Acknowledgments
Antimicrobial

Joe Rubin, DVM, PhD
Associate Professor
Department of Veterinary Microbiology
University of Saskatchewan
Disclosures

• Received research grants from
  • Zoetis and Elanco/Novartis
Objectives

• To summarize the scope of the problem of AMR
• To inspire the intent to change/reevaluate/improve prescribing practices
• To provide tools to use antimicrobials more effectively
  • Antimicrobial mechanisms of action and resistance
  • Introduction to intrinsic resistance
The Post-Antibiotic Era

Estimated Attributable Deaths in 2050
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*

---

**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

**ANTIBIOTIC RESISTANCE THREATS in the United States, 2013**
Broad spectrum β-lactamases

**EXTENDED SPECTRUM β-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE**

- **26,000** drug-resistant infections
- **1,700** deaths
- **140,000** Enterobacteriaceae infections per year

**THREAT LEVEL**

**SERIOUS**

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

**ANTIBIOTIC RESISTANCE THREATS in the United States, 2013**
Methicillin-resistant *Staph aureus*
Emerging Resistance Concerns

• ESKAPE organisms
  • *Enterococcus faecium*
    • (VRE, penicillin resistance)
  • *Staphylococcus aureus (pseudintermedius)*
    • (MRSA, MDR)
  • *Klebsiella pneumoniae*
    • (ESBL, CPO, aminoglycoside, fluoroquinolone)
  • *Acinetobacter baumannii*
    • (Carbapenems and colistin)
  • *Pseudomonas aeruginosa*
    • (CPO, MDR, PanR)
  • *Enterobacter spp.*
    • (ESBL, CPO, MDR, PanR)

Emerging Resistance in Canada

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

<table>
<thead>
<tr>
<th></th>
<th>2011 (n=142)</th>
<th>2012 (n=150)</th>
<th>2013 (n=208)</th>
<th>2014 (n=318)</th>
<th>2015 (n=430)</th>
<th>2016 (n=779)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>89</td>
<td>63</td>
<td>53</td>
<td>125</td>
<td>168</td>
<td>314</td>
</tr>
<tr>
<td>NDM</td>
<td>33</td>
<td>40</td>
<td>101</td>
<td>132</td>
<td>155</td>
<td>227</td>
</tr>
<tr>
<td>OXA-48-like</td>
<td>9</td>
<td>26</td>
<td>18</td>
<td>33</td>
<td>65</td>
<td>160</td>
</tr>
<tr>
<td>SME</td>
<td>8</td>
<td>17</td>
<td>31</td>
<td>22</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>OXA-48/NDM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>160</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>21</td>
<td>24</td>
</tr>
</tbody>
</table>
Changing Resistance?

FIGURE 38: Resistance to selected antimicrobials among Salmonella isolates from chicken meat samples collected at retail stores, 2006-2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Ampicillin</th>
<th>Ceftriaxone</th>
<th>Gentamicin</th>
<th>Nalidixic acid</th>
<th>Streptomycin</th>
<th>Tetracycline</th>
<th>Trimethoprim-sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>14.9%</td>
<td>9.6%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>28.7%</td>
<td>31.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>2007</td>
<td>17.9%</td>
<td>10.2%</td>
<td>1.7%</td>
<td>0.0%</td>
<td>32.4%</td>
<td>34.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>2008</td>
<td>17.0%</td>
<td>12.6%</td>
<td>1.0%</td>
<td>0.0%</td>
<td>31.7%</td>
<td>34.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>2009</td>
<td>31.1%</td>
<td>22.0%</td>
<td>0.8%</td>
<td>0.0%</td>
<td>27.9%</td>
<td>34.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>2010</td>
<td>27.6%</td>
<td>22.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>26.0%</td>
<td>28.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>2011</td>
<td>31.6%</td>
<td>29.9%</td>
<td>0.6%</td>
<td>0.0%</td>
<td>35.5%</td>
<td>26.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>2012</td>
<td>29.9%</td>
<td>26.1%</td>
<td>0.9%</td>
<td>0.0%</td>
<td>25.5%</td>
<td>36.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2013</td>
<td>27.9%</td>
<td>26.3%</td>
<td>4.9%</td>
<td>0.0%</td>
<td>27.9%</td>
<td>28.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2014</td>
<td>21.3%</td>
<td>21.0%</td>
<td>2.6%</td>
<td>0.3%</td>
<td>19.0%</td>
<td>28.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2015</td>
<td>21.3%</td>
<td>12.8%</td>
<td>1.1%</td>
<td>3.3%</td>
<td>31.7%</td>
<td>18.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>2016</td>
<td>14.2%</td>
<td>14.2%</td>
<td>3.3%</td>
<td>1.4%</td>
<td>36.1%</td>
<td>33.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
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!
The Pre-Antibiotic Era 🕍

• Largely powerless to stop invasive infections
• Interesting accounts of infectious disease in conflict settings (WW1)
  • Infected wounds progressed
    • Cut = infection = sepsis = death
  • Quiescent tubercles ubiquitous in urban areas
  • Sexually transmitted infections were ‘moral’ rather than medical issues
    • Occurred at a rate of 272/1,000 soldiers in US army in WW1

Importance of antibiotics cannot be overstated... estimate to have led to 10 year increase in life expectancy!
The Dark Ages

Mercury based preparations for the treatment of venereal disease. Specimen photographed at the State Library of Victoria, Melbourne Australia.
**Fleming's Observation**

*Fig. 1.* Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.
ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF B. INFLUENZÆ.

ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St Mary’s Hospital, London.

Received for publication May 10th, 1929.

The Finding that Changed it All

Ernst Boris Chain  Sir Howard Florey
History of Drug Discovery

[Diagram showing the history of drug discovery with key milestones and classifications of drugs such as actinomycete natural products, synthetic antibiotics, and sulphonamides.]
Resistance Follows Usage

![Antibiotic Resistance Timeline](https://www.cdc.gov/drugresistance/about.html)
How Antibiotics Work

- Attack physiological processes unique to bacteria
  - Inside/Outside
    - Cell wall
    - Cell membrane
  - Central Dogma
    - Nucleic acids
      - Nucleic acid synthesis
      - DNA metabolism
      - RNA polymerase
    - Protein synthesis
How Bacteria Resist

• Decreased permeability
• Active Efflux
• Enzymatic Degradation/Alteration
• Target Modification
• Alternate Pathways
• Resistance by Absence

Bacteria can deploy these strategies intrinsically or after gaining genetic competence.
Where Resistance Comes From

ATTCGGT
TAACGGCA

ATCGCCGT
TAGCGGCA

Mutation
Where Resistance Comes From

ATTTGCCTGTAAACGGCA

ATCGGCGGTAGCGGGCA

Mutation
Conjugation
Where Resistance Comes From

![Genetic Modification Diagram]

Mutation
Conjugation
Transduction
Where Resistance Comes From

- **Mutation**
- **Conjugation**
- **Transduction**
- **Transformation**

ATTTGCCGTTAACGGGCA

ATCGCCGTTAGCGGGCA

R R R
Words of Wisdom for New Tools

“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

https://www.youtube.com/watch?v=plVk4NVlUh8
## Evolutionary Power

<table>
<thead>
<tr>
<th>Time</th>
<th>Human Generations Since Species Origin</th>
<th>Bacterial Generations in Antimicrobial Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation Length</td>
<td>25 Years</td>
<td>~2 Million Years</td>
</tr>
<tr>
<td>Generations</td>
<td>80,000</td>
<td>~80 Years</td>
</tr>
<tr>
<td></td>
<td>20 Minutes</td>
<td>2,102,400</td>
</tr>
</tbody>
</table>
Antimicrobial Use Animals

**Figure 51**: Quantity of medically important antimicrobials (kilograms) distributed for sale for use in animals, by province, 2012-2016

