

Antimicrobial Resistance and Prudent Use of Antimicrobials



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Objectives for This Session...

- Describe in general terms:
 - Mechanisms of antimicrobial resistance and resistance development
 - The concept of rational use of antimicrobials
 - How to use antimicrobials in ways that are...
 - ✓ Most likely to lead to treatment success
 - ✓ Less likely to lead to adverse effect such as treatment failure
 - ✓ Less likely to lead to the development of antimicrobial resistant bacteria

Much of this information was adapted from:
http://dairybeef.ucdavis.edu/section5_1.htm



Other good sources of info:

http://www.fda.gov/cvm/cvm_scriptanimation.htm

http://www.cdc.gov/ncidod/aip/research/ar.html#what_ar

Antibiotic vs Antimicrobial

According to the FDA:

- Antibiotic - "A chemical substance produced by a microorganism that has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms."

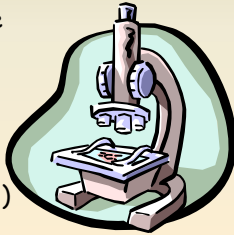
- Antimicrobial - Compound that inhibits the growth/kills microorganisms
 - Includes antibiotics in addition to compounds that are not of microorganism origin
 - Includes synthetic products such as sulfas, quinolones, and nitrofurans

Antimicrobial Classifications

- Antimicrobials inhibit the growth of bacteria (bacteriostatic)

Or

- Kill bacteria (bactericidal)



Antimicrobials Work in One of Five Ways (5 target areas)

- Disruption of cell wall synthesis
 - β -lactams (penicillin, amoxicillin, cephalosporins)
- Disruption of cell membrane synthesis
 - Polymyxin
- Inhibition of ribosomal protein synthesis
 - Aminoglycosides, Tetracyclines, Macrolides, Lincosamides
- Alteration of metabolism/ enzyme system
 - Tiamulin, Sulfas
- Inhibition of DNA replication
 - (e.g. Fluoroquinolones)

Concerns Abound Regarding Antimicrobials and Public Health

- Antimicrobial resistance among animal and human microbes increasing over time
 - Complicates therapy
 - Associated with increased morbidity/ mortality
- Animal antimicrobial usage is under increasing scrutiny
 - Issues re: foodborne problems - resistance and residues
 - Concern that food animal resistance problems are the root of human resistance problems

Resistance Concerns Have Impacted Animal Agriculture

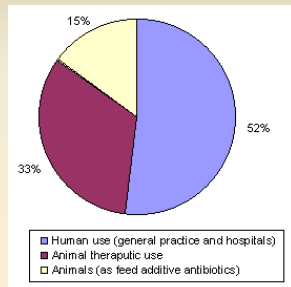
- Slowed/ delayed approval of new antimicrobials in animal ag
- New guidelines for approval of new antimicrobials
- Removal/ restrictions of antibiotics from use in food animal agriculture

Are Food Animals the Culprit?

Organism	Animal Source of Resistance?
Methicillin-resistant <i>Staphylococcus aureus</i>	NO
<i>Mycobacterium tuberculosis</i>	NO
<i>Streptococcus pneumoniae</i>	NO
<i>Streptococcus pyogenes</i>	NO
<i>Neisseria meningitidis</i>	NO
<i>Neisseria gonorrhoea</i>	NO
<i>Campylobacter</i> spp	Possible
<i>Salmonella</i> spp	Possible
<i>E coli</i> (arogen, O157)	Possible
Vancomycin-resistant <i>Enterococci</i>	Possible
<i>Pseudomonas aeruginosa</i>	NO
<i>Klebsiella</i> spp	NO
<i>Acinetobacter</i> spp	NO
<i>Enterobacter</i> spp	NO

Note. From "Opinion of the Scientific Steering Committee on Antimicrobial Resistance," report by the European Commission, DG XXIV, Consumer Policy and Consumer Health Protection, 1999; and from "Antibiotic Growth Promoters, Villains, or Scapegoats?" by R.G. Bywater, 2000, paper presented at the Royal Society Medicine Meeting on Antibiotic Resistance, p. 2, table 1.

