Antimicrobial Medications

Chapter 21

The Dawn of Antibiotics

- Paul Ehrlich (1910)
  - Wanted to find the “magic bullet” for syphilis
  - Worked at staining tissues and first to come up with the idea behind “selective toxicity”
  - Nobel Prize in 1908

Antimicrobial Drugs - History

Ehrlich - magic bullet

Syphilis (Treponema pallidum)
  - Primary - 3 wks after infection; chancre, highly infectious
Antimicrobial Drugs - History

Ehrlich - magic bullet
Syphilis (Treponema pallidum)

Primary
Secondary - rash; 2 - 10 weeks later; lasts weeks to years; highly infectious

Secondary
Tertiary - neurosyphilis, cardiovascular syphilis, gumma formation; years later (1/3 of the time); not infectious

Tertiary

Congenital - damage to the fetus
Antimicrobial Drugs - History

Ehrlich - magic bullet
Syphilis (*Treponema pallidum*)

- Primary
- Secondary
- Tertiary
- Congenital

Salvarsan
Chemotherapeutic agent

Discovery of Antibiotics

- Antimicrobial drugs naturally produced by microorganisms

- Fleming - discovered penicillin
  1929

- Chain and Florey - first to purify penicillin
  1940's

Penicillium
*Streptomyces, Bacillus*

Example - β-lactam Drugs
Example - β-lactam Drugs

Penicillin G
Target - peptidoglycan synthesis
- Transpeptidases
  aka penicillin-binding proteins (PBPs)
- High therapeutic index
  (note: allergies)
- Not effective against most Gram-negatives

Penicillin Weaks the Cell Wall
Example - β-lactam Drugs

Penicillin G
Target - peptidoglycan synthesis

Transpeptidases
aka penicillin-binding proteins (PBPs)

• High therapeutic index
  (note: allergies)

• Not effective against most Gram-negatives
• Acid-sensitive
• Destroyed by penicillinase (a β-lactamase)

Family of Penicillins

• Natural penicillins
• Penicillinase-resistant penicillins
• Broad-spectrum penicillins
• Penicillins + β-lactamase inhibitor
Example - β-lactam Drugs

Determining the susceptibility of a bacterial strain to an antimicrobial drug - Minimum Inhibitory Concentration (MIC)

Resistant
Determining the susceptibility of a bacterial strain to an antimicrobial drug - Disk diffusion (Kirby-Bauer) test

Resistance to Antimicrobial Drugs

Rising Threat of Infections Unfazed by Antibiotics

A minor-league pitcher in his younger days, Richard Armbruster kept playing baseball recreationally into his 70s, until his right hip started bothering him. Last February he went...for what was to be a routine hip replacement. By late March, Mr. Armbruster, then 78, was dead. After a series of postsurgical complications, the final blow was a bloodstream infection that sent him into shock and resisted treatment with antibiotics.

The bacteria (Acinetobacter baumannii), classified as Gram-negative because of their reaction to the so-called Gram stain test..... Their cell structure makes them more difficult to attack with antibiotics than Gram-positive organisms like MRSA.
Mechanisms of Resistance

Acquisition of Resistance

Spontaneous mutation

Single-step

$S \rightarrow R$

Multi-step

$S \rightarrow S \rightarrow S \rightarrow R$

Spontaneous mutation

Single-step

$S \rightarrow R$

Multi-step

$S \rightarrow S \rightarrow S \rightarrow R$
Acquisition of Resistance

Spontaneous mutation

Single-step

$S \rightarrow R$

Multi-step

$S \rightarrow S \rightarrow S \rightarrow R$

1 per $10^9$

1 per $10^7$
Acquisition of Resistance

Spontaneous mutation

Single-step
S → R

Combination therapy (multiple drugs)

1 per $10^6$
1 per $10^7$
1 per $10^{13}$

Multi-step
S → S → R

Patient compliance
Acquisition of Resistance

Spontaneous mutation

Single-step
- $S \rightarrow R$
  - $1 \text{ per } 10^6$
  - $1 \text{ per } 10^7$
  - $1 \text{ per } 10^{13}$

Multi-step
- $S \rightarrow S \rightarrow R$
  - Patient compliance

Combination therapy (multiple drugs)
Acquisition of Resistance

Spontaneous mutation

Single-step

\[ S \rightarrow R \]

1 per \(10^6\)

1 per \(10^7\)

1 per \(10^{13}\)

Multi-step

\[ S \rightarrow S \rightarrow S \rightarrow R \]

Patient compliance

Combination therapy (multiple drugs)

Acquisition of Resistance

Gene transfer

Resistance plasmids

(R plasmids)

Can encode resistance to multiple medications

Don’t use antimicrobial medications except when necessary!!!!!
Examples of Emerging Resistance

*Neisseria gonorrhoeae*


*More Antibiotics Ineffective Against Gonorrhea*

New evidence from Hawaii and Missouri indicates that gonorrhea is becoming resistant to a wider variety of antibiotics, federal health officials said yesterday.