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>74,376</td>
<td>38,680</td>
<td>47,351</td>
<td>60,067</td>
<td>52,738</td>
</tr>
<tr>
<td>AB</td>
<td>381,193</td>
<td>189,245</td>
<td>206,573</td>
<td>210,475</td>
<td>189,870</td>
</tr>
<tr>
<td>SK</td>
<td>77,971</td>
<td>50,961</td>
<td>50,333</td>
<td>50,708</td>
<td>39,976</td>
</tr>
<tr>
<td>MB</td>
<td>178,577</td>
<td>151,675</td>
<td>147,088</td>
<td>179,660</td>
<td>128,715</td>
</tr>
<tr>
<td>ON</td>
<td>386,917</td>
<td>249,621</td>
<td>303,240</td>
<td>336,049</td>
<td>296,916</td>
</tr>
<tr>
<td>QC</td>
<td>440,364</td>
<td>392,312</td>
<td>348,387</td>
<td>343,544</td>
<td>276,971</td>
</tr>
<tr>
<td>NB</td>
<td>50,797</td>
<td>23,850</td>
<td>14,696</td>
<td>11,092</td>
<td>8,066</td>
</tr>
<tr>
<td>NS</td>
<td>7,959</td>
<td>6,172</td>
<td>5,782</td>
<td>6,780</td>
<td>4,463</td>
</tr>
<tr>
<td>PE</td>
<td>3,781</td>
<td>4,164</td>
<td>1,134</td>
<td>1,147</td>
<td>1,378</td>
</tr>
<tr>
<td>NL</td>
<td>17,322</td>
<td>15,023</td>
<td>1,883</td>
<td>1,740</td>
<td>1,357</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-sulfas (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.¹⁹

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

- Large study out of UK
  - 216 practices
  - >400,000 dogs
  - >200,000 cats

<table>
<thead>
<tr>
<th>Antimicrobial agent class</th>
<th>Total</th>
<th>Systemic</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>12.0</td>
<td>11.4-12.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Amphenicol</td>
<td>1.9</td>
<td>1.6-2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Other antimicrobial agent</td>
<td>7.2</td>
<td>6.6-7.8</td>
<td>0.0</td>
</tr>
<tr>
<td>β-lactam</td>
<td>43.6</td>
<td>42.3-44.8</td>
<td>73.8</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>4.1</td>
<td>3.6-5.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>18.2</td>
<td>17.4-19.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lincosamide</td>
<td>4.7</td>
<td>4.2-5.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Macrolide</td>
<td>0.2</td>
<td>0.0-0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>4.7</td>
<td>4.0-5.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Nitroimidazole-macroline</td>
<td>0.8</td>
<td>0.5-1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>0.0</td>
<td>&lt;0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Sulphonamide</td>
<td>1.5</td>
<td>1.1-1.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Tetacycline</td>
<td>1.2</td>
<td>1.0-1.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 3
Percentage breakdown of canine antimicrobial agent prescriptions by antimicrobial agent class prescribed for total, systemic and topical prescriptions from a network of United Kingdom small animal veterinary premises.

<table>
<thead>
<tr>
<th>Class of antimicrobial agent</th>
<th>Total prescription</th>
<th>Systemic prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Cat</td>
<td>Dog</td>
</tr>
<tr>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>5.3</td>
<td>4.1-6.5</td>
</tr>
<tr>
<td>Amphenicol</td>
<td>0.4</td>
<td>0.0-0.8</td>
</tr>
<tr>
<td>First generation cephalosporin</td>
<td>8.4</td>
<td>7.8-9.0</td>
</tr>
<tr>
<td>Second generation cephalosporin</td>
<td>0.04</td>
<td>0.01-0.07</td>
</tr>
<tr>
<td>Third generation cephalosporin</td>
<td>0.9</td>
<td>0.7-1.0</td>
</tr>
<tr>
<td>Clavulanic acid potentiated amoxicillin</td>
<td>28.6</td>
<td>27.4-29.8</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.03</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>Total</td>
<td>43.6</td>
<td>70.8</td>
</tr>
</tbody>
</table>

Table 5
Percentage breakdown of β-lactam antimicrobial agent prescription by species and β-lactam sub-categories as a percentage of total and systemic antimicrobial agent prescriptions from a network of small animal veterinary premises in the United Kingdom.

<table>
<thead>
<tr>
<th>Class of antimicrobial agent</th>
<th>Total prescription</th>
<th>Systemic prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Cat</td>
<td>Dog</td>
</tr>
<tr>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>5.3</td>
<td>4.1-6.5</td>
</tr>
<tr>
<td>Amphenicol</td>
<td>0.4</td>
<td>0.0-0.8</td>
</tr>
<tr>
<td>First generation cephalosporin</td>
<td>8.4</td>
<td>7.8-9.0</td>
</tr>
<tr>
<td>Second generation cephalosporin</td>
<td>0.04</td>
<td>0.01-0.07</td>
</tr>
<tr>
<td>Third generation cephalosporin</td>
<td>0.9</td>
<td>0.7-1.0</td>
</tr>
<tr>
<td>Clavulanic acid potentiated amoxicillin</td>
<td>28.6</td>
<td>27.4-29.8</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.03</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>Total</td>
<td>43.6</td>
<td>70.8</td>
</tr>
</tbody>
</table>

- Table 3: Percentage breakdown of canine antimicrobial agent prescriptions by antimicrobial agent class prescribed for total, systemic and topical prescriptions from a network of United Kingdom small animal veterinary premises.
- Table 5: Percentage breakdown of β-lactam antimicrobial agent prescription by species and β-lactam sub-categories as a percentage of total and systemic antimicrobial agent prescriptions from a network of small animal veterinary premises in the United Kingdom.
We're somewhere in the middle, so there's probably room to improve.
β-lactams

• Inhibit cell wall synthesis
  • Bind to penicillin binding proteins
    • Transpeptidases and carboxypeptidases
    • Prevent final stage of peptidoglycan synthesis

• Super family of antimicrobials
  • Penicillins
  • Cephalosporins
  • Carbapenems
  • β-lactamase inhibitors
β-lactam Basic Structure

- **Penicillins**

- **Cephalosporins**

- **Carbapenems**

- **Monobactams**
β-lactams - Penicillins

- **Penicillinase-stable penicillin**

- oxacillin, methicillin, cloxacillin, flucloxacillin

  No Gram-negative, anaerobic or enterococcal coverage

- Staphylococcus

- Wimpy
  - Anaerobes

- Enterococcus

- Streptococcus

- Escherichia

- Pseudomonas
β-lactams - Penicillins

Penicillin
- penicillin G, penicillin V, procaine penicillin
  - Gram-positives aerobes, wimpy Gram-positive and negative anaerobes

Penicillinase-stable penicillin
- oxacillin, methicillin, cloxacillin, flucloxacillin
  - No Gram-negative, anaerobic or enterococcal coverage

Staphylococcus
- Wimpy Anaerobes
- H₂

Enterococcus

Streptococcus

Escherichia

Pseudomonas
β-lactams - Penicillins

- **Penicillinase-stable penicillin**
  - oxacillin, methicillin, cloxacillin, flucloxacillin
    - No Gram-negative, anaerobic or enterococcal coverage

- **Penicillin**
  - penicillin G, penicillin V, procaine penicillin
    - Gram-positives aerobes, wimpy Gram-positive and negative anaerobes

- **Aminopenicillin**
  - amoxicillin, ampicillin
    - Same as penicillin + improved Gram-negative coverage. Resistance increasingly encountered in common organisms
β-lactams - Penicillins

Penicillinase-stable penicillin
- oxacillin, methicillin, cloxacillin, flucloxacillin
  - No Gram-negative, anaerobic or enterococcal coverage

Penicillin
- penicillin G, penicillin V, procaine penicillin
  - Gram-positives aerobes, wimpy Gram-positive and negative anaerobes

Aminopenicillin
- amoxicillin, ampicillin
  - Same as penicillin + improved Gram-negative coverage. Resistance increasingly encountered in common organisms

