Antibiotics and alternative strategies to control infections

Dr. Vassie Ware
Bioscience in the 21st Century
12/6/2017

www.biochemj.org/bj/330/0581/bj3300581.htm

http://blog.microbiologics.com/wp-content/uploads/2015/12/Acinetobacter-baumannii-232x300.jpg

http://blog.microbiologics.com/wp-content/uploads/2015/12/Acinetobacter-baumannii-232x300.jpg

www.biochemj.org/bj/330/0581/bj3300581.htm

Head Space - WordPress.com

Wikipedia
OUTLINE

1. Your thoughts about the value of antibiotics

2. General information about antibiotics and their targets

3. Development of bacterial antibiotic resistance

4. What response is needed globally?

5. Alternative strategies: Phage Therapy
PERSPECTIVE

• Widespread use of antibiotics after WWII to improve global health

• Increasing antibiotic resistance in bacterial pathogens coupled with a lag in the development of additional antibiotics by pharmaceutical companies poses an escalating problem in the 21st century

  2005: ~19,000 deaths from bacterial infections.
  Today: 2 million people infected; ~23,000 deaths/year in US from bacterial infections!!!(from cdc.gov)

• Challenge to design effective new generation antibiotics among the growing impact of superbugs, overuse of antibiotics, and decline in research and development of new prospects

• Use of structure-based drug design to develop novel drugs based on high resolution structures of drug targets and their resistance mutants

  ciss.blog.olemiss.edu
"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer," ....would later say, "But I suppose that was exactly what I did."

Who said this and what was the antibiotic?

Antibiotics

• Natural or synthetic compounds that either kill (bactericidal) or inhibit growth (bacteriostatic) of bacteria (or other microorganisms)

• Antibiotics may be classified in several ways. Most common classification schemes are based on chemical structure of the antibiotic
Antibacterial agents, suitable for therapy:

Natural —
Derived from natural sources such as fungi and soil bacteria.
Penicillin as the classic example, derived from the fungus *Penicillium*
Pharmaceutical industry produces penicillin from cultures of *Penicillium chrysogenum* that are adapted for high yield
Others: many aminoglycosides from soil bacteria (e.g., streptomycin)

Semi-synthetic -
Natural products that have been chemically modified to improve effectiveness of the product or to reduce side effects, etc
Examples include the β-lactams ampicillin, amoxicillin, etc, derived from fungi

Completely synthetic –
Products are synthesized completely in the laboratory
Sulfa drugs, folic acid analogs are examples
Bacterial types distinguished by cell wall features

**GRAM-NEGATIVE**
- Outer membrane
- Lipoproteins
- Peptidoglycan
- Periplasmic space
- Cytoplasmic membrane
- Lipopolysaccharides
- Porin
- Protein

**GRAM-POSITIVE**
- Lipoproteins
- Peptidoglycan
- Cytoplasmic membrane
Antibiotic Targets in Bacterial Cells

- **Cell Wall Synthesis**
  - D-cycloserine
  - Vancomycin
  - Bacitracin
  - Penicillins
  - Cephalosporins
  - Cephamycins

- **Cell Wall Integrity**
  - β-lactamases

- **DNA Synthesis**
  - Metronidazole
  - DNA Gyrase
  - Quinolones

- **RNA Polymerase**
  - Rifampicin

- **Replication**
- **Transcription**

- **Ribosomes**
  - 50S
  - 30S

- **Cytoplasmic Membrane**
  - Phospholipid Membranes
  - Polymyxins

- **Protein Synthesis**
  - 50S Inhibitors
    - Erythromycin
    - Chloramphenicol
    - Cindamycin
    - Lincomycin
  - 30S Inhibitors
    - Tetracyclines
    - Streptomycin
    - Spectinomycin
    - Kanamycin
How do bacteria become resistant to antibiotics?

Bacteria acquire genes that encode proteins that shield or protect them from the effects of the antibiotic. Bacteria develop resistance by mutations in their proteins (derived from mutations in genes).

These genes may have arisen by mutation of existing genes OR they may have been acquired from other resistant bacteria through the transfer of genetic information between bacteria.

Antibiotic resistance genes are often carried on plasmids and can be exchanged between bacteria.
Resistance to Antibiotics can occur through two general genetic mechanisms

1. **Intrinsic resistance**
   Some bacteria are naturally more resistant to certain classes of antibiotics than others.
   Examples:
   - certain bacteria may lack a transport system for an antibiotic
   - bacteria may lack the target of the antibiotic molecule
   - the cell wall is covered with an outer membrane blocks entry of the antibiotic (as in the case for Gram negative bacteria).

