Fundamental Concepts of Antibiotic Resistance in Animals and Humans

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**What is the definition of an antibiotic?**

- Substance produced by one microorganism that selectively inhibits growth of another.

- [A medicine or chemical that can destroy harmful bacteria in the body or limit their growth]
The impact of antibiotics on health in the US

-the death rate from non infectious causes has remained nearly constant;
--a short-lived spike in the death rate occurred in 1918 that is attributable to the 1918 influenza pandemic;
--the death rate from infectious disease has plummeted dramatically.

Slide courtesy Dr. Gene Madsen
Different types of antibiotics

- There are different kinds of antibiotics, and they are classified based on their mechanism of action (i.e. if on the cell membrane, cell wall, or metabolism), chemical structure, spectrum of activity (i.e. if targeting gram-negative or gram-positive bacteria), or by mode of administration (e.g. oral, intravenous, or topical).
Modes of Action for Antibiotics

**Cell wall synthesis**
- Cycloserine
- Vancomycin
- Bacitracin
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

**DNA gyrase**
- Quinolones
  - Nalidixic acid
  - Ciprofloxacin
  - Novobiocin

**RNA elongation**
- Actinomycin

**DNA-directed RNA polymerase**
- Rifampin
- Streptovaricins

**Protein synthesis**
- (50S inhibitors)
  - Erythromycin (macrolides)
  - Chloramphenicol
  - Clindamycin
  - Lincomycin

**Protein synthesis**
- (30S inhibitors)
  - Tetracyclines
  - Spectinomycin
  - Streptomycin
  - Gentamicin
  - Kanamycin
  - Amikacin
  - Nitrofurans

**Folic acid metabolism**
- Trimethoprim
- Sulfonamides

**Cytoplasmic membrane structure**
- Polymyxins
- Daptomycin

**PABA**

**Cytoplasmic membrane**

**Cell wall**

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Slide courtesy Dr. Gene Madsen
Table 8.12 Mechanisms of antibiotic resistance in bacteria. The genes for each of these resistance traits can be transferred between bacteria [Source: Davies, 1994]

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Antibiotic</th>
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<tbody>
<tr>
<td>Reduced uptake into cell</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Active efflux from cell</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Modification of target to eliminate or reduce binding of antibiotic</td>
<td>β-lactams (e.g., penicillin G, amoxicillin)</td>
</tr>
<tr>
<td>Inactivation of antibiotic by enzymic modification:</td>
<td>Erthyromycin</td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>Lincomycin</td>
</tr>
<tr>
<td>Derivatization</td>
<td>β-lactams</td>
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<tr>
<td></td>
<td>Erythromycin</td>
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<tr>
<td></td>
<td>Aminoglycosides</td>
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<tr>
<td></td>
<td>Chloramphenicol</td>
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<tr>
<td></td>
<td>Fosfomycin</td>
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<tr>
<td></td>
<td>Lincomycin</td>
</tr>
<tr>
<td>Sequestration of antibiotic by protein binding</td>
<td>β-lactams</td>
</tr>
<tr>
<td></td>
<td>Fusidic acid</td>
</tr>
<tr>
<td>Metabolic bypass of inhibited reaction</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Binding of specific immunity protein to antibiotic</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td></td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Overproduction of antibiotic target (titration)</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim</td>
</tr>
</tbody>
</table>
Different types of antibiotics

- Some antibiotics are important for treatment of diseases in humans
- An example of an antibiotic that is not ‘medically important’ is monensin = rumensin, an ionophore isolated from *Streptomyces cinnamononensis* and used to prevent coccidiosis, increase the production of propionic acid in the rumen, and prevent bloat
What’s all the Fuss About?

“Every year, more than 2 million persons in the United States are infected with antibiotic-resistant bacteria and approximately 23,000 persons die as a result of these infections.”

How bacteria develop resistance

1. Lots of germs. A few are drug resistant.
2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3. The drug-resistant bacteria are now allowed to grow and take over.
4. Some bacteria give their drug-resistance to other bacteria, causing more problems.

www.cdc.gov
Is antibiotic resistance new?

- penicillin discovered by Alexander Fleming in 1928
- widely used in WWII for surgical and wound infections: “miracle drug”
- penicillin-R *Staphylococcus* identified in 1940
- Fleming warned of bacteria becoming resistant in his acceptance speech for the Nobel prize in 1945
- resistant bacteria in soil, in native habitat
Resistance Develops Rapidly

<table>
<thead>
<tr>
<th>Antibiotic introduced</th>
<th>Resistance identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline – 1950</td>
<td>Tetracycline-R <em>Shigella</em> 1959</td>
</tr>
<tr>
<td>Erythromycin – 1953</td>
<td>Erythromycin-R <em>Streptococcus</em> 1968</td>
</tr>
<tr>
<td>Methicillin – 1960</td>
<td>Methicillin-R <em>Staphylococcus</em> 1962</td>
</tr>
<tr>
<td>Gentamicin – 1967</td>
<td>Gentamicin-R <em>Enterococcus</em> 1979</td>
</tr>
<tr>
<td>Ceftazidime – 1985</td>
<td>Ceftazidime-R enterobacteria 1987</td>
</tr>
<tr>
<td>Levofloxacin – 1996</td>
<td>Levofloxacin-R pneumococcus 1996</td>
</tr>
<tr>
<td>Ceftaroline - 2011</td>
<td>Ceftaroline-R <em>Staphylococcus</em> 2011</td>
</tr>
</tbody>
</table>