Ureidopenicillin
- piperacillin
  - Enhanced Gram-negative spectrum, including most Enterobacteriaceae and susceptible *Pseudomonas aeruginosa*

Staphylococcus
- Wimpy
  - Anaerobes

Escherichia
- Enterococcus
- Streptococcus
- Pseudomonas
β-Lactams/Inhibitor Combinations

• Currently available:
  • Clavulanic acid (amoxicillin + clavulanic acid)
  • Sulbactam (ampicillin + sulbactam)
  • Tazobactam (piperacillin + tazobactam)

• Act by irreversibly binding to the serine catalytic site of certain bacterial β-lactamases
  • Only active against Class A enzymes
  • NOT ALL β-LACTAMASES can be inhibited
β-lactams - Cephalosporins

1st Generation

cefazolin, cephalexin, cefadroxil
Primarily active against Gram-positives, moderate Gram-negative activity if susceptible

Staphylococcus

Streptococcus

Escherichia

Wimpy

Narrow Spectrum β-lactamases

SPICE

Anaerobes

Pseudomonas
**β-lactams - Cephalosporins**

1st Generation
- cefazolin, cephalexin, cefadroxil
  - Primarily active against Gram-positives, moderate Gram-negative activity if susceptible

2nd Generation
- cefuroxime, cefaclor
  - Improved Gram-negative spectrum, somewhat less Gram-positive

- Wimpy
- Narrow Spectrum β-lactamases
- SPICE
- H₂
  - Anaerobes

- Staphylococcus
- Streptococcus
- Escherichia
- Pseudomonas
Only certain 3rd generation cephalosporins have good activity against Gram-positives, can anyone think of an example? Be aware of your target organism and the spectrum of activity of your drug.
β-lactams - Cephalosporins

Generally speaking, as we increase generation we get improved activity against Gram-negatives and increasing resilience to β-lactamases.
β-lactams - Cephalosporins

1st Generation
- cefazolin, cephalexin, cefadroxil
  - Primarily active against Gram-positives, moderate Gram-negative activity if susceptible

2nd Generation
- cefuroxime, cefaclor
  - Improved Gram-negative spectrum, somewhat less Gram-positive

3rd Generation
- cefovecin, ceftiofur, ceftriaxone
  - Further enhanced Gram-negative activity, some have good activity against Staph, Strep.

4th Generation
- cefepime
  - Highly active against Gram-negatives, good activity against Gram-positives

Cephamycins
- cefoxitin, cefotetan
  - Good Gram-positive and negative activity. Also, anaerobic coverage.

Staphylococcus
- Wimpy
  - Escherichia
  - Narrow Spectrum β-lactamases
  - Escherichia

SPICE
- Pseudomonas

Anaerobes
Other β-lactams

Very broad spectrum, most Gram-pos, neg and anaerobes. Ertapenem has no activity against enterococci or *Pseudomonas*

- **Aztreonam**
- **Monobactams**
- **Carbapenems**
- **Imipenem, Meropenem**
Mechanisms of β-lactam Resistance

- Altered Targets
- Altered PBP
- Decreased Permeability
- Porin Deficiencies
- β-lactamases
- Enzymatic degradation

**Why is it particularly important for clinicians to understand mechanisms of β-lactam resistance?**
**β-lactamase Diversity**

- **Class A**
  - Ampicillin/Amoxicillin
  - 1st Gen Cephalosporins

- **Class B**
  - 3rd Gen Cephalosporins

- **Class C**
  - β-lactam + inhibitor
  - Cephamycins

- **Class D**
  - Carbapenems

- **Narrow spectrum TEM SHV**
- **ESBLs**
- **AmpC type**
- **KPC**
- **NDM, VIM, IMP**
- **OXA-48 like**

Enterobacteriaceae including plasmid mediated
β-lactamase Diversity

Class A
- Ampicillin/Amoxicillin
- 1st Gen Cephalosporins

Class B
- 3rd Gen Cephalosporins

Class C
- β-lactam + inhibitor
- Cephamycins

Class D
- Carbapenems

Enterobacteriaceae including plasmid mediated

Narrow spectrum TEM SHV

ESBLs

AmpC type
- SPICE intrinsic

KPC

NDM, VIM, IMP

OXA-48 like
β-lactamase Diversity

Class A
- Ampicillin/Amoxicillin
- 1\textsuperscript{st} Gen Cephalosporins

Class B
- 3\textsuperscript{rd} Gen Cephalosporins

Class C
- β-lactam + inhibitor
- Cephemycins

Class D
- NDM, VIM, IMP
- OXA-48 like
- Major carbapenemases
- Carbapenems

Narrow spectrum
TEM SHV

ESBLs

AmpC type

KPC

NDM, VIM, IMP

OXA-48 like
β-lactamase Diversity

Class A
- Ampicillin/Amoxicillin
- 1st Gen Cephalosporins

Class B
- 3rd Gen Cephalosporins
- β-lactam + inhibitor

Class C
- Cephemycins

Class D
- Carbapenems

ESBLs
- Narrow spectrum TEM SHV
- AmpC type
- KPC
- NDM, VIM, IMP
- OXA-48 like

Major carbapenemases
β-lactamase Diversity

Class A
- Ampicillin/Amoxicillin
- 1st Gen Cephalosporins

Class B
- 3rd Gen Cephalosporins
- β-lactam + inhibitor
- Cephemycins

Class C
- NDM, VIM, IMP
- OXA-48 like
- Carbapenemases

Class D
- Narrow spectrum TEM SHV
- ESBLs
- AmpC type
- KPC
- Major carbapenemases
Protein synthesis inhibitors

• Bacteria use a 30S and 50S ribosomal subunits
  • Distinct from Eukaryotes – 40S and 60S
• Targets for many drug classes
  • Tetracyclines
  • Aminoglycosides
  • MLS\textsubscript{B}K
  • Phenicols
  • Streptogramins

Proline (P)
Arginine (R)
STOP
Threonine (T)
Glutamate (E)
Isoleucine (I)
Asparagine (N)
Tetracyclines

Binds to 30S ribosomal subunit reversibly - bacteriostatic

Increasing Lipophilicity

Tetracycline
Doxycycline
Minocycline

What does increasing lipophilicity mean for you as a clinician?

Minocycline has activity against *Stenotrophomonas* and *Mycobacterium marinum*

Increasingly important as MRSP becomes more common

The ‘weirdos’, intracellular parasites, *Mycoplasma*

Methicillin

Broad spectrum agents. Gram positive activity more limited than Gram negative. Resistance is common, so susceptibility testing essential.

*Staphylococcus* MRSA/MRSP

*Rickettsia*

*Vibrio*

*Brucella*
Mechanisms of Tetracycline Resistance

• **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**
Aminoglycosides

Binds to 30S ribosomal subunit but also effects electron transport chain, DNA metabolism and cell membrane - bactericidal

Streptomycin

Gentamicin

Amikacin

Neomycin

Spectinomycin*

*Aminocyclitol, related drug class

ONLY AEROBIC BACTERIA!

β-lactam + Amikacin = synergy

Plague
Tularemia
Brucella
Bioterrorism
Zoonoses

Gram Negative Rods

Pseudomonas

Enterococcus

Methicillin

MRSA/MRSP

Mycoplasma

Nocardia
Aminoglycosides

Binds to 30S ribosomal subunit but also effects electron transport chain, DNA metabolism and cell membrane - bactericidal

**Streptomycin**

**Gentamicin**

**Amikacin**

**Neomycin**

**Spectinomycin**

*Aminocyclitol, related drug class*

ONLY AEROBIC BACTERIA!

\[ \text{O}_2 \]

**ONLY AEROBIC BACTERIA!**

**β-lactam** + **Amikacin** = synergy

Some of the best anti-pseudomonal activity

**Methicillin**

**Methicillin**

**MRSA/MRSP**

**Mycoplasma**

**Nocardia**

**Plague**

**Tularemia**

**Brucella**

**Bioterrorism**

**Zoonoses**

**Pseudomonas**

**Enterococcus**
Aminoglycosides

Binds to 30S ribosomal subunit but also affects electron transport chain, DNA metabolism and cell membrane - bactericidal

**Streptomycin**

**Gentamicin**

**Amikacin**

**Neomycin**

**Spectinomycin***

* Aminocyclitol, related drug class

ONLY AEROBIC BACTERIA!

