ANTIMICROBIAL STEWARDSHIP:
GETTING THE MOST OUT OF CULTURE
AND SUSCEPTIBILITY TESTS
INSIGHTS FROM A MICROBIOLOGIST

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DISCLOSURES

• Received research grants from
  • Zoetis
  • Elanco/Novartis
• I am a microbiologist and not a practitioner!
OBJECTIVES

- To give an overview of the scope of the problem of AMR
- To inspire the intent to change/improve/reevaluate prescribing practices
- To provide tools to use antimicrobials more effectively
  - Antimicrobial mechanisms of action and resistance
  - Introduction to intrinsic resistance
  - Overview of key emerging resistance in veterinary medicine
IF NOT TACKLED, RISING AMR COULD HAVE A DEVASTATING IMPACT

By 2050, the death toll could be a staggering one person every three seconds if AMR is not tackled now.

Estimated Attributable Deaths in 2050

https://amr-review.org/
CURRENT THREATS

### Urgent Threats
- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae

### Serious Threats
- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococcus (VRE)
- 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

### Concerning Threats
- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

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**Estimated minimum number of illnesses and deaths caused by antibiotic resistance***:

At least **2,049,442** illnesses, **23,000** deaths

* bacteria and fungus included in this report

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**Antibiotic Resistance Threats in the United States, 2013**
BROAD SPECTRUM β-LACTAMASES

EXTENDED SPECTRUM β-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

- Threat Level: Serious
- This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

- 26,000 Drug-Resistant Infections
- 1,700 Deaths
- 140,000 Enterobacteriaceae Infections Per Year
- $40,000 in Excess Medical Costs Per Year for Each Infection

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013
METHICILLIN RESISTANT STAPH AUREUS

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

THREAT LEVEL: SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

- 80,461 severe MRSA infections per year
- 11,285 deaths from MRSA per year

STAPH BACTERIA ARE A LEADING CAUSE OF HEALTHCARE-ASSOCIATED INFECTIONS

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013
EMERGING RESISTANCE IN CANADA

FIGURE 15: Count of CPE isolates by resistance gene, 2011-2016

<table>
<thead>
<tr>
<th>Year</th>
<th>KPC</th>
<th>NDM</th>
<th>OXA-48-like</th>
<th>SME</th>
<th>OXA-48/NDM</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>87</td>
<td>33</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>63</td>
<td>40</td>
<td>26</td>
<td>17</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2013</td>
<td>53</td>
<td>101</td>
<td>18</td>
<td>31</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2014</td>
<td>125</td>
<td>132</td>
<td>23</td>
<td>22</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>2015</td>
<td>168</td>
<td>155</td>
<td>65</td>
<td>21</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>2016</td>
<td>314</td>
<td>227</td>
<td>160</td>
<td>24</td>
<td>160</td>
<td>24</td>
</tr>
</tbody>
</table>

Infection rate per 10,000 patient-days

Canadians

ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM
2017 REPORT
Canada
FIGURE 38: Resistance to selected antimicrobials among *Salmonella* isolates from chicken meat samples collected at retail stores, 2006-2016

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>2006 (n=34)</th>
<th>2007 (n=252)</th>
<th>2008 (n=482)</th>
<th>2009 (n=470)</th>
<th>2010 (n=281)</th>
<th>2011 (n=210)</th>
<th>2012 (n=326)</th>
<th>2013 (n=238)</th>
<th>2014 (n=247)</th>
<th>2015 (n=183)</th>
<th>2016 (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>14.9%</td>
<td>17.9%</td>
<td>17.0%</td>
<td>31.1%</td>
<td>27.6%</td>
<td>31.6%</td>
<td>29.9%</td>
<td>27.9%</td>
<td>21.3%</td>
<td>14.2%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Ceftiraxone</td>
<td>9.6%</td>
<td>10.2%</td>
<td>12.6%</td>
<td>22.0%</td>
<td>22.0%</td>
<td>29.9%</td>
<td>26.1%</td>
<td>26.3%</td>
<td>21.0%</td>
<td>12.8%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.0%</td>
<td>1.7%</td>
<td>1.0%</td>
<td>0.8%</td>
<td>0.0%</td>
<td>0.6%</td>
<td>0.9%</td>
<td>4.9%</td>
<td>2.6%</td>
<td>1.1%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.3%</td>
<td>1.4%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>28.7%</td>
<td>32.4%</td>
<td>31.7%</td>
<td>27.9%</td>
<td>26.0%</td>
<td>35.5%</td>
<td>25.5%</td>
<td>27.9%</td>
<td>19.0%</td>
<td>31.7%</td>
<td>36.1%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>31.9%</td>
<td>34.1%</td>
<td>34.0%</td>
<td>28.8%</td>
<td>26.5%</td>
<td>36.8%</td>
<td>28.9%</td>
<td>28.2%</td>
<td>18.7%</td>
<td>33.5%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1.1%</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.8%</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.1%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Antimicrobial use in companion animals

In 2016, the predominant classes of antimicrobials used in companion animals were cephalosporins, β-lactams, and trimethoprim-sulfon (Figure 54). All three of these classes are antimicrobials of high importance to humans according to the classification system of the Veterinary Drugs Directorate, Health Canada.

