Antibiotics

Joel Goodman
STARS Minisymposium
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Outline

• The spectrum of infectious agents and the global problem of human infections
• Classification of bacteria
• Intro to antibiotic classes, drug targets and resistance
• Three antibiotics in detail
  – Sulfonamides
  – Penicillin
  – Streptomycin
Statement by

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World Health Organization

Before the

Committee on International Relations
U.S. House of Representatives

29 June 2000

“The Urgency of a Massive Effort
Against Infectious Diseases”
Most deaths among young people in developing countries are caused by just a few illnesses.

Ages 0 - 44 in South-East Asia and Africa

- AIDS
- malaria
- TB
- diarrhoea
- measles
- ARI
- maternal & perinatal conditions
- other
Leading Infectious Killers

Millions of deaths, worldwide
All ages, 1998 estimate

ARI
AIDS
Diarrhoeal diseases
TB
Malaria
Measles

Over age five
Under age five

World Health Organization - CDS
Projected changes in life expectancy in African countries with high HIV prevalence, 1995–2000


Average life expectancy at birth, in years

- Botswana
- Zimbabwe
- Zambia
- Uganda
- Malawi

World Health Organization - CD
Frequent Flyers
Most Popular Air Routes Between Countries, 1997

Percentage increase in international arrivals, 1993 to 1997

32%
Americas

27%
Europe

44%
Africa

46%
Middle East

32%
South Asia

29%
East Asia & Pacific

World Health Organization - CD
Defending national borders
A strong defense must include protecting the population from microbial invaders

**DISEASE**
150 million deaths
From AIDS, TB and malaria since 1945

**WAR**
23 million deaths
Military and civilian from war 1945 -1993

**DEATHS**

**PREVENTION**
$15 billion
Estimated global spending for prevention and control of AIDS, TB and malaria, 1995

**BUDGET**
$864 billion
Global military spending, 1995

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World Health Organization - CDS
The Discovery and Loss of Penicillin in treating *Staphylococcus aureus*

- **1928**  
  Penicillin discovered

- **1942**  
  Penicillin introduced

- **1945**  
  Fleming warns of possible resistance in bacteria

- **1946**  
  14% hospital strains resistant

- **1950**  
  59% hospital strains resistant

- **1960 - 1970**  
  Resistance spreads in communities

- **1980 - 1990**  
  Resistance exceeds 80% in community strains, 95% in hospital strains
“The highly unnatural journey of No. 534, from calf to steak”
Cows rarely live on feedlot diets for more than six months, which might be about as much as their digestive systems can tolerate. “I don’t know how long you could feed this ration before you’d see problems,” Metzen said; another vet said that a sustained feedlot diet would eventually “blow out their livers” and kill them. As the acids eat away at the rumen wall, bacteria enter the bloodstream and collect in the liver. More than 13 percent of feedlot cattle are found at slaughter to have abscessed livers.

What keeps a feedlot animal healthy — or healthy enough — are antibiotics. Rumensin inhibits gas production in the rumen, helping to prevent bloat; tylosin reduces the incidence of liver infection. Most of the antibiotics sold in America end up in animal feed — a practice that, it is now generally acknowledged, leads directly to the evolution of new antibiotic-resistant “superbugs.” In the debate over the use of antibiotics in agriculture, a distinction is usually made between clinical and nonclinical uses. Public-health advocates don’t object to treating sick animals with antibiotics; they just don’t want to see the drugs lose their efficacy because factory farms are feeding them to healthy animals to promote growth. But the use of antibiotics in feedlot cattle confounds this distinction. Here the drugs are plainly being used to treat sick animals, yet the animals probably wouldn’t be sick if not for what we feed them.

I asked Metzen what would happen if antibiotics were banned from cattle feed. “We just couldn’t feed them as hard,” he said. “Or we’d have a higher death loss.” (Less than 3 percent of cattle die on the feedlot.) The price of beef would rise, he said, since the whole system would have to slow down.