Plague
Tularemia
Brucella
Bioterrorism
Zoonoses

Gram Negative Rods

Amikacin + β-lactam = synergy

Some of the best anti-pseudomonal activity

Pseudomonas

Enterococcus

+ β-lactam

Methicillin

Last line of defense against MRSP

Mycoplasma

Nocardia

MRSA/MRSP
Aminoglycosides

Binds to 30S ribosomal subunit but also affects electron transport chain, DNA metabolism and cell membrane - bactericidal

**Streptomycin**

**Gentamicin**

**Amikacin**

**Neomycin**

**Spectinomycin***

* *Aminocyclitol, related drug class

ONLY AEROBIC BACTERIA!

**β-lactam** + **Amikacin** = synergy

**Plague**

**Tularemia**

**Brucella**

**Bioterrorism**

**Zoonoses**

**Mycoplasma**

**Enterococcus**

**Methicillin**

**MRSA/MRSP**

**Gram Negative Rods**

**Pseudomonas**
Aminoglycosides

Binds to 30S ribosomal subunit but also effects electron transport chain, DNA metabolism and cell membrane - bactericidal

- Streptomycin
- Gentamicin
- Amikacin
- Neomycin
- Spectinomycin*

*Aminocyclitol, related drug class

ONLY AEROBIC BACTERIA!

Plague
Tularemia
Brucella
Bioterrorism
Zoonoses

Gram Negative Rods

β-lactam
Amikacin

+ β-lactam = synergy

Pseudomonas
Enterococcus

Methicillin
MRSA/MRSP

Mycoplasma
Nocardia

O₂
Aerobes
Mechanisms of Resistance
Aminoglycosides

• Enzymatic inactivation
  • Aminoglycoside modifying enzymes
  • Most common mechanism of resistance

• Decreased permeability
  • Cross resistance to other antimicrobials
Phenicols

Banned in food animals, rare idiosyncratic aplastic anemia in people (1:20,000-40,000)

Chloramphenicol

Florfenicol

Aplastic anemia not associated with florfenicol

Reversible binding to 50S ribosomal subunit - bacteriostatic

Broad spectrum agents

Anaerobes

Bacterial conjunctivitis caused by variety of organisms

Methicillin

An option for MRSP

Actinobacillus
Fusobacterium
Trueperella
Pasteurella

Streptococcus
Escherichia

MRSA/MRSP
Phenicols

Reversible binding to 50S ribosomal subunit - bacteriostatic

Broad spectrum agents

Anaerobes

Gram +ve

Plasma Membrane

Cell Wall

Gram -ve

Plasma Membrane

Cell Wall

Banned in food animals, rare idiosyncratic aplastic anemia in people (1:20,000-40,000)

Chloramphenicol

Florfenicol

Aplastic anemia not associated with florfenicol

Actinobacillus

Fusobacterium

Trueperella

Pasteurella

Bacterial conjunctivitis caused by variety of organisms

Methicillin

An option for MRSP

Escherichia

Streptococcus

MRSA/MRSP

Phenicols

Florfenicol
MLS<sub>BK</sub>

**Macrolides**
- Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin
  - Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

**Lincosamides**
- Clindamycin, lincomycin
  - Similar to macrolides

**Ketolides**
- Clarithromycin
  - Similar to macrolides with enhanced Gm pos activity

**Azalides**
- Azithromycin, gamithromycin
  - Similar to macrolides with enhanced Gram neg activity including Enterobacteriaceae

**Streptogramins**
- Vinginiamycin
  - Gm pos cocci and bacilli, Gm neg cocci, anaerobes

**Resistance increasingly common, susceptibility testing VERY important**

**Reversible binding to to 50S ribosomal subunit - bacteriostatic**
Resistance increasingly common, susceptibility testing VERY important
Reversible binding to 50S ribosomal subunit - bacteriostatic

**MLS**

### Macrolides
- Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin
  - Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

### Lincosamides
- Clindamycin, lincomycin
  - Similar to macrolides

### Ketolides
- Clarithromycin
  - Similar to macrolides with enhanced Gm pos activity

### Azalides
- Azithromycin, gamithromycin
  - Similar to macrolides with enhanced Gram neg activity including Enterobacteriaceae

### Streptogramins
- Vinginiamycin
  - Gm pos cocci and bacilli, Gm neg cocci, anaerobes

**Anaerobes**
- Brachyspira
- Trueperella
- Pasteurella
- Rhodococcus

**Gram +ve**
- Staphylococcus
- Streptococcus
- Mycoplasma

**H2**
- Clostrium Clostridioides

**Plasma Membrane Cell Wall**
Macrolides
- Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin
  - Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

Lincosamides
- Clindamycin, lincomycin
  - Similar to macrolides

Ketolides
- Clarithromycin
  - Similar to macrolides with enhanced Gm pos activity

Azalides
- Azithromycin, gamithromycin
  - Similar to macrolides with enhanced Gram neg activity including Enterobacteriaceae

Streptogramins
- Vinginiamycin
  - Gm pos cocci and bacilli, Gm neg cocci, anaerobes

Resistance increasingly common, susceptibility testing VERY important
Reversible binding to 50S ribosomal subunit - bacteriostatic
**MLS\textsubscript{BK}**

- **Macrolides**: Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin. Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

- **Lincosamides**: Clindamycin, lincomycin. Similar to macrolides.

- **Ketolides**: Clarithromycin. Similar to macrolides with enhanced Gm pos activity.

- **Azalides**: Azithromycin, gamithromycin. Similar to macrolides with enhanced Gram neg activity including Enterobacteriaceae.

- **Streptogramins**: Vinginiamycin. Gm pos cocci and bacilli, Gm neg cocci, anaerobes.

**Resistance increasingly common, susceptibility testing VERY important**

Reversible binding to 50S ribosomal subunit - bacteriostatic.
MLS_BK

Macrolides
- Erythromycin, tylosin, tildipirosin, tilmicosin, tulathromycin
  - Primarily active against Gram pos, including Gm pos anaerobes, gets some specific Gram negs.

Lincosamides
- Clindamycin, lincomycin
  - Similar to macrolides

Ketolides
- Clarithromycin
  - Similar to macrolides with enhanced Gm pos activity

Streptogramins
- Vinginiamycin
  - Gm pos cocci and bacilli, Gm neg cocci, anaerobes

Resistance increasingly common, susceptibility testing VERY important

Reversible binding to to 50S ribosomal subunit - bacteriostatic

Anaerobes
- Clostridium
g-ve

Gram +ve
- Staphylococcus
- Streptococcus
- Mycoplasma
- Pasteurella

Rhodococcus
- Brachyspira
- Actinobacillus
- Bordetella
Mechanisms of Resistance MLS$_B$K

- **Target Modification**
  - Ribosomal methylases
    - *erm* gene family
  - Be aware of inducible resistance

- **Active Efflux**

- **Enzymatic Inactivation**

> Inducible clindamycin resistance in *S. aureus*
Detection requires specialized laboratory tests
Agents Affecting Nucleic Acids

- Agents act at many steps along the process
  - Folate production
  - Disrupting DNA production
  - DNA organization and replication
  - RNA synthesis
Folate Synthesis Inhibitors

Competitive Inhibition

Para-aminobenzoic acid (PABA)

Dihydropteroic acid

Dihydrofolate synthetase

Dihydrofolate reductase

Dihydrofolate

Enzymatic Inhibition

Tetrahydrofolate

Diaminopyrimidines

Various Metabolic Products

DNA, RNA and Protein Synthesis

Basic Sulfa

PABA

Competitive Inhibition

Dihydropteroate synthetase

Diaminopyrimidines

Enzymatic Inhibition

Dihydroyolate reductase
Folate Synthesis Inhibitors

Trimethoprim + Sulfamethoxazole

Mechanisms of Resistance

- 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

Broad bacterial spectrum

Notable Exceptions
- Enterococci, *Pseudomonas aeruginosa*
- Group A Strep (more human)

Methicillin
- Another option for MRSP

Activity against some Protozoans and Toxoplasma

Oldies but goodies!
Nitroimidazoles (Metronidazole)

Disrupts DNA production by production of radical anions following intracellular metabolism - bactericidal

Broad spectrum anaerobic coverage

Activity limited to anaerobes!