**FIGURE 54**: Relative quantities of antimicrobial classes distributed for use in companion animals (percentages based on kg active ingredient), 2016.

**NOTE**: Data sources: Canadian Animal Health Institute. Antimicrobials used were assigned to animal type according to label data and in the situations where mixed species were indicated on the label, the species were assigned to the top to animal: "Companion animal" or "Production animal". Values do not include antimicrobials imported under the "hive use" provision or imported as active pharmaceutical ingredients used in compounding. "Other antimicrobials" for 2015 included: aminoglycosides, bacitracin, bambermycin, chloramphenicol, diclofenac, fluoroquinolones, nitroimidazoles, rifamycins, rifamycin, sulfonamides, tetracyclines, tilmicosin, and vancomycin.
ANTIMICROBIAL USE
COMPANION ANIMALS

• Large study out of UK
  • 216 practices
  • Included data from >400,000 dogs and >200,000 cats
    • Beta-lactams most commonly used
      • Amox + clav in dogs
      • 3rd Generation cephalosporins in cats
Figure 57: J01 Antimicrobial consumption (DDDs per 1,000 inhabitant-days), Canada (CA) and Europe (EU)

Figure 58: Sales of antimicrobials (adjusted by populations and weights) for Canada (2014) and countries participating in the European Surveillance of Veterinary Antimicrobial Consumption (2015)

NOTE: Data source: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-Food Canada, Eurovet Canada, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). PCU = predatory consumption unit. The Canadian data used for the horizontal bars represent data from 2013 and from 2013 to 2014, whereas data from 2015 are not available. For the Canadian data, values do not include non-food data. Imported data under this "food use" are provided in or imported as active pharmaceutical ingredients used in compounding. The PCU denominator was harmonized to the greatest extent possible with ESVAC. ESVAC denominator does not include feed uses, whereas in Canada feed uses are a significant population and are included. The ESVAC approach excludes companion animal data.
“The term “antimicrobial stewardship” is used to describe the multifaceted and dynamic approaches required to sustain the clinical efficacy of antimicrobials by optimizing drug use, choice, dosing, duration, and route of administration, while minimizing the emergence of resistance and other adverse effects.”
STEWARDSHIP – WHAT IS IT?

“…a coherent set of actions which promote using antimicrobials responsibly… translated into context-specific and time-specific actions.”
STEWARDSHIP – WHAT IS IT?

- Active stewardship – changing behaviors
- Greatest impact on antimicrobial use
  - Specialist consultation on patient management (ID specialists, pharmacists)
  - Laboratory reports
    - Nudging
    - Suppressing
    - Framing
  - Active monitoring of antimicrobial usage (at an institutional level)
  - Audit and feedback
STEWARDSHIP – WHAT IS IT?

- Passive stewardship – providing knowledge
- Less effective
  - Prudent use guidelines
  - Educational opportunities (CE like today!)
PROXIMATE RISKS OF ANTIMICROBIALS ADVERSE DRUG EVENTS

Antibiotics are responsible for almost 1 out of 5 emergency department visits for adverse drug events.

Antibiotics are the most common cause of emergency department visits for adverse drug events in children under 18 years of age.
ADVERSE DRUG EVENTS

• 20% of hospitalized patients given antimicrobials had ADE
  • 19% of ADE occurred in patients not needing antimicrobials
ADVERSE DRUG EVENTS

“…ADEs are common among inpatients receiving antibiotics, some of which may be avoidable with more judicious use of antibiotics.”

“…antibiotic-associated ADEs may not be recognized by clinicians because ADEs have varied manifestations…”
ADVERSE DRUG EVENTS

• >140,000 annual emergency department visits in the United States for antibiotic associated ADE

Although the risk of an ED visit for an antibiotic-associated adverse event is small for an individual patient, when antibiotics are commonly prescribed for indications for which they have no benefit, the burden of preventable adverse events in the population is great.

Emergency Department Visits for Antibiotic-Associated Adverse Events

Nadine Shehah, Priti R. Patel, Arjus Stinivasan, and Daniel S. Budeitz
Division of Healthcare Quality Promotion, National Center for Detection, Preparedness, and Control of Infectious Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Clinical Infectious Diseases 2018;67:375-43
WHAT STEWARDSHIP MEANS TO ME:

1. Thinking
2. Utilizing your knowledge of:
   - Drug mechanisms of action (spectrum of activity)
   - Mechanisms of resistance
   - Intrinsic resistance
3. Using a diagnostic lab, asking questions when you need more information
4. Being nimble and adapting to emerging resistance
5. Lifelong learning
MECHANISMS OF ACTION

- Cell Wall
  - β-lactams
- Protein Synthesis
  - Tetracyclines, macrolides (MLSBK), aminoglycosides, chloramphenicol
- DNA Metabolism
  - Fluoroquinolones, metronidazole,
- Anti-metabolites
  - Folate synthesis inhibitors (sulfas)
B-LACTAMS