[www.cdc.gov/drugresistance/about.html](http://www.cdc.gov/drugresistance/about.html)
The CDC has prioritized bacteria into three categories

1. Urgent
   - *Clostridium difficile*
   - Carbapenem-resistant Enterobacteriaceae
   - Drug-resistant *Neisseria gonorrhoeae*

2. Serious
   - Multidrug-resistant *Acinetobacter*
   - Drug-resistant *Campylobacter*
   - Extended spectrum beta-lactamase producing Enterobacteriaceae
The CDC has prioritized bacteria into three categories

2. Serious, continued

- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella Typhi*
- Drug resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis
The CDC has prioritized bacteria into three categories

3. Concerning threats
   - Vancomycin-resistant *Staphylococcus aureus*
   - Erythromycin-resistant Group A *Streptococcus*
   - Clindamycin-resistant Group B *Streptococcus*
What’s all the Fuss About?

- many of these bacteria don’t commonly cause disease in cattle
- many of these antibiotics aren’t used in veterinary medicine
- how can the antibiotic resistance problem possibly originate with livestock?
How bacteria share resistance – Plasmids

- Circular DNA molecules
- Separate from cell chromosome
- Can replicate independently
- Carry genes that benefit bacterial survival, such as antibiotic resistance genes
- Can transfer to other bacteria, other species, by conjugation, transformation or transduction

Images from Wikipedia
How beef cattle might be to blame

+ or =

Bacteria

E. coli
How beef cattle might be to blame

+ or =

E. coli

Bacteria
Or chickens! The colistin story

- an old antibiotic that was toxic to the kidneys
- useful to kill very resistant Gram-negative bacteria
- plasmid resistance has been identified, transferable
- resistant *E. coli* found in poultry and pork in China, where colistin is fed extensively
- Lancet estimates that agriculture purchases 12,000 tonnes of colistin a year (tonne = 1000kg)
- Not approved for any food animal in the US
Or humans!

- doctors and patients inappropriately overusing antibiotics
- in hospitals, antibiotic resistance is spread by high rates of antibiotic drug use and inadequate infection control processes
- in communities, antibiotics are prescribed when not needed – to meet patient demands or to be ‘safe rather than sorry’
- In 2000, 30 prescriptions/100 persons/yr – 4 kg of antibiotics per 100 persons/yr
Preventing the spread of drug-resistant infections in humans!

- immunizations
- safe food preparation
- handwashing
- using antibiotics as directed and only when necessary
- up to half of the current antibiotic use in humans is unnecessary (CDC)
Preventing the spread of drug-resistant infections in humans!

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Examples of How Antibiotic Resistance Spreads

Animals get antibiotics and develop resistant bacteria in their guts.

Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.

Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.

Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.

George gets antibiotics and develops resistant bacteria in his gut.

George stays at home and in the general community. Spreads resistant bacteria.

George gets care at a hospital, nursing home or other inpatient care facility.

Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.

Resistant bacteria spread to other patients from surfaces within the healthcare facility.

Patients go home.

Simply using antibiotics creates resistance. These drugs should only be used to treat infections.
Antibiotic resistance

Slide courtesy Dr. Gene Madsen
What’s all the Fuss About?

- “The National Action Plan provides a roadmap to guide the Nation in rising to the challenge of antibiotic resistance and potentially saving thousands of lives.” – 5 yr plan – by 2020:
  - Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.
  - Elimination of the use of medically-important antibiotics for growth promotion in food-producing animals.
What quantity of antibiotics is used in US food animals?
Medically necessary treatments are not under threat
Ionophores – Rumensin and Bovatec - are not under threat
Antibiotics to increase rate of gain will not be permitted

Costs of production are expected to increase
Dead bacteria do not pass on resistance

“Always administer antibiotics at a dosage and for a period of time that will eliminate the pathogen”
Dead Bacteria Do Not Pass On Resistance

- if an inadequate dose or duration is given, or the wrong drug is given, the bacteria will not all be killed and are likely to adapt and replicate and pass their resistance onwards
- sublethal doses allow stronger bacteria to survive
- the animal’s immune system finishes the job
- antibiotic stewardship is key to preventing resistance
Preventing the spread of drug-resistant infections in humans!

- immunizations
- safe food preparation
- handwashing
- using antibiotics as directed and only when necessary
- up to half of the current antibiotic use in humans is unnecessary (CDC)
Preventing the spread of drug-resistant infections in cattle!

- vaccinations
- high quality feed
  - for growth and healthy immune system
  - free of salmonella, listeria, Johne’s
- sanitation
- ventilation
- biosecurity – don’t buy problems
If you think that you understand antibiotic resistance, then it hasn’t been explained to you very well!

Dr. Guy Loneragan, DVM, PhD
West Texas Texas A&M, 2010