Usage of Antibiotics in Human and Animals in the EU (1997)



Antibiotic Resistance In The EU—Science, Politics, And Policy, Ghislain Follet

Prudent Antimicrobial Use: Residues vs Resistance

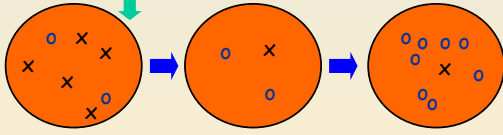
- Residues
 - Detectable amounts of drugs in meat or milk
 - Avoided by careful attention to withdrawal recommendations (label/ extra-label issues)
 - Withhold the sale of milk (or delay sending animal to market) until it no longer poses a risk to human health

Prudent Antimicrobial Use: Residues vs Resistance

- Resistance
 - Ability of a bacterium to resist or overcome the effects of an antibiotic
 - No longer able to kill (or inhibit growth)
 - In any large population of bacteria, a few will be present which possess resistances traits
 - Susceptible organisms (lack the advantageous trait) will be eliminated, leaving the remaining resistant populations behind
 - Survival of the fittest
 - Antibiotic action is an environmental pressure
 - Resistant ones are able to live, reproduce, pass along their traits

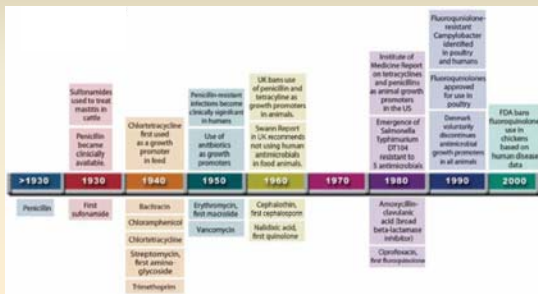
Selection for Resistance

Antibiotic Given



X - Bacteria sensitive to drug
O - Bacteria resistant to drug

Not a New Problem...



http://www.cdc.gov/narms/get_smart.htm

Lessons Learned About Antibiotic Resistance

- Given enough antibiotic and time, resistance will appear
 - Penicillin-resistant *Streptococcus pneumoniae* took 25 years to become a clinical problem
 - Fluoroquinolone-resistant Enterobacteriaceae took 10 years to emerge clinically
 - *Staph aureus* could be treated successfully with penicillin in the 1940s and 1950s. Now, nearly all strains are resistant to penicillin, and many are resistant to nafcillin
- Resistance is progressive, moving from low to intermediate to high levels
 - Organisms resistant to one antibiotic will likely become resistant to others
 - Once selected, drug resistance will not disappear, but it may decline slowly

(Levy SB. Multidrug resistance--a sign of the times [Editorial]. N Engl J Med 1998;338:1376-8)

Bacteria Have 3 Primary Biochemical Mechanisms to Resist Effects of Antimicrobials

- Mutation
- Destruction / Inactivation
- Efflux

Mutation

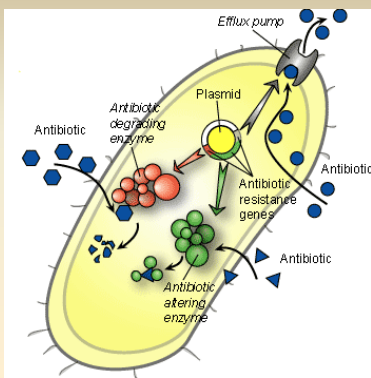
- Spontaneous change in a portion of the DNA
- Once the gene has been changed the mRNA transcribed from that gene will now carry an altered message
- Change could be deadly, neutral or advantageous
 - Deadly - bacterium dies
 - Advantageous - new DNA incorporated for future generations

Destruction or Inactivation

- Many bacteria possess genes which produce enzymes that chemically degrade or deactivate the antimicrobial, rendering them ineffective against the bacterium.
- Here the antimicrobial is either degraded or modified by enzymatic activity before it can reach the target site and damage the bacterial cell.