- Inhibit cell wall synthesis
  - Bind to penicillin binding proteins
  - Prevent final stage of peptidoglycan synthesis
- Bacteriocidal
- Super family of antimicrobials
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - β-lactamase inhibitors (clavulanic acid, sulbactam)
B-LACTAMS

Variable side chain yields different penicillins

4-membered β-lactam ring

5-membered penicillin ring

R - CO - N

CH₃

COOH

CH₃
# B-Lactams

## Penicillins

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Antimicrobial Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl penicillins</td>
<td>penicillin G</td>
<td>Gm +</td>
</tr>
<tr>
<td>Orally absorbed benzyl penicillins</td>
<td>penicillin V</td>
<td>Gm +</td>
</tr>
<tr>
<td>Anti-staphylococcal penicillins</td>
<td>cloxacillin, oxacillin</td>
<td>Staphylococci</td>
</tr>
<tr>
<td>Extended-spectrum penicillins</td>
<td>ampicillin, amoxicillin</td>
<td>Gm + and -, but not β-lactamase stable</td>
</tr>
<tr>
<td>Anti-pseudomonal penicillins</td>
<td>piperacillin</td>
<td>Gm – (less Gm +)</td>
</tr>
<tr>
<td>β-lactamase resistant penicillins</td>
<td>temocillin</td>
<td></td>
</tr>
</tbody>
</table>
# B-LACTAMS

## CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Generation</th>
<th>Examples</th>
<th>Antimicrobial Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>cephalothin, cefazolin, cephalexin</td>
<td>Staphylococci, susceptible Enterobacteriaceae</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>cefuroxime</td>
<td>Enterobacteriaceae, anaerobes</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>cefevocin, ceftiofur, cefpodoxime, ceftriaxone</td>
<td>β-lactamase producing Enterobacteriaceae</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>cefepime, cefpirome</td>
<td>Gram negatives, non-fermenters</td>
</tr>
</tbody>
</table>
TETRACYCLINES

- Protein synthesis inhibitors
  - Bind to the 30S ribosomal subunit
  - Bacteriostatic
- Oxytetracycline, doxycycline, minocycline
  - Increasing lipophilicity
- Broad spectrum
  - Gram positives and negatives, intracellular parasites *Rickettsia, Ehrlichia*
  - When you think ‘weird’ organisms, think tetracyclines!
FLUOROQUINOLONES

The “Goldilocks” Zone

- Interfere with DNA metabolism
  - Gyrases and topoisomerases which supercoil DNA
- Concentration dependent
  - Biphasic (less active at very low and very high concentrations)
- Naladixic acid – limited spectrum (Gram negative)
- Ciprofloxacin/enrofloxacin – broad spectrum (Gram positive and negative, intracellular pathogens)
AMINOGLYCOSIDES

- Protein synthesis inhibitors +
  - Also effects: electron transport chain, DNA metabolism, cell membrane structure
- Concentration dependent
- Some of the best anti-Gram negative drugs
  - Enterobacteriaceae, P. aeruginosa
- Anti-staphylococcal activity (important for MRSP)
- NO anaerobic activity – oxygen dependent uptake of drug by cell
• Super-family of antimicrobials
  • Macrolides, lincosamides, streptogramins and ketolides
• Protein synthesis inhibitors
• Bacteriostatic
• Good activity against Gram positives, some Gram negatives well (*Brucella*, *Campylobacter* spp.,) and anaerobes.
• Generally poor activity against Enterobacteriaceae and non-fermenters (*P. aeruginosa*).
<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Spectrum of Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides</td>
<td>Erythromycin, tylosin</td>
<td>Gm +, some Gm – (Haemophilus, Moraxella, Pasteurella spp., and Bordatella spp. The ‘odd ones’ Legionella pneumophila, Chlamyphila psittaci, Leptospira, Treponema pallidum, Mycoplasma. Anaerobes – better against Gm + anaerobes than Gm - anaerobes</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Clindamycin, lincomycin</td>
<td>Gm +, anaerobes and the “odd ones” – see macrolides</td>
</tr>
<tr>
<td>Streptogramin B</td>
<td>Virginiamycin, quniupristin-dalfopristin</td>
<td>Gm + cocci and bacilli, Gm –ve cocci, Moraxella, Bordatella, intracellular organisms (Chlamydia, Rickettsia, Mycobacterium tuberculosis), anaerobes</td>
</tr>
<tr>
<td>Ketolides</td>
<td>Telithromycin, clarithromycin</td>
<td>Encompasses the spectrum of the macrolides and has better Gram + coverage.</td>
</tr>
<tr>
<td>Azalides</td>
<td>Azithromycin</td>
<td>Similar spectrum of activity as the macrolides but with better Gram negative activity.</td>
</tr>
</tbody>
</table>
CHLORAMPHENICOL

- Banned in food animals!
- Idiosyncratic aplastic anemia associated in people
  - Rare (1-20,000-40,000)
- Protein synthesis inhibitor
  - Bacteriostatic
- Broad spectrum of activity
  - Gram positives and negatives
- Florfenicol is a veterinary drug related to chloramphenicol
  - Not associated with aplastic anemia
METRONIDAZOLE

