Antimicrobial Selection Strategies in Veterinary Medicine

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Outline

Antimicrobial Selection Strategies in Veterinary Medicine:

• **Beyond “which drug to use”...**
  • Key principles for “holistic” antimicrobial stewardship

• **Antimicrobial selection decisions:**
  • Factors affecting antimicrobial choices in vet med
  • Data available to guide selection decision
  • Veterinary resources to assist antimicrobial selection
Antimicrobial Stewardship…
Beyond “which drug should I use?”

“Striking differences between animal species make a one-size-fits-all approach to antimicrobial stewardship difficult.

However, there is a basic logical thought process which can enable antimicrobial stewardship across all animal species and therapeutic challenges.”

Logical process requires:

(i) veterinary guidance in constructing case definitions and validating the definitions through caretaker training and diagnostics;

   Veterinary oversight, appropriate case selection for antimicrobial use

(ii) Consideration of possible alternatives to prevent, control, or treat the bacterial disease;

   Strategies to **AVOID** antimicrobial use in the first place

(iii) Choice of a first-line agent for empiric treatment, if there are no alternatives to antimicrobials;

   **WHICH** antimicrobial to choose?

(iv) safe and effective usage of the selected agent

   **HOW** to best use the selected antimicrobial?
So you’ve decided to prescribe an antimicrobial… How do you actually decide?
So you’ve decided to prescribe an antimicrobial... What factors influence your selection?

“Medical”
- Likely pathogen
- Typical C&S profile of likely pathogen
- Patient status & underlying conditions
- AMR concerns & other adverse events

“Non-medical”
- Cost
- Client compliance
- Animal husbandry / handling / welfare
- Formulation availability
- Withdrawal period (food animal)
If only all compliance was this easy!
High Quality Evidence available to guide veterinary antimicrobial selection
High Quality Evidence available to guide veterinary antimicrobial selection

“We some data indicate that therapeutic antimicrobial use in various animal species contributes to antimicrobial resistance among animal pathogens, but there is a relative paucity of information compared to that in the human literature and a profound lack of information on specific drugs and drug classes that produce the greatest risk.”

Weese et al. ACVIM Consensus Statement on Therapeutic Antimicrobial Use in Animals and Antimicrobial Resistance, JVIM 2015

- Selection focused **BETWEEN** antimicrobials...what about **WITHIN**?
  - Dose, route, duration?
  - Dose regimens typically compared based on efficacy & safety...not AMR
Comparing antimicrobial regimens for UTIs in dogs

For efficacy only

Table 2. Clinical and microbiological cure rates in female dogs treated for bacterial cystitis with short-duration sulfonamide treatment versus long-duration beta-lactam treatment.

<table>
<thead>
<tr>
<th></th>
<th>Clinical Cure</th>
<th>Microbiological Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDS</td>
<td>LDBL</td>
</tr>
<tr>
<td>Day 3 of tx.</td>
<td>89% (17 of 19)</td>
<td>94% (17 of 18)</td>
</tr>
<tr>
<td>Day 4 after tx.</td>
<td>85% (17 of 20)</td>
<td>72% (13 of 18)</td>
</tr>
<tr>
<td>&gt;30 days after tx.</td>
<td>50% (9 of 18)</td>
<td>65% (11 of 17)</td>
</tr>
</tbody>
</table>

All data are reported as percent (n of total). SDS, short-duration sulfonamide treatment; LDBL, long-duration beta-lactam treatment; tx., treatment; N/A, not applicable for assessment.

- Clinical cure rate for group 1 (enrofloxacin, sid x 3 d) was 31/35 (88.6%)
- Clinical cure rate for Group 2 (Clavamox, bid x 14 d) = 29/33 (87.9%)
  “Statistical non-inferiority”
Pyoderma therapy comparison in dogs…for efficacy only

Group T (n = 31): topical 4% chlorhexidine shampoo (twice weekly) and solution (once daily) for 4 weeks.
Group S (n = 20): treated orally with amoxicillin–clavulanic acid (25 mg/kg) twice daily for 4 weeks

Stewardship Principles for Veterinary Antimicrobial Selection

If an antimicrobial is to be used:
• Use an antimicrobial of limited importance in human medicine

• Use a narrower-spectrum antimicrobial vs broad-spectrum

• Local exposure preferable to systemic

• In a herd scenario, treat only those affected
  • What about those likely to be affected? (metaphylaxis)

• Use an appropriate dosage regimen for the antimicrobial class
  • Concentration vs time-dependent
  • Duration of use?
Health Canada Antimicrobial Categorization

<table>
<thead>
<tr>
<th>Category</th>
<th>Preferred option for treatment of serious human infections^</th>
<th>No or limited alternatives available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Very High Importance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>II – High Importance</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>III – Medium Importance</td>
<td>No</td>
<td>No/Yes</td>
</tr>
<tr>
<td>IV Low Importance</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

\^ A positive outcome for treatment of serious human infections indicates the drug is of high importance.

Just follow the label?