Efflux

- An efflux pump is essentially a channel that actively exports antimicrobial and other compounds out of the cell
- The antimicrobial enters the bacterium through a channel termed a porin
 - It is then pumped back out of the bacterium by the efflux pump
 - Efflux pumps prevent the intracellular accumulation of antimicrobial necessary to exert their lethal activity inside the cell



Resistance Occurs... The Key is How Quickly

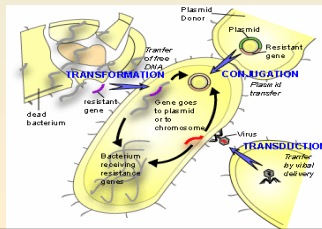
- Forces increasing resistance:
 - Inappropriate/ overuse of antibiotics in human health
 - Overuse of antibacterial cleaning products in homes, health care facilities
 - Overexposure of environmental bacteria
 - Via products in effluents or ground water
 - Via antibiotic use on crops like fruit trees
 - Inappropriate/ overuse of antibiotics in animal agriculture

Two Primary Methods of Acquiring Resistance

- Extrinsic - Gene acquisition (gene transfer from other bacteria)
 - Beta-lactamases encoded onto extrachromosomal DNA plasmids
 - Plasmids easily transferred from one bacteria to another
 - Plasmids can jump across strains of bacteria
- Intrinsic - Chromosomal mutation
 - Less common
 - Ex: Mutation in transpeptidase-encoding gene affecting ability to bind to a particular betalactam (*S. Aureus* resistance to Methcillin)

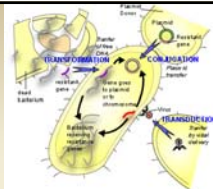
Extrinsic Resistance: Horizontal Gene Transfer

- Genetic material can be transferred between bacteria by several means, most often by:
 - Conjugation
 - Transformation
 - Transduction



(Extrinsic) Conjugation (Plasmid-Mediated)

- Plasmid is a form of circular DNA
 - Replicates independently of the chromosomes
- Plasmids may contain genes that confer resistance to antimicrobials
- When two cells are in close proximity to each other, a hollow bridge-like structure, known as a pilus, forms between two cells.
- Allows a copy of the plasmid, as it is duplicated, to be transferred from one bacterium to another.
- Enables a susceptible bacteria to acquire resistance to a particular antimicrobial agent

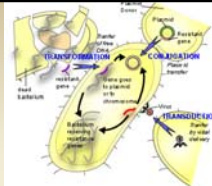


(Extrinsic)
Transformation



- Transfer of genes from one bacterium to another as "naked" DNA
- Cells die and break apart
 - DNA can be released into the environment
 - Other bacteria that are close can scavenge this free-floating DNA
 - It becomes incorporated into their own DNA

(Extrinsic)
Transduction



- Bacterial DNA is transferred from one bacterium to another inside a virus that infects bacteria
 - These viruses are called bacteriophages or phages.
- When a phage infects a bacterium, takes over the bacteria's genetic processes to produce more phage
- Bacterial DNA may inadvertently be incorporated into the new phage DNA
- Upon bacterial death and lysis, these new phages go on to infect other bacteria.
- Moves genes from one bacterium to another

(Intrinsic)
Mutation

- A change in the DNA can sometimes cause a change in the gene product, which is the target of the antimicrobial.
- Ex: Fluoroquinolones and DNA gyrase
 - Fluoroquinolones can bind to an enzyme called DNA gyrase
 - DNA gyrase is required for DNA replication
 - Normally, fluoroquinolones bind to DNA gyrase and block bacterial DNA replication → cell death
 - With a spontaneous mutation in genes encoding for DNA gyrase, can no longer bind
 - Bacteria continue DNA replication unimpeded

Antimicrobial Use in Animal Agriculture

- 3 primary uses:
 - Treat disease
 - Prevent illness
 - Promote growth
- Antimicrobial use in livestock has created *part* of the problem, particularly as growth promotants
- 2 Big Concerns:
 - Decreased ability to treat disease
 - Possible spread of resistant bacteria from farm

Review of Resistance Processes

- Mechanisms of Resistance: 2 Methods of Acquisition
- Mutation
 - Intrinsic
 - Mutation
 - Destruction / Inactivation
 - Efflux
 - Extrinsic (gene acquisition)
 - Conjugation
 - Transformation
 - Transduction

