- 1 received the correct dose and duration


Slide from Ebbing Lautenback, University of Pennsylvania
### Study on CAP Patients and Therapy

#### Retrospective study on 175 CAP patients in New York

- **Exclusion criteria**
  - Hospitalization ≥ 2 days within 90 days
  - Residence in nursing home
  - Prior isolation of MDR organism

#### Rate of multidrug resistant organism detected within 90 days

- 15% patients on fluoroquinolone
- 4% of patients on cephalosporin/macrolide
Misuse of Antibiotics Can Lead to Other Medical Issues

Pneumonia may be treated with fluoroquinolone

Disrupts normal intestinal flora

O27 strain of *C. difficile* is specifically resistant to fluoroquinolone
Pathogenesis of CDAD

*Clostridium difficile* is spread via the fecal-oral route. The organism is ingested either as the vegetative form or as hardy spores, which can survive for long periods in the environment and can traverse the acidic stomach.

In the small intestine, spores germinate into the vegetative form.

In the large intestine, *C. difficile*-associated disease can arise if the normal flora has been disrupted by antibiotic therapy.

*Clostridium difficile* reproduces in the intestinal crypts, releasing toxins A and B, causing severe inflammation. Mucous and cellular debris are expelled, leading to the formation of pseudomembranes.

Toxin A attracts neutrophils and monocytes, and toxin B degrades the colonic epithelial cells, both leading to colitis, pseudomembrane formation, and watery diarrhea.
Antibiotic-Associated Diarrhea: Life’s a Beach with *C. difficile*

- Normal Gut Flora
- Gut after Antibiotics
- *C. diff* finds a nice spot
- *C. diff* Infection
Clinical Manifestations of CDAD

Asymptomatic Colonisation
- No Symptoms

Diarrheal illness
- Diarrhea - Mild to severe (explosive)
- Abdominal Pain
- Fever

PMC
- Toxic megacolon

Increasing disease severity
Treatment for relapsing *C. difficile*
Fecal transplant
Pneumonia in the United States

Estimated 4.5 million cases of pneumonia annually. Approximately 1.1 million are hospitalized.¹

Pneumonia, along with influenza, is the eighth leading cause of death in the United States.²

Third in the top 20 hospital discharge diagnosis groups for emergency department visits.³

---

2. CDC Website: Deaths Preliminary Data for 2011
3. National Hospital Ambulatory Medical Care Survey: 2010 Emergency Department Summary Tables
Etiological Agents of Respiratory Disease

Newborns (0 to 30 days)

- Group B *Streptococcus*, *Lysteria monocytogenes*, or Gram negative rods are common
- RSV in premature babies

Infants and toddlers

- 90% of lower respiratory tract infections are viral with the most common being RSV, Influenza A&B, and parainfluenza. Bacterial infections are rare, but could be *S. pneumoniae*, Hib, or *S. aureus*. 
Etiological Agents

Outpatient

• *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses

Inpatient (non-ICU)

• With the above agents, add *L. pneumophila*

Inpatient (ICU)

• *S. pneumoniae*, *S. aureus*, *L. pneumophila*, Gram-negative bacteria, and *H. influenzae*
Recommended by the 2007 IDSA/ATS Community-Acquired Pneumonia (CAP) Guidelines for all adult patients with severe pneumonia

- Recommended Diagnostic Tests for Etiology (page S39)
- Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. (Strong recommendation; level II evidence.)
- The spectrum of antibiotic therapy can be broadened, narrowed, or completely altered on the basis of diagnostic testing.
Recommended by the 2007 IDSA/ATS Community-Acquired Pneumonia (CAP) Guidelines for all adult patients with severe pneumonia (con’t)

• Patients with severe CAP should have blood samples drawn for culture, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* performed, and expectorated sputum samples collected for culture.
Importance of Testing During Respiratory Season

**S. pneumoniae: A secondary complication to flu**

- 2009 pandemic influenza A (H1N1) & Spanish flu 1918
  - Many deaths were attributed to the flu combined with the secondary complication of pneumonia.\(^1\)
  - Testing for both flu and *S. pneumoniae* will enable appropriate antibiotic therapy.
- Is it flu? Is it pneumonia? Is it both?
- Is it bacterial or viral?

---

Are there other issues with the abuse of antibiotics?

Data suggests link between antibiotic use and obesity in children

Yeast infections
Antibiotic Stewardship Programs

These programs focus on:

- Proper use of antibiotics to provide the best patient outcomes
- Lessen the risk of adverse effects (C. *diff*, toxicity damage to organs, etc.)
- Promote cost-effectiveness
- Reduce or stabilize levels of resistance
Antibiotic Stewardship Programs

- IDSA/SHEA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship – 2006
  - [http://www.idsociety.org](http://www.idsociety.org)

- Core members include:
  - Infectious Disease Physician
  - Emergency Department Physician / Manager
  - Clinical Pharmacist – ideally with infectious disease training
  - Clinical Microbiologist
  - Infection Control Professional
  - Information System Specialist
Antibiotic Stewardship Programs

Program components:

• Education
• Guidelines and **clinical pathways**
  • Includes diagnostic testing
• Antimicrobial cycling
• Antimicrobial order forms
• Combination therapy
• Streamlining or de-escalation of therapy
• Dose optimization
• Parenteral to oral conversion
Conclusions

Treating for one condition may lead to unintended consequences

Diagnostic testing can help direct the appropriate therapy

Directed therapy can prolong the effectiveness for broad spectrum antibiotics
Discussion