“There is a common misconception that the use of antimicrobial agents according to the label is always consistent with the principles of prudent use...

However, the label dose, dosing interval, and indications for older drugs are not always consistent with current principles of antimicrobial drug use.”

• Procaine penicillin G (USA)
• Tylosin for reduction of liver abscesses in feedlots
So where can vets turn for specific advice?

• Species- or indication-specific guidance from specialty groups
  • “consensus statements”
    • Demonstrable value in changing antimicrobial use in vet med?

• Electronic antimicrobial guidance available:
  • CVMA Guidelines for Veterinary Antimicrobial Use
  • Other free information for veterinarians:
    • Compendium of Veterinary Products app (label information)
    • FOI summaries (efficacy & safety, little for AMR)
    • USP monographs (mostly PK information)
    • Antimicrobial Agents in Veterinary Medicine textbook, 5th Ed.
### Table 4. Summary of systemic antimicrobial treatment options for superficial bacterial folliculitis in the dog

<table>
<thead>
<tr>
<th>Category</th>
<th>When used</th>
<th>Suggested AMBs and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First tier</strong></td>
<td>Primary choice empirical therapy of known or suspected SDF</td>
<td>Clindamycin or lincomycin&lt;br&gt;First generation cephalosporins (e.g., cefalexin, cefadroxil),&lt;br&gt;Amoxicillin–clavulanate&lt;br&gt;Trimethoprim- and ormetoprim-potentiated sulphonamides</td>
</tr>
<tr>
<td></td>
<td>Additional choices only if local regional susceptibility of <em>Staphylococcus pseudintertnadius</em> is known</td>
<td></td>
</tr>
<tr>
<td><strong>First or second tier</strong></td>
<td></td>
<td>Third generation cephalosporins (cefotaxim, ceftriaxone). There is insufficient evidence for this working group to reach consensus on categorization of these agents as first or second tier drugs (see text under ‘Systemic antimicrobial therapy’ and concerns about selection of ESBL-producing <em>Escherichia coli</em>).</td>
</tr>
<tr>
<td><strong>Second tier</strong></td>
<td>When empirical selection of first tier systemic AMD and topical therapy are not appropriate and when cultures indicate susceptibility</td>
<td>Doxycycline or minocycline&lt;br&gt;Chloramphenicol&lt;br&gt;Fluoroquinolones (such as enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin and ciprofloxacin) (should only be used when other feasible options are not available)&lt;br&gt;Rifampicin. Commonly used in combination with another drug to which the causative organism is susceptible; however, this process may not reduce development of resistance in <em>Staphylococcal</em> infection&lt;sup&gt;79&lt;/sup&gt;&lt;br&gt;Aminoglycosides, including gentamicin and amikacin. See Table 5 for comments on nephrotoxicity and ototoxicity&lt;br&gt;First tier AMD (clindamycin, lincomycin and potentiated sulphonamides) may also be considered when cultures indicate susceptibility</td>
</tr>
<tr>
<td><strong>Third tier</strong></td>
<td>When first and second tier are not appropriate and cultures indicate susceptibility</td>
<td>Linezolid, teicoplanin, vancomycin. Regardless of the fact that most (or all) MRSP are susceptible, the use of these three AMBs is strongly discouraged. These drugs can be considered ‘reserved for the treatment of serious MRSA infections in humans’.</td>
</tr>
</tbody>
</table>
Summary of the Clinical Consensus Guidelines

Recommendations for approaches to meticillin-resistant staphylococcal (MRS) infections of small animals: diagnosis, therapeutic considerations and preventative measures

1. *Staphylococcus pseudintermedius*, *S. schleiferi* (including the coagulase-negative variant) and *S. aureus* are the primary pathogens encountered in small animal dermatology practice. Clinical isolates of all three species commonly express meticillin resistance and multidrug resistance.

2. In addition, several other species of coagulase-negative *Staphylococcus* (CoNS) have been reported to cause skin and soft tissue infections, and the pathogenic role of a CoNS must be deduced by the clinician on a case-by-case basis.

3. The pathogenic potential of any CoNS isolate obtained from a secondary skin lesion or a contaminated body site should be interpreted in light of the clinical disease process (urgency, co-morbidities, risk for adverse reactions to specific antibacterial drugs) and with respect to any other pathogenic species of bacteria that may be co-isolated with it.

4. Minimum reporting by microbiology laboratories should include complete speciation of staphylococci—regardless of tube coagulase status—and an antibiogram for all cultured isolates.

5. **Topical therapy**, using antibacterial agents and biocides with proven anti-staphylococcal efficacy, is the recommended treatment modality for any surface or superficial pyoderma involving MRS; particularly those with localized lesions, and for otitis and superficial wound infections.

6. **Topical therapy** should be used as the sole on-animal antibacterial treatment for surface and superficial infections whenever the pet and owner can be expected to be compliant.

7. Geographical differences exist in the availability and licensure of antimicrobial drugs for use in animals. Judicious use decisions need to take into account regional prescribing recommendations in veterinary and human medicine.
Empirical drug selection for systemic therapy is always contraindicated when a MRS infection is suspected based on historical factors, due to the high prevalence of multidrug resistance within these strains.