- Banned in food animals!
  - Carcinogenic
- Damage DNA and interfere with repair mechanisms
  - Bacteriocidal
- Active against anaerobic bacteria
  - Gram positive and negative bacteria
  - Protozoans (*Tritrichomonas foetus, Giardia*)
- Drug that we don’t know tons about vis-a-vis resistance
  - Avoid the temptation of “dog with diarrhea = metronidazole”
FOLATE SYNTHESIS INHIBITORS

- Sulfonamides and diaminopyrimidines (trimethoprim)
- Bacteriostatic
- Broad spectrum
  - Gram positive and negative
  - Protozoans and *Toxoplasma*
Folate Synthesis Pathway

Para-aminobenzoic acid (PABA)

Dihydropteroate synthetase

L-glutamate

Dihydrofolate synthetase

Dihydrofolate reductase

Diaminopyrimidines

Competitive Inhibition

Enzymatic Inhibition

Basic Sulfa

DNA, RNA and Protein Synthesis
GENERAL MECHANISMS OF RESISTANCE

1. Decreased permeability
2. Increased efflux
3. Enzymatic alteration of drug
4. Target modification
5. Alternate metabolic pathways
WHERE DOES RESISTANCE COME FROM?

• Natural phenomenon!
  • Soil organisms survive in an environment that contains antimicrobial compounds
  • Enteric organisms need to survive in the presence of bile acids

• Resistance to every drug that has, is or will be used in the future already exists
  • Drug resistance is often a byproduct of something else
  • ANY/ALL drug use (appropriate or inappropriate) results in selection pressure
    • If you use a drug it better be worth it!
“It is a neck-and-neck race in which many of us tend to underestimate the opponent. Staphylococci will not be defeated by the haphazard use of each new antibiotic. As new antibacterial agents are discovered, let us use them with discrimination.”

Dr. Mary Barber - 1955
### The Evolutionary Power of Bacteria

#### Human Generations in our History as a Species

<table>
<thead>
<tr>
<th>Time</th>
<th>Generation Length</th>
<th>Generations in Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Million Years</td>
<td>25 years</td>
<td>80,000</td>
</tr>
</tbody>
</table>

#### Bacterial Generations in the History of Antimicrobials

<table>
<thead>
<tr>
<th>Time</th>
<th>Generation Length</th>
<th>Generations in Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 years</td>
<td>20 minutes</td>
<td>2,049,840</td>
</tr>
</tbody>
</table>
BASIC DEFINITION – WHAT IS RESISTANCE?

- Resistance can be sub-divided into intrinsic and acquired
- Intrinsic resistance is constitutive for an organism
  - Natural “superbugs”, it’s just part of what they are

Pseudomonas aeruginosa
BASIC DEFINITION – WHAT IS RESISTANCE?

- Resistance can be sub-divided into intrinsic and acquired
- Intrinsic resistance is constitutive for an organism
- Acquired resistance is not inherent to the organism, these bugs have something that makes them “super”

Staphylococcus aureus
MECHANISMS OF RESISTANCE

• How do bacteria acquire resistance “genes”?
  • Mutation – single nucleotide polymorphisms
  • Conjugation – exchange between bacteria (mobile genetic elements)
  • Transduction - phages
  • Transformation – acquisition of exogenous DNA
MECHANISMS OF RESISTANCE
B-LACTAMS

- Enzymatic inactivation
  - Primary mechanism of resistance among Enterobacteriaceae
  - β-lactamases
    - Great diversity of enzymes
- Altered binding sites
  - Streps, enterococci, methicillin-resistant Staph
MECHANISMS OF RESISTANCE
TETRACYCLINES

• Efflux
  • Common in Gram positive and negative
    • Resistance not necessarily across class...
      • If you want to use a drug test it!

• Ribosomal protection
  • Very common
    • *S. pseudintermedius* (tetM)
  • Conformational change in tetracycline binding site on 30S subunit of ribosome
  • Ribosomal mutations, enzymatic inactivation also occur
MECHANISMS OF RESISTANCE
FLUOROQUINOLONES

- Target mutations (Gram positive and negative)
  - *gyrA* and *parC* particularly
  - Step-wise resistance (MIC creep)
- Efflux
  - Multidrug resistance
- Plasmid mediated
  - *qnr* (target protection)
  - *qep* (efflux)
  - *aac6-lb-cr* (enzymatic inactivation – cross resistance with aminoglycosides)
MECHANISMS OF RESISTANCE
AMINOGlycOSIDES

• Enzymatic inactivation
  • Aminoglycoside modifying enzymes
  • Most common mechanism of resistance
• Decreased permeability
  • Cross resistance to other antimicrobials
MECHANISMS OF RESISTANCE $\text{MLS}_B^K$

- Target Modification
  - Ribosomal methylases
    - $\text{erm}$ gene family
  - Be aware of inducible resistance
- Active Efflux
- Enzymatic Inactivation

Inducible clindamycin resistance in $\textit{S. aureus}$
Detection requires specialized laboratory tests
MECHANISMS OF RESISTANCE FOLATE SYNTHESIS INHIBITORS