Seattle Times 4/13/2007

*Treatment options narrow for gonorrhea*

The sexually transmitted disease gonorrhea is among the superbugs resistant to common antibiotics, causing U.S. health officials to recommend wider use of a different class of drugs to avert a public-health crisis.

"We are running out of options to treat this disease," added Douglas, who said there are "no new drugs for gonorrhea in the drug-development pipeline."
Examples of Emerging Resistance

*Neisseria gonorrhoeae*

*Enterococcus* species
  - VRE - vancomycin-resistant enterococci

*Staphylococcus aureus*
  - MRSA - methicillin-resistant *Staphylococcus aureus*
  - VISA - vancomycin-intermediate *Staphylococcus aureus*
  - VRSA - vancomycin-resistant *Staphylococcus aureus*

Family of Penicillins

- Natural penicillins
- Penicillinase-resistant penicillins
- Broad-spectrum penicillins
- Penicillins + β-lactamase inhibitor
Figure 8.28 Resistant to most other antibiotics

Resistant to most other antibiotics

Resistant to most other antibiotics

Resistant to most other antibiotics
Examples of Emerging Resistance

*Neisseria gonorrhoeae*
- Enterococcus species
  - VRE - vancomycin-resistant enterococci
- *Staphylococcus aureus*
  - MRSA - methicillin-resistant *Staphylococcus aureus*
  - VISA - vancomycin-intermediate *Staphylococcus aureus*
  - VRSA - vancomycin-resistant *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Mycobacterium tuberculosis*
  - 2-4 drugs, 6-9 months
  - MDR-TB - alternative drugs; 2 yr
  - XDR-TB

Seattle Times, Feb. 27 2008

TB increasingly resistant to some drugs

About one in every 20 new cases of tuberculosis worldwide is now resistant to two or more drugs, and in some regions of the former Soviet Union the proportion is closer to one in every five cases, the World Health Organization (WHO) reported Tuesday.

In addition, "extensively drug-resistant" tuberculosis (XDR-TB), a relatively new subtype of the disease ...has now been found in 45 countries. TB epidemiologists estimate 40,000 new cases emerge each year, and the death rate in untreated or poorly treated cases is close to 100 percent.
Examples of Emerging Resistance

*Neisseria gonorrhoeae*
- Enterococcus species
  - VRE - vancomycin resistant enterococci
*Staphylococcus aureus*
  - MRSA - methicillin-resistant *Staphylococcus aureus*
  - VISA - vancomycin-intermediate *Staphylococcus aureus*
  - VRSA - vancomycin-resistant *Staphylococcus aureus*
*Streptococcus pneumoniae*
*Mycobacterium tuberculosis*
  - 2-4 drugs, 6-9 months
  - MDR-TB - alternative drugs; 2 yr
  - XDR-TB

Slowing the Emergence and Spread of Antimicrobial Resistance

Responsibilities of physicians and other health care workers
- prescribe medications only when appropriate

Responsibilities of patients
- take medications as prescribed

Importance of an educated public

*Poll Finds Americans Are Ignorant Of Science*

...For example, 63 percent said incorrectly that antibiotics kill viruses as well as bacteria. So when doctors tell patients their illness is caused by a virus, they may take antibiotics in a fruitless effort to cure their ailment.
Slowing the Emergence and Spread of Antimicrobial Resistance

Responsibilities of physicians and other health care workers
- prescribe medications only when appropriate

Responsibilities of patients
- take medications as prescribed

Importance of an educated public
- **antibiotics are NOT effective against viruses**

Global impacts of the use of antimicrobial drugs
- animal feeds? prescription vs. over-the-counter?

Increasingly drug-resistant infections in rich and developing nations alike are threatening to make once treatable diseases incurable.
- World Health Organization, 2000

Resistant Pathogens and Public Health

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - 19,000 deaths/year in U.S.
  - $3-$4 billion in health care costs

- MDR and XDR strains of *Mycobacterium tuberculosis*
  - Rising threat in developing worlds
  - MDR/two year course of treatment
  - XDR difficult to cure and often fatal

- Multidrug-resistant (MDR) and pandrug-resistant (PDR) Gram-negative bacteria
  - *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*
  - Present a grave threat of untreatable infections