2. **Acquired resistance**
   Bacteria acquire resistance to antibiotics for which they were previously susceptible through
   - spontaneous gene mutation (rate of $10^{-8}$–$10^{-9}$) and fixation of mutation in the population through rapid cell division (vertical evolution)
   - horizontal gene transfer mechanisms, such as conjugation, transformation, or transduction. Impact of this can be significant. For example, in 10 years' time between 1985 and 1995, the percentage of ampicillin-resistant *Shigella* (causes intestinal illness) grew from 32% to 67%! 
Plasmid-encoded genes that can activate an antibiotic
Several mechanisms (shown in red) exist to inactivate an antibiotic. Mechanism(s) used depend on the genes found in the resistant bacteria of interest, such as:

Synthesis of enzymes that break down the antibiotic:
Penicillinase (a type of β-lactamase, breaks the β-lactam ring, thereby destroying the antibiotic). Other enzyme types are also prevalent (e.g., cephalosporinases). New Delhi metallo-beta lactamase (NDM-1), an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics (creating resistant “superbugs”)

Penicillin 6
Mechanisms, continued:

- Modification of their own enzymes that would normally be targets of the antibiotic (e.g., DNA gyrase)

- Synthesis of “pumps” inserted into the cell membrane to remove the antibiotic from the interior of the cell

- Addition of chemical groups onto the target so that the antibiotic does not recognize the target. (e.g., erythromycin resistance)

- Modification of the antibiotic so that it no longer recognizes its target (e.g., kanamycin resistance)

- Modification of the peptidoglycan cell wall to avoid the antibiotic effect
Recent discovery reported in *Nature* 2015:

A new antibiotic called teixobactin isolated from a newly discovered bacterial species, *Eleftheria terrae*, kills pathogens without detectable resistance

Significance of this discovery:

- A new class of antibiotic active against Gram positive bacteria (e.g., *Staphylococcus aureus, Mycobacterium tuberculosis*)
- First new class of antibiotic discovered in ~30 years
- Binds to lipids (NOT proteins) which are precursors to cell wall synthesis
- Discovered with a new isolation method of culturing bacteria in soil using iChip
- Discovery improves hopes of isolating new antibiotics using different culturing methods
- Not as yet in human clinical trials
What can government do to help solve the antibiotic crisis?

Three main components to the report (2014):
• improve surveillance of antibiotic-resistant bacteria and stop outbreaks;
• increase the life of current antibiotics and develop new ones, as well as promote research accelerating clinical trials;
• increase economic incentives to develop new antibiotics.
An Alternative to Antibiotics

The Life Cycle of a Phage

http://en.citizendium.org/wiki/Bacteriophage

http://www.bacteriophagetherapy.info
Alternative strategies to control human infections

- Widely used in Russia, Poland, Georgia; nearly a century of research on phages at Eliava Institute in Georgia (1923)

- First European large, multicenter clinical trial of phage therapy for human infections called Phagoburn

- Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection in US (collaboration between UCSD, U.S. Navy Medical Research Center – Biological Defense Research Directorate (NMRC-BDRD), Texas A&M University, AmpliPhi, San Diego State University)

- Development of phage cocktails with multiple phage within. Why?
Phage Therapy Case Study

• March 2016: first known person in USA to be treated by IV bacteriophage therapy - Tom Patterson, Ph.D., psychiatrist from UCSD

• Contracted life-threatening infection with MDR strain of *Acinetobacter baumannii* (Gram negative) in Egypt in 2015. Patient in months-long coma

• At UC San Diego Health, received emergency approval (emergency investigational new drug application) for FDA for IV phage therapy specifically targeting *A. baumannii*.

• Condition improved almost immediately

• Rationale for exploring this as alternative to antibiotics amid growing resistance problem.

https://health.ucsd.edu/news/topics/phage-therapy/Pages/default.aspx
Phage therapy: advantages and challenges

Advantages:
• Phages typically infect one bacterial type (or very closely related types); advantage over broad-spectrum antibiotics
• Phages are plentiful in the biosphere \(10^{31}\)
• Phages require bacteria for replication; therefore they replicate where the pathogen resides (if accessible)
• Generally thought to be safe (commonly used prior to antibiotic revolution after WWII)
• Indiscriminate against antibiotic-sensitive and antibiotic-resistant bacteria

Challenges:
• More research needed to determine efficacy and safety
• Accessibility challenges for pathogens that are intracellular (for example, TB at certain stages)
• Delivery challenges to get to target and to avoid neutralization by immune system
• Can be carriers of other genetic material and deliver to bacterial pathogen (transduction)
SUMMARY

• Bacterial antibiotic resistance is an increasingly serious global health problem

• Several mechanisms exist that allow bacteria to escape the effects of antibiotics

• Global scientific research imperatives:
  - Development of new derivatives of antibiotics
  - Discovery of new classes of antibiotics with novel mechanisms of action
  - Development of new approaches to treating bacterial infections

• Government and industrial partnerships are essential to foster new antibiotic drug development

• Bacteriophages are being used in phage cocktails is an alternative strategy to treat infection