BANNED in food animals

Metronidazole

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{CH}_3 \\
\text{OH}
\end{array}
\]

Shown to reduce colonization resistance for important pathogens (Salmonella and E. coli) and increase intestinal inflammation

Mechanisms of Resistance:
- Reduced uptake
- Efflux
- Reducing the rate of reductive activation
- Inactivating enzymes
- Increased DNA repair

Anaerobes

Aerobes

Trichomonas, Giardia, Entamoeba

Parasites

Clostridium
Clostridoides
Brachyspira
(Fluoro)quinolones

Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

**Quinolones**

**1st Generation FQ**
- Ofloxacin
  - Gm neg

**2nd Generation FQ**
- Enrofloxacin, ciprofloxacin
  - Improved Gm neg, and Gm pos spectrum

**3rd Generation FQ**
- Pradofloxacin
  - Broad spectrum Gm neg, pos, anaerobe

**Nalidixic Acid**
- Only Enterobacteriaceae

**Gram -ve**
- Escherichia
- Pseudomonas

**Gram +ve**
- Gram +ve

**Anaerobes**
- Mycoplasma

**Plasma Membrane**
- Cell Wall
- Plasma Membrane
(Fluoro)quinolones

Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

Quinolones

1st Generation FQ
- Nalidixic Acid
  - Only Enterobacteriaceae
- Ofloxacin
  - Gm neg

2nd Generation FQ
- Enrofloxacin, ciprofloxacin
  - Improved Gm neg, and Gm pos spectrum

3rd Generation FQ
- Pradofloxacin
  - Broad spectrum Gm neg, pos, anaerobe

H₂

Anaerobes

Escherichia

Gram -ve

Pseudomonas

Gram +ve

Mycoplasma
Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

1\textsuperscript{st} Generation FQ
- Ofloxacin
  - Gm neg

2\textsuperscript{nd} Generation FQ
- Enrofloxacin, ciprofloxacin
  - Improved Gm neg, and Gm pos spectrum

3\textsuperscript{rd} Generation FQ
- Pradofloxacin
  - Broad spectrum Gm neg, pos, anaerobe

Quinolones
- Nalidixic Acid
  - Only Enterobacteriaceae

Gram -ve
- Escherichia
- Pseudomonas

Gram +ve
- Plasma Membrane
- Cell Wall

Anaerobes
- Plasma Membrane

Mycoplasma

(Fluoro)quinolones
(Fluoro)quinolones

Inhibits DNA gyrase and topoisomerase IV, prevents replication and organization (supercoiling) - bactericidal

Quinolones

1st Generation FQ

Ofloxacin
Gm neg

2nd Generation FQ

Enrofloxacin, ciprofloxacin
Improved Gm neg, and Gm pos spectrum

3rd Generation FQ

Pradofloxacin
Broad spectrum Gm neg, pos, anaerobe

Nalidixic Acid
Only Enterobacteriaceae

Escherichia
Gram -ve

Pseudomonas
Gram +ve

Plasma Membrane
Cell Wall

H2
Anaerobes

Plasma Membrane
Cell Wall

Mycoplasma

Plasma Membrane
Cell Wall
Ansamycins (Rifampin)

- Primarily for Gram-positives and some *Mycobacteria*

  Never used as a monotherapy - resistance develops quickly.

  In people also used for prophylaxis following exposure to *Neisseria meningitidis* or to treat invasive *Haemophilus influenzae* or *Streptococcus pneumoniae* infections.

**Mechanism of Resistance**

1. Through mutations in the genes encoding the machinery for transcription
Polymyxins
Polymyxins disrupt the outer membrane surrounding Gram-negative bacteria. They are active only against Gram-negatives which disrupt the outer membrane surrounding Gram-negative bacteria.

• Only active against Gram-negatives

These are last line of defense drugs against Gram negatives, often the last agents to which MDR organisms remain susceptible.

Some Gram negatives are intrinsically resistant, including members of the Enterobacteriaceae (Edwardsiella spp., Morganella morganii, Proteus spp., Providentia spp., Serratia spp.). Mechanism not known.

Mechanisms of Resistance

1. Modification of LPS - chromosomally encoded
2. Plasmid mediated - mcr-1 exact mechanism unknown, but this encodes a protein homologous to one in Paenibacillus spp. which product polymyxins.
Key Definitions

• MIC (minimum inhibitory concentration)
  • The lowest antimicrobial concentration inhibits growth
  • By convention, a doubling dilution series
    • e.g. 0.12μg/ml, 0.25μg/ml, 0.5μg/ml, 1μg/ml, 2μg/ml, 4μg/ml

**Susceptible**
When a patient has an infection with a susceptible organism, there is a high likelihood of clinical success when treated with a drug according to the drug label indication

**Resistant**
When a patient has an infection with a resistant organism, clinical failure is predicted when treated with a drug according to the label indication
Susceptibility Test Methods

• Categorical methods
  • Only tell you whether the organism is susceptible or resistant

• Quantitative methods
  • Yield an MIC which describes exactly how susceptible or resistant the isolate is
  • An MIC can be translated into a categorical result

<table>
<thead>
<tr>
<th></th>
<th>Diffusion Methods</th>
<th>Dilution Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical</td>
<td>Kirby-Bauer (Disks)</td>
<td></td>
</tr>
<tr>
<td>Quantitative</td>
<td>Gradient strips (E-tests)</td>
<td>Agar dilution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Broth micro/macro dilution</td>
</tr>
</tbody>
</table>
Kirby-Bauer Disk Testing
Gradient Strips

MIC = 6
By convention, this is rounded to 8
Broth Micro-Dilution

Tetracycline

1 2 4 8 16

++++

No Growth

MIC = 16μg/ml
Interpretation of Tests

• Standardized interpretive criteria critical
  • Clinical and Laboratory Standards Institute (CLSI) – USA
  • European Committee on Antimicrobial Susceptibility Testing (EUCAST) – Europe
## Interpretation of Tests

### Enterobacteriaceae

**EUCAST Clinical Breakpoint Tables v. 6.0, valid from 2016-01-01**

Disk diffusion (EUCAST standardised disk diffusion method)  
Medium: Mueller-Hinton agar  
Incubation: 35°C, 16-18 h  
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.  
Quality control: *Escherichia coli* ATCC 25922. For control of the inhibitor component of beta-lactam-inhibitor combination disks, use either *Escherichia coli* ATCC 35218 or *Klebsiella pneumoniae* ATCC 700605.