“Hell, if you gave them lots of grass and space,” he concluded dryly, “I wouldn’t have a job.”
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Drug Resistance ca. 2006

• Half the time, prescriptions for antibiotics are inappropriate. Antibiotic use promotes outgrowth of resistant organisms!

• Antibiotics in cattle feeds account for ~ 50% of use; cross-resistance occurs. Antibiotics are ubiquitous in the environment.

• Until very recently, no classes of antimicrobial drugs have been developed since 1970. Big Pharma is reluctant to get involved! Resistance has developed to ALL these classes of antibiotics.
Classes of Bacteria
Classes of Bacteria

• Gram stain distinguishes two classes
Gram stain stains cell wall

- Gram positive bacteria have exposed cell wall (peptidoglycan)
- Gram negative bacteria have an outer membrane that surrounds the cell wall

http://pathmicro.med.sc.edu/fox/bact-mem.jpg
Function of envelope

Protects cells from toxic substances
Keeps important proteins concentrated in periplasm
Maintains integrity of cytoplasm
Generates a proton gradient and ATP

Osmoprotection
Maintains cell shape

http://pathmicro.med.sc.edu/fo
http://textbookofbacteriology.net/structure.html
Shapes of Bacteria

cocci, diplococci
streptococci
tetrad, sarcinae
staphylococci
bacillus
cocobacillus
diplobacillus
not diplobacillus
streptobacillus
spirochete

http://www.mansfield.ohio-state.edu/~sabedon/biol2010.htm
How do you treat all these bugs??
Dawn of the Antibiotic Age

• 1870s - Robert Koch - discovered the anthrax bacterium.
• 1877 - Louis Pasteur - discovered that common bacteria can prevent anthrax from growing in culture.
• 1890s - Paul Ehrlich - chemicals can be “magic bullets”. Development of Salvarsan.
• 1908 - Paul Gelmo - textile azo dyes can kill bacteria; led to sulfonamides in 1930s.
• 1928 - Alexander Fleming - discovery of penicillin. First patient cured in 1941.
Sites of Drug Action (1)

1. Cell wall: Beta-lactams (Penicillins, Cephalosporins), Glycopeptides, Bacitracin
2. Plasma membrane: Daptomycin
3. C₁ transfer: Sulfonamides, Trimethoprim (Bactrim)
Sites of Action (2)

4 DNA synthesis: Fluoroquinolones (ex. Ciprofloxacin)

5 RNA synthesis: Rifampin, fluoroquinolones

6 Translation: Aminoglycosides (ex. streptomycin), Tetracyclines, Chloramphenicol, MLSK drugs, Linezolid, Streptogramins
Sulfonamides
Prontosil

Gerhard Domagk
Sulfanilamide, the active drug

Prontosil

Sulfanilamide

Para-aminobenzoic acid (pABA)
Folic Acid

pteridine

$p$-aminobenzoic acid  glutamate
Folic acid carries methyls for.

- Purine biosynthesis
  - C2 and C8 carbons are delivered by THF
- Thymidylate synthesis
  - Catalyzed by thymidylate synthetase
- Amino acid synthesis
  - Serine (from glycine)
  - Methionine (from homocysteine)
We can import folic acid.

Many bacteria cannot. . .
They must synthesize it.
Folate synthesis (bacteria)

Dihydropteroic Acid Synthase (DAS)

\[ p\text{ABA} \rightarrow \text{dihydropteridine} \]

Dihydrofolate reductase (DHFR)

\[ \text{tetrahydrofolate} \]
Sulfonamides are Competitive Inhibitors of DAS

Sulfonamide $\text{H}_2\text{N}\text{SO}_2\text{NHR}$

Dihydropteroic Acid Synthase (DAS)

$p\text{ABA}$

dihydropteridine

Dihydrofolate reductase (DHFR)

tetrahydrofolate

dihydrofolate

glutamic acid
Selective action of sulfa

• Mammals cannot make folic acid; they must import it. We do not possess DAS, the drug target. Instead we have a folic acid transporter.