• Altered enzymes
  • $dfr$ genes (trimethoprim resistance)
    • Gram positive and negative
  • $sul$ genes (sulfa resistance)
    • Gram negative bacteria
    • Often found in multi-resistant bacteria, linkage to other resistance genes
• Hyper-production of PABA
• A good grasp of normal allows lab data to be interpreted
  • What do all of those “R’s” really mean?
• Intrinsic resistance is independent of antibiotic exposure
• “Wild-type” phenotype
• *Mycoplasma* spp. intrinsically resistant to penicillin
  • They lack a cell wall and therefore don’t have the drug target
INTRINSIC RESISTANCE ENTEROBACTERIACEAE

- ALL Enterobacteriaceae intrinsically resistant to:
  - Benzylpenicillin (original penicillin)
  - Macrolides
  - Lincosamides (clindamycin)
- SPICE organisms:
  - *Serratia*, *Providencia*, *Proteus vulgaris* (indole positive), *Citrobacter* and *Enterobacter*
- Resistant to many β-lactams including clavamox
# Intrinsic Resistance Non-Fermenters

Table 2. Intrinsic resistance in non-fermentative Gram-negative bacteria. Non-fermentative Gram-negative bacteria are also generally intrinsically resistant to benzylpenicillin, first and second generation cephalosporins, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

| Rule no. | Organisms | Ampicillin | Amoxicillin/Clavulanic acid | Ticarcillin | Ticarcillin-clavulanic acid | Piperacillin | Piperacillin-tazobactam | Cefotaxim, Ceftriaxone, Cefadroxil | Cefadroxil | Cefaclor, Cefepime, Ceftriaxone | Cefepime | Aztreonam | Imipenem | Meropenem | Ciprofloxacin | Chloramphenicol | Aminoglycosides | Trimethoprim | Fosfomycin | Tetracyclines | Polymyxin B/Colistin |
|----------|-----------|------------|-----------------------------|------------|-----------------------------|------------|------------------------|----------------------------------|------------|-----------------------------|------------|------------|------------|-----------|----------------|----------------|----------------|----------------|-------------|-------------|-------------|----------------|
| 2.1      | Acinetobacter baumannii, Acinetobacter pittii, Acinetobacter nosocomialis and Acinetobacter calcoaceticus complex | R | R | Note¹ | R | R | R | R | R | R | R | R | R | R² | Note² | |
| 2.2      | Achromobacter xylosoxydans | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |
| 2.3      | Burkholderia cepacia complex³ | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |
| 2.4      | Elizabethkingia meningoseptica | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |
| 2.5      | Ochrobactrum anthropi | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |
| 2.6      | Pseudomonas aeruginosa | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |
| 2.7      | Stenotrophomonas maltophilia | R | R | R | R | R | R | R | R | R | R | R | R | R | R | |

* R = resistant
• *Enterococci* intrinsically resistant to many drugs
• Accurate speciation is important
• *E. faecalis* intrinsically clindamycin resistant
• *E. faecium* NOT intrinsically clindamycin resistant
• *Enterococcus* spp. don’t tend to produce β-lactamases, amoxicillin + clavulanic acid does not offer advantage over amoxicillin

### Table 4. Intrinsic resistance in Gram-positive bacteria. Gram-positive bacteria are also intrinsically resistant to aztreonam, temocillin, polymyxin B/collistin and nalidixic acid

<table>
<thead>
<tr>
<th>Rule no.</th>
<th>Organisms</th>
<th>Fusidic acid</th>
<th>Ceftaroline</th>
<th>Ceftobiprole</th>
<th>Aminoglycosides</th>
<th>Macrolides</th>
<th>Clindamycin</th>
<th>Glycopeptides</th>
<th>Vancomycin</th>
<th>Teicoplanin</th>
<th>Te fosfamid</th>
<th>Fosfomycin</th>
<th>Novobiocin</th>
<th>Sulphonamides</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td><em>Staphylococcus saprophyticus</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.2</td>
<td><em>Staphylococcus cohnii</em></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.3</td>
<td><em>Staphylococcus xylosus</em></td>
<td>R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.4</td>
<td><em>Staphylococcus capitis</em></td>
<td>R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.5</td>
<td>Other coagulase-negative staphylococci and</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td>R</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>4.6</td>
<td><em>Streptococcus spp.</em></td>
<td>R</td>
<td>R</td>
<td>R²</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>4.7</td>
<td><em>Enterococcus faecalis</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4.8</td>
<td><em>Enterococcus gallinarum, Enterococcus casseliflavus</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.9</td>
<td><em>Enterococcus faecium</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td>R</td>
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</tr>
<tr>
<td>4.10</td>
<td><em>Corynebacterium spp.</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td>R</td>
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</tr>
<tr>
<td>4.11</td>
<td><em>Listeria monocytogenes</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.12</td>
<td><em>Leuconostoc spp., Peptococcus spp.</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>4.13</td>
<td>*Lactobacillus spp. (L. casei, L. casei var.</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
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<tr>
<td></td>
<td>rhamnosus)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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</tr>
<tr>
<td>4.14</td>
<td><em>Clostridium ramosum, Clostridium innocuum</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

R = resistant

1 Low-level resistance (LLR) to aminoglycosides. Combinations of aminoglycosides with cell wall inhibitors (penicillin and glycopeptides) are synergistic and bactericidal against isolates that are susceptible to cell wall inhibitors and do not display high-level resistance to aminoglycosides.