### Penicillins

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>8&lt;sup&gt;1&lt;/sup&gt; 8&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10</td>
<td>14&lt;sup&gt;3&lt;/sup&gt; 14&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>8&lt;sup&gt;3&lt;/sup&gt; 8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>20-19</td>
<td>19&lt;sup&gt;3&lt;/sup&gt; 19&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid (uncomplicated UTI only)</td>
<td>92&lt;sup&gt;1&lt;/sup&gt; 92&lt;sup&gt;2&lt;/sup&gt;</td>
<td>20-19</td>
<td>18&lt;sup&gt;4&lt;/sup&gt; 18&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>6</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Tazobactam</td>
<td>6</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Tazobactam</td>
<td>6</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Tazobactam-clavulanic acid</td>
<td>8&lt;sup&gt;3&lt;/sup&gt; 8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>75-19</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

1. Wild-type *Enterobacteriaceae* are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild-type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint 8 > 0.8 mg/L and the corresponding zone diameter breakpoint 8 > 50 mm.
2. For susceptibility testing purposes, the concentration of amoxicillin is fixed at 4 mg/L.
3. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
5. *Mesorhinus ptychomycetis* breakpoints relate to *E. coli*, *Klebsiella spp.* and *P. mirabilis* only.
6. Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agar.
7. Susceptibility inferred from amoxicillin.
8. Ignore isolated colonies within the inhibition zone for *E. coli*.

---

**E. coli, Klebsiella spp. and P. mirabilis**

- Benzylpenicillin
- Amoxicillin
- Amoxicillin-clavulanic acid
- Tazobactam
- Piperacillin
- Tazobactam-clavulanic acid
- Mecillinam (uncomplicated UTI only)
### Definition Based on

<table>
<thead>
<tr>
<th>Species</th>
<th>Indication</th>
<th>Drug</th>
<th>Dosing Regimen</th>
<th>Breakpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dogs</strong></td>
<td>Skin, soft tissue</td>
<td>Amoxicillin-clavulanate</td>
<td>E. coli</td>
<td>–</td>
</tr>
<tr>
<td>A</td>
<td>UTI</td>
<td>Amoxicillin-clavulanate</td>
<td>E. coli</td>
<td>–</td>
</tr>
<tr>
<td><strong>Cats</strong></td>
<td>Skin, soft tissue, UTI</td>
<td>Amoxicillin-clavulanate</td>
<td>E. coli</td>
<td>–</td>
</tr>
</tbody>
</table>

(19) Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of amoxicillin in dogs. The dosage regimen used for PK-PD analysis of amoxicillin was 11 mg/kg administered every 12 hours orally.

(20) With the exception of isolates from UTIs, E. coli and other Enterobacteriaceae should be reported as resistant to ampicillin, amoxicillin, and amoxicillin-clavulanate because the drug concentrations achieved according to the labeled dosing regimen are not high enough to reach the therapeutic target. For uncomplicated UTIs, see comment (21).

(21) This breakpoint was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg were administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs > 300 μg/mL.

See comment (20).

(23) Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of amoxicillin in cats at a dosage of 12.5 mg/kg (amoxicillin) administered every 12 hours orally.
<table>
<thead>
<tr>
<th></th>
<th>Test/Report Group</th>
<th>Antimicrobial Agent</th>
<th>Human EC</th>
<th>Disk Content</th>
<th>Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm</th>
<th>Interpretive Categories and MIC Breakpoints, μg/mL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antibiotic Resistance (mg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Skin, soft tissue</td>
<td>Ampicillin</td>
<td>E. coli</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1.0</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>UTI</td>
<td>Ampicillin</td>
<td>E. coli</td>
<td>≤8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Skin, soft tissue, UTI</td>
<td>Ampicillin</td>
<td>E. coli</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1.0</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Metritis</td>
<td>Ampicillin</td>
<td>E. coli</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1.0</td>
<td></td>
</tr>
</tbody>
</table>

(22) Systemic breakpoints were derived from microbiological and PK-PD data. The dosage regimen used for PK-PD analysis of amoxicillin was 22 mg/kg every 12 hours orally.

(13) Except for lower UTI, E. coli and other Enterobacteriaceae will test resistant to ampicillin and amoxicillin.

(14) This breakpoint for UTIs was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs > 300 μg/mL.

(15) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.

(16) Breakpoints were derived from microbiological and PK-PD data. The dose of ampicillin trihydrate used to derive this breakpoint was 11 mg/kg every 24 hours IM.

22 mg/kg q12 hours
11 mg/kg q8 hours
12.5 mg/kg q8 hours
11 mg/kg q24 hours
12.5 mg/kg q12 hours

15 mg/kg q24 hours

11 mg/kg q24 hours
Read the Monograph!!!!

Off label use of a product, reduces the predictive power of a susceptibility test.

ex. higher dose might result in clinical success despite resistance

ex. treating a different type of infection may result in clinical failure despite susceptibility
Resistance Defined

• 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*  
*versus*  
(MRSA)
Intrinsic resistance

• 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

Table 1. Intrinsic resistance in Enterobacteriaceae. Enterobacteriaceae are also intrinsically resistant to benzylpenicillin, glycopeptides, fusidic acid, macrolides (with some exceptions\(^1\)), lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

<table>
<thead>
<tr>
<th>Rule no.</th>
<th>Organisms</th>
<th>Ampicillin</th>
<th>Amoxicillin-Clavulanic acid</th>
<th>Ampicillin-Sulbactam</th>
<th>Ticarcillin</th>
<th>Cefazolin, Cefalotin, Cefoxitin, Cefadroxil</th>
<th>Cefoxitin(^2)</th>
<th>Cefuroxime</th>
<th>Tetracyclines</th>
<th>Tigecycline</th>
<th>Polymyxin B, Collistin</th>
<th>Nitrofurantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Citrobacter koseri,Citrobacter amalonicus(^a)</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>Citrobacter freundii(^d)</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>Enterobacter cloacae complex</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>Enterobacter aerogenes</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>Escherichia hermannii</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>Hafnia alvei</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td>Klebsiella pneumoniae</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>Klebsiella oxytoca</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9</td>
<td>Morganella morganii</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.10</td>
<td>Proteus mirabilis</td>
<td>R</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.11</td>
<td>Proteus penneri</td>
<td>R</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.12</td>
<td>Proteus vulgaris</td>
<td>R</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.13</td>
<td>Providencia rettgeri</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.14</td>
<td>Providencia stuartii</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.15</td>
<td>Raoultella spp.</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16</td>
<td>Serratia marcescens</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.17</td>
<td>Yersinia enterocolitica</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.18</td>
<td>Yersinia pseudotuberculosis</td>
<td>R</td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Azithromycin is effective in vivo for the treatment of typhoid fever and erythromycin may be used to treat travellers' diarrhoea.

ALL Enterobacteriaceae intrinsically Resistant to:
- Benzylpenicillin (original penicillin)
- Macrolides
- Lincosamides
A group to remember

- SPICE organisms
  - *Serratia*
  - *Providentia*
  - Indole positive Proteae*
  - *Citrobacter*
  - *Enterobacter*

- Produce AmpC β-lactamases
  - Can become de-repressed (over-produced) with therapy

- Intrinsic 3rd generation cephalosporin resistance

- In a veterinary context I would recommend avoiding all β-lactams

*Includes Proteus vulgaris and Morganella spp.*
Intrinsic Resistance Non-Fermenters

<table>
<thead>
<tr>
<th>Rule no.</th>
<th>Organisms</th>
<th>Ampicillin</th>
<th>Amoxicillin-Clavulanic acid</th>
<th>Ticarcillin</th>
<th>Ticarcillin-clavulanic acid</th>
<th>Piperacillin</th>
<th>Piperacillin-tazobactam</th>
<th>Cefuroxime</th>
<th>Cefotaxime</th>
<th>Cefadroxil</th>
<th>Cefradine</th>
<th>Cefepime</th>
<th>Aztreonam</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Ceftazidime</th>
<th>Cefoperazone</th>
<th>Ticarcillin</th>
<th>Collistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Acinetobacter baumannii, Acinetobacter pittii, Acinetobacter nosocomialis and Acinetobacter calcoaceticus complex</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.2</td>
<td>Achromobacter xylosoxydans</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.3</td>
<td>Burkholderia cepacia complex³</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.4</td>
<td>Elizabethkingia meningoseptica</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.5</td>
<td>Ochrobactrum anthropl</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.6</td>
<td>Pseudomonas aeruginosa</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2.7</td>
<td>Stenotrophomonas maltophilia</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