Common Antimicrobials and Methods of Resistance

<u>Antibiotic</u>	<u>Method of Resistance</u>
Tetracycline	Active efflux from cell
β-lactams	Hydrolysis or protein binding
Sulfonamides	Overproduction of antibiotic target
Fluoroquinolones	Modification of antibiotic binding site
Aminoglycosides	Enzymatic modification of antimicrobial

Goals of Prudent Drug (Antimicrobial) Use

- Slow down rate of developing drug resistance
- Prolong the usefulness of antimicrobials in FA ag
- Promote responsible use of antimicrobials
- Protect the integrity of the food supply

Basic Principles for Prudent Use of Antimicrobials

- Antimicrobials should be used to treat specific bacterial diseases
- Antimicrobials should be administered to animals correctly
 - Correct dose, correct route, correct duration
- Non-therapeutic uses are discouraged
- Off-label drug use is done only by veterinary prescription

Recommendations for Reducing Resistance and Residue Risks

- Promote health/ prevention of disease
 - Improve comfort/ housing
 - Improve nutritional management
 - Reduce effects of environmental stressor
- Identify diseases earlier (chronic disease requires longer, more aggressive therapy)
- Provide more focused treatment
- Use antimicrobials correctly and only when needed
- Follow prescribed withdrawal periods

Sources of Antimicrobial Use on Dairies

- Baby calves (milk replacers) ←
- Dry cow therapy
- Fresh cow programs (metritis) ←
- Other sick cows
 - Mastitis
 - Pneumonia
 - Hoof problems

Types/ Sources of Antimicrobials Use in "Wet" Calves

- Antibiotics in milk replacer
 - Tetracycline/ Neomycin, primarily
 - Low levels of antimicrobials in waste milk
 - Antimicrobials used for scours
 - Antimicrobials used for pneumonia

Management to ↓ Antimicrobial Use in Calves

- Colostrum management
 - Colostrum deficient calves are up to 5x more likely to need/ receive antimicrobials
- Feed milk replacer without antibiotics
- Provide high quality feeds and water
- Provide clean, dry, comfortable environment
- Education/ training efforts

Fresh Cow Monitoring and Treatment Protocols

- A management routine often used to monitor newly calved (fresh) cows
- Goals:
 - Catch disease early and treat it
 - Reduce chance of dz becoming more severe
 - Reduce risk of further economic loss, animal discomfort

Fresh Cow Monitoring and Treatment Program

- Daily evaluation of each fresh cow
 - Visual observation
 - Rectal temperature
 - Physical exam for other diseases
 - +/- ketone evaluation
- Evaluated front AND rear of the cow
- Follow prescribed treatment protocols when problems identified



Sample Protocol for Acute Puerperal Metritis

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Excenel 25/ 30 cc IM	X	X	X	X	X	Metritis Protocol 2 (if needed)
Aspirin 4 boluses PO	X	X	Re- evaluate			
Check for ketosis/ DA	X	X	X	X	X	X

- Metritis:
 - Rectal temperature > 103.5 AND
 - Presence of fetid odor OR discharge
- 1st lactation animals receive 25 cc/ day, cows get 30 cc/ day of Excenel
- Record event in record system
- Milk withdrawal = 0 hours; Meat withdrawal = 72 hrs after last Excenel
- May also combine with Ketosis protocol if needed

Ketosis Protocol

Treatment	Day 1	Day 2	Day 3
IV Dextrose (1 bottle)	X	X	Re-evaluate
Propylene Glycol 10 oz orally	X	X	Re-evaluate
Check for DA	X	X	X

- Record event in computer system
- Milk withdrawal = 0
- Meat withdrawal = 0

Review: Key Points of Prudent Antimicrobial Use

- Reduce use of antimicrobials at "below tx" levels (sub-therapeutic)
- Get a diagnosis prior to treating sick cows
- Develop written tx protocols for your clients
- Provide worker training to ensure antimicrobials are used properly
- Apply preventive medicine strategies to reduce the number of sick cows/ calves

Thanks For Your Attention!



QUESTIONS?

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