2 In addition to LLR to aminoglycosides, *Enterococcus faecium* produces a chromosomal AAC(6′)-I enzyme that is responsible for the loss of synergy between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillin or glycopeptides.
METHICILLIN RESISTANCE
EMERGENCE OF METHICILLIN RESISTANCE

- MRSA first identified in people in 1961
- In 1990s spread into the community
- In people associated with
  - Higher mortality and health care costs
- In dogs, the similar negative healthcare outcomes not demonstrated
- In Saskatoon, methicillin resistance first recognized in mid to late 2000s
  - Canine MRSA first recognized in 2006
  - Canine MRSP first recognized in 2008
EMERGENCE OF METHICILLIN RESISTANCE

- Unfortunately little BC specific data – 2015 report found 12.9% MR among dermatological isolates including BC

**Brief Communication** Communication brève

Prevalence of methicillin-resistant staphylococci in canine pyoderma cases in primary care veterinary practices in Canada: A preliminary study

Daniel Joffe, Fiona Goulding, Ken Langelier, Gabor Magyar, Les McCurdy, Moe Milstein, Kia Nielsen, Stephanie Vilemaire
WHAT IS METHICILLIN RESISTANCE?

• More than just resistance to methicillin!
• Resistance to **ALL β-LACTAMS**
• *meca* (*mec* family) gene
  • Codes altered penicillin binding protein (PBP2a)
    • Decreased binding affinity β-lactams drugs
    • Resistance to penicillins, cephalosporins and carbapenems
    • β-lactamase inhibitors won’t help!
• Frequently multidrug resistant
## Identification of Methicillin Resistance

<table>
<thead>
<tr>
<th>Test</th>
<th><em>S. aureus</em></th>
<th><em>S. pseudintermedius</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>mecA</em></td>
<td>Gold Standard</td>
<td>Gold Standard</td>
</tr>
<tr>
<td>PBP2a Latex Agglutination</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phenotypic Resistance</td>
<td>Cefoxitin or Oxacillin</td>
<td><strong>ONLY Oxacillin</strong></td>
</tr>
</tbody>
</table>

**PCR Amplification of mecA**

**Agglutination of PBP2a**

**Phenotypic β-lactam resistance**
## The Current State of MRSP...

<table>
<thead>
<tr>
<th>Drug</th>
<th>1986-2000 Clinical (n=60)</th>
<th>2008 Colonized (n=153)</th>
<th>2014 Colonized (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>7</td>
<td>40</td>
<td>73</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>13</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>34</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
The Current State of MRSP...

- Survey of diagnostic isolates from PDS – 2013-2015
  - Urinary and dermatological
- Overall dermatological isolates more resistant than urinary
  - 51 dermatological isolates, 6 MRSP (16%)
  - 50 urinary isolates, 1 MRSP (2%)
- Macrolide and chloramphenicol resistance also more common among dermatological than urinary isolates
METHICILLIN RESISTANCE TAKE AWAYS

1. MR = resistance to ALL β-lactam drugs
2. Because MR is NOT due to the production of β-lactamases, drugs like amoxicillin + clavulanic acid are NOT helpful
3. Susceptibility profiles of Staphylococci are changing, and laboratory guidance is VERY important for aiding therapeutic selection
4. MR doesn’t just affect companion animals, watch out for these bugs in livestock:
   - Mastitis in cattle
   - Bumble foot in chickens
   - S. hyicus greasy pig disease or MRSA skin infection in pigs
ESBLS AND CARBAPENEMASES
WHAT ARE ESBLS AND CARBAPENEMASES?

- Gram-negative problem
- These broad spectrum β-lactamases are going to be the “Next Big Thing” in the veterinary AMR world
  - There is a lack of awareness of these enzymes in the profession
  - We know remarkably little about the incidence of distribution of these resistance mechanisms in animals
- Often transmissible between bacteria
- These β-lactamases are emerging unnoticed in animals!
<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Ambler Class</th>
<th>Examples</th>
<th>Spectrum of Resistance</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESBLs</strong></td>
<td>Class A</td>
<td>TEM (other than parent enzymes TEM-1, 2 and 13), SHV (other than parent enzyme SHV-1), CTX-M</td>
<td>Penicillins, Cephalosporins, Monobactams</td>
<td>Clavulanic acid, Tazobactam, Sulbactam</td>
</tr>
<tr>
<td><strong>AmpC</strong></td>
<td>Class C</td>
<td>CMY, FOX, ACT, MOX, ACC, DHA</td>
<td>Penicillins, Cephalosporins, Cephamycins, Monobactams</td>
<td>Cloxacillin, Boronic acid</td>
</tr>
<tr>
<td><strong>Carbapenemases (MBL)</strong></td>
<td>Class B</td>
<td>NDM, VIM, IMP</td>
<td>Penicillins, Cephalosporins, Cephamycins, Carbapenems</td>
<td>EDTA and other metal chelators</td>
</tr>
<tr>
<td><strong>KPC type</strong></td>
<td>Class A</td>
<td>KPC</td>
<td>Penicillins, Cephalosporins, Cephamycins, Carbapenems</td>
<td>Clavulanic acid (weak inhibition), Tazobactam, Boronic acid</td>
</tr>
<tr>
<td><strong>OXA type</strong></td>
<td>Class D</td>
<td>OXA-48</td>
<td>Penicillins, Carbapenems</td>
<td>NaCl</td>
</tr>
</tbody>
</table>
IDENTIFICATION AND IMPLICATIONS OF β-LACTAMASES