R = resistant
Intrinsic Resistance
Gram-Positives

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

<table>
<thead>
<tr>
<th>Rule no.</th>
<th>Organisms</th>
<th>Fusidic acid</th>
<th>Ceftazidime</th>
<th>Carboxypeptidase A (except ceftazidime)</th>
<th>Aminoglycosides</th>
<th>Macrolides</th>
<th>Clindamycin</th>
<th>Quinupristin - daltepinol</th>
<th>Vancomycin</th>
<th>Telocinlin</th>
<th>Fosfomycin</th>
<th>Novobiocin</th>
<th>Sulfonamides</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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td><em>Staphylococcus cohnii</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.3</td>
<td><em>Staphylococcus xylosus</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.4</td>
<td><em>Staphylococcus capitis</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>Other coagulase-negative staphylococci and</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6</td>
<td><em>Streptococcus</em> spp.</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.7</td>
<td><em>Enterococcus faecalis</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.8</td>
<td><em>Enterococcus gallinarum, Enterococcus casseliflavus</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.9</td>
<td><em>Enterococcus faecium</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.10</td>
<td><em>Corynebacterium</em> spp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.11</td>
<td><em>Listeria monocytogenes</em></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.12</td>
<td><em>Leuconostoc</em> spp., <em>Pediococcus</em> spp.</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.13</td>
<td><em>Lactobacillus</em> spp. (<em>L. casei, L. casei var. rhamnosus</em>)</td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.14</td>
<td><em>Clostridium</em> spp., <em>Clostridium innocuum</em></td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R = resistant

1 Low-level resistance (LLR) to aminoglycosides. Combinations of aminoglycosides with cell wall inhibitors (penicillins 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 synergism between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillins or glycopeptides.
What is Stewardship?

“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.”
What is Stewardship?

“...a coherent set of actions which promote using antimicrobials responsibly... translated into context-specific and time-specific actions.”

Clinical Microbiology and Infection 23 (2017) 793–798

Review

What is antimicrobial stewardship?

O.J. Dyar¹,*, B. Hutten², J. Schouten³, C. Pulcini⁴, on behalf of ESGAP (ESCMID Study Group for Antimicrobial stewardship)
What is Stewardship?

• 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 (institutional level)

• Audit and feedback
What is Stewardship?

• Passive stewardship – providing knowledge
  • Less effective
    • Prudent use guidelines
    • Continuing education
Principles of Rational AMU

Box 3
General principles of rational antimicrobial use

- Antimicrobials should be used only when there is evidence or at least a well-founded clinical suspicion of bacterial infection
- Antimicrobials should not be used for treatment of self-limiting infections
- Antimicrobial, pathogen, infection site, and patient factors should be considered when choosing an appropriate treatment
- Cytology should be used as a point-of-care test to guide antimicrobial choice for relevant disease conditions (eg, otitis and urinary tract infections)
- Antimicrobial susceptibility testing should be performed if
  - There is suspicion of a complicated or life-threatening infection
  - The patient does not respond to initial treatment
  - The patient has a recurring or refractory infection
  - The patient is immunosuppressed
  - There is a need to monitor the outcome of therapy (eg, long treatment period)
  - The patient is at risk of infection with multidrug-resistant bacteria
Principles of Rational AMU

- As narrow a spectrum therapy as possible should be used
- Topical therapy should be preferred over systemic therapy for treatment of superficial skin infections
- Antimicrobials should be used for as short a time as possible
- Extra-label use should be avoided when on-label options are reasonable
- Use of critically important antimicrobials not authorized for veterinary use should at least be restricted to rare and severe patient conditions (e.g., diagnosed, life-threatening bacterial infections that cannot be treated by any other available antimicrobials, provided that treatment has a realistic chance of eliminating infection)
- Antimicrobial therapy should never be used as a substitute for good infection control, and good medical and surgical practices
- Perioperative prophylaxis should be used only when indicated, and follow standard guidelines
- Clients should be educated to ensure compliance
Prescribing Decisions

• Pathogen identified (or likely pathogen)
• Susceptibility of organism
  • Knowledge of local resistance epidemiology
• Animal species
• Signalment
• Site/type of infection
• Co-morbidities
• Route of administration

• Cost
  • Client compliance
  • Label indication
  • Withdrawal time
Prescribing Decisions

- Business factors

Business factors
Veterinary surgeons talked about the tensions, which they experienced, between maintaining a viable business, client satisfaction and appropriate antibiotic prescribing:

... people are our customers and they are what keeps the business going, so if we annoy them and there is another veterinary surgeon practice they can go to where they may just be handed out antibiotics [they will potentially do that] (Veterinary surgeon 1)
Prescribing Decisions

- Business factors
- Fear factors

Fear factors

The fear of missing an infection, and potential professional consequences, were also magnified for veterinary surgeons with the forever present possibility of client complaint or disciplinary action through their professional bodies:

... vets are completely paranoid the Royal Veterinary College [sic Royal College of Veterinary Surgeons] is going to cause them damage or get them struck off (Veterinary surgeon 5)
Prescribing Decisions

- Business factors
- Fear factors
- Habitual practice factors

Habitual practice factors
Many of the veterinary surgeons talked about prescribing patterns which had been established over time and which influenced clients’ expectations of when their pet would receive an antibiotic. The examples of kennel cough and the treatment of cat abscesses were often used by veterinary surgeons to illustrate this point:

There is some kind of pattern generated ... this is what I’ve always treated this with, a jag (Scottish version of the word injection) of penicillin for a cat bite abscess. It’s a hard habit to get out of. (Veterinary surgeon 2)
Prescribing Decisions

• Business factors
• Fear factors
• Habitual practice factors

Peer influence was viewed to be a powerful factor in shaping prescribing behaviours within veterinary surgeon practice:

... the new grads are initially more prone to not give antibiotics because they were taught, well actually it's bad, and they stand their ground more. But then as they get in to practice and get more experience and maybe they just get worn down or maybe the daily life ... then they start giving antibiotics more loosely. (Veterinary surgeon 4)
Prescribing Decisions

- Business factors
- Fear factors
- Habitual practice factors
- Pharmaceutical factors

Pharmaceutical factors
Veterinary surgeons also identified that pharmaceutical companies influenced antibiotic prescribing. This opportunity to influence prescribing was created by the marketing of products to address challenges around the administration of antibiotics, such as, difficulties in getting cats to consume tablets.

... we do use [antibiotic injections] in cats and we know the problems with it, but we do it when we feel that the owners will not be able to give tablets ... we prescribe it quite often to be honest. ... I am not aware of much evidence that it contributes to specific antimicrobial resistance, but it is a third generation Cephalosporin ... (Veterinary surgeon 11)
Drugs vs. Brands

Ceci n’est pas une pipe.

Ce n’est pas un antibiotique

René Magritte
Drugs vs. Brands

• Recognize impact of marketing
  • Who only refers to a drug by the trade name?

• Understanding the active ingredient is critical!
  • The antibiotic is the active ingredient NOT the band

• A lot of useful information can be gained from pharmaceutical companies
  • Critically evaluate science vs. sales
Proximate Risks of AMU

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

Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamma, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

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...”