• Bacteria cannot import folic acid (no transporter); they must synthesize it.
Sulfa facts

- Usually administered as a combination of sulfamethoxazole and trimethoprim (Bactrim)
- Broad spectrum, but bacteriostatic
- Usually safe, but many suffer GI distress or rashes
- Commonly used for urinary tract infections
Beta-lactams
History

- Fleming discovered penicillin (1928)
History

- Fleming discovered penicillin (1928)
- Florey, Chain and Abraham isolated it and determined structure (1940)
- First cure in human (1941)
- Critically important on the field in WWII
- Park & Strominger deduced mechanism (1965)
The Oxford Group

Ernst Chain
1906-1979

Howard Walter Florey
1898-1968

Dorothy Hodgkin
1910-1994
Figure 74. First clinical trial of penicillin in the United States: penicillin therapy of β-hemolytic streptococcal septicemia.
The biosynthesis of cell wall peptidoglycan, showing the sites of action of five antibiotics (shaded bars; 1 = fosfomycin, 2 = cycloserine, 3 = bacitracin, 4 = vancomycin, 5 = β-lactam antibiotics). Bactoprenol (BP) is the lipid membrane carrier that transports building blocks across the cytoplasmic membrane; M = N-acetylmuramic acid; Glc = glucose; NAcGlc or G = N-acetylglucosamine.
Grooves in carboxypeptidase/transpeptidase, complexed with Cephalosporin I

Green - first strand
Yellow, second strand

Lee et al., (2001) :PNAS 98:1427
Penicillin Structure

Hence, β lactam

Lactam = cyclic amide
Classes of $\beta$-lactams

- PenG
- Ampicillin
- Ticarcillin
- Pipericillin

- Penicillins

- Cephalothin
- Cefaclor
- Ceftriaxone
- Cefepime

- Cephalosporins

- Imipenem

- Carbapenems

- Aztreonam

- Monobactams
Penicillin and other beta-lactams

• Very active against gram positive organisms (MICs as low as 0.01 µg/ml)
• Inhibits crosslinking of the peptidoglycan
• Releases autolysins -> cell death
• Side effects: ALLERGY!!
• Resistance: bacteria make beta lactamases, which destroy penicillin
Ribosome Binders

- **30S binders**
  - Aminoglycosides
  - Tetracyclines

- **50S binders**
  - MLSK family
    - Macrolides
    - Lincosamides
    - Streptogramins
    - Ketolides
  - Chloramphenicol

- **Linezolid** (binds both subunits)
Aminoglycosides

Gentamycin C

René Dubos

Selman Waksman
A NEW PARADIGM FOR MASSAGE BASED ON SUBTLE ENERGY AND QUANTUM SCIENCE

PART 1: SUBTLE ENERGY

Albert Schatz and Mary Brewster

Contents

An invitation to visit a new world..

What is a paradigm?.

We need a philosophy of massage.

Why is massage beneficial?.

The old paradigm.

Inadequacies of the old paradigm.

Two centuries after Peter Ling.
Binding of streptomycin to 30S


Figure 5 Interaction of streptomycin with the 30S ribosomal subunit. a, Difference Fourier maps showing the binding site of streptomycin. Mutations in ribosomal protein S12 that confer resistance are shown in red. b, Chemical structure of streptomycin, showing interactions of the various groups with specific residues of the ribosome. c, The streptomycin-binding site, showing its interaction with H27, the 530 loop (H18), H44 and ribosomal protein S12. d, A view of the 30S showing streptomycin in a space-filling model, and the surrounding RNA and protein elements
Aminoglycosides

- Used for serious gram negative infections
- Binds to ribosomes, inhibits protein synthesis and causes misreading of mRNA
- Resistance: Bugs synthesize transferases that inactivate drugs
- Toxic effects: Ototoxicity (hearing and balance loss) and nephrotoxicity
Mechanisms of resistance

- Drug inactivation
  - Penicillins, aminoglycosides

- Alteration of target sites
  - Beta-lactams, fluoroquinolones

- Decrease in accessibility
  - Tetracyclines

- Increase in competing metabolites
  - Sulfonamides