- The first thing you’ll see is β-lactam resistance
- Diagnostic labs not doing genotyping routinely
- Will most likely affect your practice dealing with Enterobacteriaceae

<table>
<thead>
<tr>
<th>Resistance Genes</th>
<th>Resistance Seen</th>
<th>Treatment Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow spectrum</td>
<td>Pen + 1GC</td>
<td>Potentiated Penicillin</td>
</tr>
<tr>
<td>ESBL</td>
<td>Pen + 1GC + 3GC</td>
<td>Non β-lactam</td>
</tr>
<tr>
<td>AmpC (CMY)</td>
<td>Pen + 1GC + 3GC + Amox/Clav + Cefoxitin</td>
<td>Non β-lactam</td>
</tr>
<tr>
<td>Carbapenemase</td>
<td>All β-lactams</td>
<td>Non β-lactam</td>
</tr>
</tbody>
</table>

Pen – penicillins (including amoxicillin and ampicillin), 1GC – first generation cephalosporins, 3GC – 3rd generation cephalosporins
CARBAPENEMASES

- Carbapenems are one of our last lines of defense!
  - Broad spectrum drugs
- Capable of degrading the vast majority of β-lactams
- Variety of enzymes with carbapenem degrading activity
  - Metallo-β-lactamases (NDM, VIM and IMP)
  - KPC type
  - Distinct epidemiological characteristics
NEW DELHI METALLO-B-LACTAMASE

- NDM-1
- First reported in 2008
  - 59 year old, male Swedish patient
  - Diabetic, had suffered multiple strokes
  - Decubital ulcers, UTI with ESBL producing *K. pneumoniae*
  - Rectal swab screening revealed carbapenem resistant *E. coli*
  - Recent history of hospitalization in India
NEW DELHI METALLO-B-LACTAMASE

- Dissemination from India, other endemic foci
  - Has been found on every continent except Antarctica
- Association with travel to Indian sub-continent
  - Pleasure and medical tourism
- Widely disseminated in India
  - Water
- Found in livestock in China
TRAVEL... MY FAVORITE ACTIVITY

A swab before the trip…

[Image of Taj Mahal]

…. and one on return

[Image of swab]

A little extra souvenir?
WHAT I PICKED UP...

- Before leaving, colonized with *E. coli*
  - Resistant to tetracycline
  - Susceptible to all beta-lactams, fluoroquinolones, aminoglycosides, sulfonamides
- On return, *E. coli*
  - Resistant to ampicillin, ceftriaxone and ciprofloxacin
  - Susceptible to cefoxitin, amoxicillin + clavulanic acid and all other drugs
HOW COMMON ARE THESE ENZYMES IN OUR PATIENTS?

• Collecting canine urinary *E. coli* isolates
  • Starting in 2013 and continuing
  • 625 Samples collected in first 5 years
  • MICs determined by broth micro-dilution
  • β-lactamases detected by PCR
The frequency of antimicrobial resistance among canine urinary *E. coli* in Western Canada from October 2013-2018

Number of isolates (n=624) exhibiting resistance across five years of a canine *E. coli* resistance surveillance program. AMP- ampicillin, AUG- amoxicillin + clavulanate, FOX- cefoxitin, AXO- ceftriaxone, XNL- ceftiofur, MER- meropenem, NAL- nalidixic acid, CIP- ciprofloxacin, GEN- gentamicin, TET- tetracycline, CHL- chloramphenicol, SOX- sulfisoxazole, SXT- trimethoprim/sulfamethoxazole, and AZI- azithromycin
EMERGENCE OF ESBL PRODUCING E. COLI IN CANINE UTIS

Table 1: Prevalence (%) of phenotypic and genotypic resistance among canine urinary E. coli (n=625) during a five year surveillance period