---

**Association of Adverse Events With Antibiotic Use in Hospitalized Patients**

Pranita D. Tamra, MD, MHS; Edina Avdic, PharmD, MBA; David Xu, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

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 Shehab, Priti R. Patel, Arjun Srinivasan, and Daniel S. Budnitz
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 2008;47:755-43
What Stewardship Means to Me

• Treating a diagnosis rather than a syndrome
• Concatenating laboratory evidence and your clinical exam into a diagnosis
  • Asking questions when you need more information
• Using evidence based empiric therapy
  • Likely pathogens, local resistance epidemiology
• Applying your knowledge of
  • Intrinsic resistance
  • Drug mechanisms of action and spectrum of activity
  • Mechanisms of resistance
What Stewardship Means to Me

- Recognizing the evolving world of infectious diseases
  - Resistance is emerging
  - Be nimble enough to adapt
- Lifelong learning - sounds cliché but:
  - Professional duty
  - If you’re not up to date you’re out of date
- Utilizing recognized therapeutic guidelines

https://www.canadianveterinarians.net/AMU-UAM
Applying Guidelines

- Canine urinary tract infection (sporadic cystitis)
- We’ll assume that a diagnosis has been made

<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><strong>Duration: 3-5d</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ALTERNATIVE TREATMENT:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Enrofloxacin: 10-20 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Marbofloxacin: 2.7-5.5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Orbifloxacin: 2.5-7.5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Pradofloxacin: 3-5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Cefpodoxime: 3-5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Cephalexin: 3-5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Cefovecin: 3-5 mg/kg PO q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. I</td>
</tr>
</tbody>
</table>

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.
Short-course Antibiotic Therapy—Replacing Constantine Units With “Shorter Is Better”

Noah Wald-Dickler\textsuperscript{1,2} and Brad Spellberg\textsuperscript{1,2}

\textsuperscript{1}Los Angeles County and University of Southern California (LAC-USC) Medical Center, and \textsuperscript{2}Division of Infectious Diseases, Keck School of Medicine at University of Southern California, Los Angeles

### Table 1. Diseases for Which Short-course Antibiotic Therapy Has Been Found to Be Equally Effective to Longer Traditional Courses of Therapy (With References)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Short (d)</th>
<th>Long (d)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia \textsuperscript{[6–14]}</td>
<td>3 or 5</td>
<td>7, 8, or 10</td>
<td>Equal</td>
</tr>
<tr>
<td>Hospital-acquired/ventilator-associated pneumonia \textsuperscript{[15, 16]}</td>
<td>7–8</td>
<td>14–15</td>
<td>Equal</td>
</tr>
<tr>
<td>Complicated urinary tract infections/pyelonephritis \textsuperscript{[17–22]}</td>
<td>5 or 7</td>
<td>10 or 14</td>
<td>Equal</td>
</tr>
<tr>
<td>Complicated/postoperative intraabdominal infections \textsuperscript{[23, 24]}</td>
<td>4 or 8</td>
<td>10 or 15</td>
<td>Equal</td>
</tr>
<tr>
<td>Gram-negative bacteremia \textsuperscript{[25]}</td>
<td>7</td>
<td>14</td>
<td>Equal</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (meta-analysis of 21 trials \textsuperscript{[26]})</td>
<td>≤5</td>
<td>≥7</td>
<td>Equal</td>
</tr>
<tr>
<td>Acute bacterial skin and skin structure infections (cellulitis/major abscess) \textsuperscript{[27–29]}</td>
<td>5–6</td>
<td>10</td>
<td>Equal</td>
</tr>
<tr>
<td>Chronic osteomyelitis \textsuperscript{[30]}</td>
<td>42</td>
<td>64</td>
<td>Equal</td>
</tr>
<tr>
<td>Empiric neutropenic fever \textsuperscript{[31]}</td>
<td>Afebrile and stable × 72 h</td>
<td>Afebrile and stable × 72 h and with absolute neutrophil count &gt; 500 cells/µL</td>
<td>Equal</td>
</tr>
</tbody>
</table>
Late-career Physicians Prescribe Longer Courses of Antibiotics

Cesar I. Fernandez-Lazaro,\textsuperscript{1,2,\dagger} Kevin A. Brown,\textsuperscript{3} Bradley J. Langford,\textsuperscript{1} Nick Daneman,\textsuperscript{1,4,5} Gary Garber,\textsuperscript{6} and Kevin L. Schwartz\textsuperscript{1,3,7}

\textsuperscript{1}Infection Prevention and Control, Public Health Ontario, Toronto, Canada; \textsuperscript{2}Department of Biomedical and Diagnostic Sciences, University of Salamanca, Spain; and \textsuperscript{3}Dalla Lana School of Public Health, University of Toronto, and \textsuperscript{4}Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada; \textsuperscript{5}Institute of Health Policy, Management and Evaluation, University of Toronto, Canada; \textsuperscript{6}Department of Medicine, Ottawa Hospital Research Institute, Canada; and \textsuperscript{7}Department of Medicine, St. Joseph's Health Centre, Toronto, Canada

CONCLUSIONS

The use of prolonged antibiotic treatments in outpatient settings is common, particularly among those family physicians in late-career stages. Moreover, there is meaningful interphysician variability in the selection of prolonged antibiotic durations, highlighting the need for multifaceted antimicrobial stewardship interventions. Future research should evaluate the optimal community-based interventions to improve prescribing behaviors.
When indicated, the benefits of shorter therapy include:

1. Decreased rate of adverse effects
2. Decreased super-infections
3. Decreased antimicrobial resistance

In a veterinary context, additional benefits conceivably include:

- Increased client compliance
- Decreased cost to client
What About Feline Dentistry?

Are prophylactic drugs used?
What drugs are used?
What patients would be treated?
The Guidelines Say...

• Dental abscesses
  • No antimicrobials
  • Unless evidence of cellulitis or bone involvement

• Dental prophylaxis
  • No antimicrobials
  • Unless history of infective endocarditis, unrepaired cyanotic congenital heart disease, PDA, subaortic or aortic stenosis, imbedded pacemaker leads.

• Dental extractions
  • No antimicrobials
  • Unless same indications as above or MARKED involvement of local soft tissue or concurrent involvement of bone

The use of antimicrobials is infrequently indicated – should be the exception NOT the rule
My Take on Guidelines

• They’re a great starting point following diagnosis
• Summary of up-to-date recommendations
  • Whether empiric therapy is warranted
  • First line therapies
  • Treatment duration
• BUT... can’t be algorithmic
  • Must have a diagnosis to apply the guidelines
  • Clinical skills required to integrate signalment, history, physical exam findings and lab results into diagnosis
When Test Result $\neq$ Outcome

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>UNEXPECTED POSITIVE CLINICAL OUTCOME</th>
<th>UNEXPECTED NEGATIVE CLINICAL OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACOKINETIC</td>
<td>High urine drug concentrations</td>
<td>Failure of drugs to penetrate protected sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug interactions decreasing absorption or activation 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 sulfonamides in purulent environments</td>
</tr>
<tr>
<td>DISEASE/PATHOLOGY</td>
<td>No infection</td>
<td>Failure to address underlying pathology or primary disease</td>
</tr>
<tr>
<td></td>
<td>Self-limiting infection</td>
<td>Indwelling device</td>
</tr>
<tr>
<td>THERAPEUTIC</td>
<td>Utilizing localized therapy, high concentrations overcoming low level resistance</td>
<td>Poor owner compliance</td>
</tr>
<tr>
<td></td>
<td>Off label use (dose, dosing frequency, route of administration)</td>
<td>Off label use (dose, dosing frequency, route of administration)</td>
</tr>
<tr>
<td>RESISTANCE ORGANISM LIFESTYLE</td>
<td></td>
<td>Development of resistance <em>in vivo</em></td>
</tr>
<tr>
<td></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>SUSCEPTIBILITY TEST</td>
<td>False positive culture (ex. contamination)</td>
<td>Mixed infection</td>
</tr>
<tr>
<td></td>
<td>Incorrectly performed or reported test</td>
<td>Incorrectly performed or reported test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inducible resistance</td>
</tr>
</tbody>
</table>

*Disagreement: clinical cure despite laboratory determined resistance OR failure to cure despite laboratory determined susceptibility*
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
  • Ask your lab about what’s going on locally
  • Keep track of test results your clinic receives
    • ex. how often do you see MRSP?
    • Use them to guide empiric therapy

• Don’t forget about intrinsic resistance

• Reflect on outcomes
  • Why did that patient recover/not recover?