<table>
<thead>
<tr>
<th></th>
<th>Pan-susceptible</th>
<th>MDR</th>
<th>CTX-M</th>
<th>CMY-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 (n=108)</td>
<td>78.7 (85)</td>
<td>4.6 (5)</td>
<td>0 (0)</td>
<td>0.93 (1)</td>
</tr>
<tr>
<td>Year 2 (n=87)</td>
<td>80.5 (70)</td>
<td>6.9 (6)</td>
<td>1.1 (1)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Year 3 (n=148)</td>
<td>75 (111)</td>
<td>6.1 (9)</td>
<td>1.4 (2)</td>
<td>2.0 (3)</td>
</tr>
<tr>
<td>Year 4 (n=130)</td>
<td>80.8 (105)</td>
<td>4.6 (6)</td>
<td>1.5 (2)</td>
<td>2.7 (4)</td>
</tr>
<tr>
<td>Year 5 (n=152)</td>
<td>83.5 (127)</td>
<td>5.3 (8)</td>
<td>0.66 (1)</td>
<td>0.66 (1)</td>
</tr>
</tbody>
</table>
# EMERGENCE OF ESBL PRODUCING E. COLI IN CANINE UTIS

<table>
<thead>
<tr>
<th>Canine</th>
<th>Urinary</th>
<th>Sporadic cystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>RECOMMENDED TREATMENT:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Amoxicillin: 11-15 mg/kg PO q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Amoxicillin/clavulanic acid: 12.5-25 mg/kg PO q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Trimethoprim-sulfonamide (TMS): 15-30 mg/kg PO q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: 3-5d</td>
</tr>
</tbody>
</table>

|        |         | **ALTERNATIVE TREATMENT:** |
|        |         | 4. Enrofloxacin: 10-20 mg/kg PO q24h |
|        |         | 5. Marbofloxacin: 2.7-5.5 mg/kg PO q24h |
|        |         | 6. Orbifloxacin: 2.5-7.5 mg/kg PO q24h |
|        |         | 7. Pradofloxacin: 3-5 mg/kg PO q24h |
|        |         | 8. Cefpodoxime: 3-5 mg/kg PO q24h |
|        |         | 9. Cephalexin: 3-5 mg/kg PO q24h |
|        |         | 10. Cefovecin: 3-5 mg/kg PO q24h |

1. II
2. I
3. II
4. I
5. I
6. I
7. I
8. I
9. II
10. I

Benefit of amoxicillin/clavulanic acid over amoxicillin is unclear. NSAIDs should be considered to control cystitis, when appropriate for that patient (e.g. consider renal function). An initial course of NSAIDs without antimicrobials can be considered.
**B-LACTAMASES TAKE AWAYS**

- By-and-large canine UTIs can still be treated with 1st line therapies
- Broad spectrum β-lactamases are increasingly common in Gram-negatives
  - You’re probably already dealing with them and don’t even realize it!
  - Stay tuned, they’re only going to become more common
- Multidrug resistance, and pan-resistance are still rare in veterinary contexts
SOMETIMES THINGS DON’T WORK AS EXPECTED…

### Possible Reasons for Disagreement Between Test Results and Clinical Outcome

<table>
<thead>
<tr>
<th>Factor</th>
<th>Positive Outcomes</th>
<th>Negative Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient/Disease Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>High urine drug concentrations</td>
<td>Failure of drugs to penetrate sequestered sites (ex. CNS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug interactions decreasing absorption or increasing elimination</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td></td>
<td>Failure of aminoglycosides in acidic or anaerobic environments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failure of folate synthesis inhibitors in purulent environments (excessive PABA in environment)</td>
</tr>
<tr>
<td>Disease/pathology</td>
<td>No infection</td>
<td>Predisposing disease or underlying pathology such as atopy, diabetes or neoplasia</td>
</tr>
<tr>
<td></td>
<td>Self-limiting infection</td>
<td>Indwelling medical device</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Utilization of localized therapy, high concentrations overcoming low level resistance</td>
<td>Off label use (dose, dosing frequency, route of administration)</td>
</tr>
<tr>
<td></td>
<td>Off label use (dose, dosing frequency, route of administration)</td>
<td>Poor owner compliance</td>
</tr>
<tr>
<td><strong>Organism/Test Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td></td>
<td>Development of resistance in vivo</td>
</tr>
<tr>
<td>Organism lifestyle</td>
<td></td>
<td>Biofilm formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracellular infections</td>
</tr>
<tr>
<td>Organism Identification</td>
<td>Mis-identified organism</td>
<td>Mis-identified organism</td>
</tr>
<tr>
<td></td>
<td>False positive culture</td>
<td>Mixed infection</td>
</tr>
<tr>
<td>Antimicrobial Susceptibility Test</td>
<td>Incorrectly performed or reported test</td>
<td>Incorrectly performed or reported test</td>
</tr>
<tr>
<td></td>
<td>Inducible resistance</td>
<td></td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGES
THE EASY AND OBVIOUS

- Antimicrobial resistance is increasing
  - The post-antibiotic era is on its way
- Treat documented (or at least infections w/ evidence!)
- Next time you think “… just in case” your next thought should be “…but what if?”
- Optimize drug/dose to infection
- Familiarize yourself with relevant guidelines (CVMA, ISCAID, industry recommendations)
- Susceptibility profiles are highly variable, laboratory guidance is **VERY** important for aiding therapeutic selection
TAKE HOME MESSAGES
THE HARDER ONES…

• Be aware of local susceptibility profiles
  • Use them to guide empiric therapy
  • Don’t forget about intrinsic resistance

• Reflect on outcomes
  • Did you ‘cure’ that animal?
QUESTIONS?

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