A restriction-of-use policy should apply to glycopeptides (vancomycin, telocplanin, telavancin), linezolid (oxazolidinon), anti-MRSA cephalosporins and potentially new compounds that may be approved in the future for treatment of multidrug resistant pathogens of people.

There is little evidence for a difference in outcome between MRS and meticillin susceptible Staphylococcus infections in animals, and the prognosis for MRS skin infections in pets is good, depending on the underlying cause and co-morbidities.

There is currently not enough evidence to recommend routine decolonization of MRS carrier animals.

Molecular strain typing methods are research tools used to investigate the epidemiology and ecology or certain outbreak situations of MRS. However, the clinical value of strain typing largely depends on the organism’s population structure, the typing method(s) used and the goals of the investigation. Strain typing rarely has impact on patient- or clinic-level management.

Hand hygiene (proper washing/drying and use of alcohol based hand sanitizers) is the mainstay of personal responsibility for infection control. No data exist regarding optimal personal protective equipment practices for handling animals infected with MRS. However, the use of some degree of enhanced precautions to reduce contamination of clothing and skin is reasonable. Typically, this would consist of a gown or dedicated laboratory coat and disposable gloves.

In contemporary veterinary practices, routine cleaning and disinfection protocols are the cornerstone of hospital infection control. MRS are susceptible to commonly used disinfectants. Protocols should be designed to reduce or eliminate pathogenic burdens in the environment and on equipment. These protocols must be communicated clearly (and often) to the hospital team and practiced correctly and consistently.
**Table 1.** First-line antimicrobial options for bacterial respiratory infections in the dog and cat.

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>First-Line Drug Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial upper respiratory infection (URI) in cats</td>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt; or amoxicillin per os (PO)</td>
</tr>
<tr>
<td>Chronic bacterial URI in cats</td>
<td>Doxycycline or amoxicillin PO</td>
</tr>
<tr>
<td>Canine infectious respiratory disease complex (bacterial component)</td>
<td>Base the choice on C&amp;S&lt;sup&gt;b&lt;/sup&gt; if available</td>
</tr>
<tr>
<td>Bacterial bronchitis (dogs or cats)</td>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt; or amoxicillin-clavulanate PO</td>
</tr>
<tr>
<td>Pneumonia in animals with extensive contact with other animals that have no</td>
<td>Doxycycline&lt;sup&gt;d&lt;/sup&gt; PO</td>
</tr>
<tr>
<td>systemic manifestations of disease (ie, fever, lethargy, dehydration)</td>
<td>Base changes if needed on clinical responses and C&amp;S if available</td>
</tr>
<tr>
<td>Pneumonia with or without clinical evidence of sepsis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt; PO</td>
</tr>
<tr>
<td></td>
<td>Base changes if needed on clinical responses and C&amp;S if available</td>
</tr>
<tr>
<td></td>
<td>Parenteral administration of a fluoroquinolone&lt;sup&gt;d&lt;/sup&gt; and a penicillin or clindamycin&lt;sup&gt;e&lt;/sup&gt; initially</td>
</tr>
<tr>
<td></td>
<td>Base oral drug choices to follow on clinical responses and C&amp;S results if available</td>
</tr>
<tr>
<td>Pyothorax (dogs or cats)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Parenteral administration of a fluoroquinolone&lt;sup&gt;d&lt;/sup&gt; and a penicillin or clindamycin&lt;sup&gt;e&lt;/sup&gt; initially combined with therapeutic lavage initially</td>
</tr>
<tr>
<td></td>
<td>Base oral drug choices to follow on clinical responses and C&amp;S results if available</td>
</tr>
</tbody>
</table>
CVMA electronic guidance now available!

https://www.canadianveterinarians.net/AMU-UAM
Antimicrobial Information

NOTE: For further information, see the following FREE! chapters from Antimicrobial Therapy in Veterinary Medicine, 5th Ed., (editors Giguere, Prescott, Dowling):

- Chapter 2 (Antimicrobial Susceptibility Testing Methods and Interpretation of Results)
- Chapter 3 (Antimicrobial Resistance and Its Epidemiology)
- Chapter 4 (Principles of Antimicrobial Drug Bioavailability and Disposition)
- Chapter 5 (The Pharmacodynamics of Antimicrobial Agents)
- Chapter 6 (Principles of Antimicrobial Drug Selection and Use)
- Chapter 7 (Antimicrobial Stewardship in Animals)
Where else to get veterinary antimicrobial info?

- [www.aavpt.org](http://www.aavpt.org)
  - Resources tab
    - Veterinary Clinical Drug Information Monographs tab
      - Access USP Vet Drug Monographs
    - PDF files by drug class – excellent for PK info
    - FREE!

- Package inserts (Compendium of Vet Products app)
  - Check Google Play Store or iOS app store

- Freedom of Information Summaries
  - Google “FOI summary...drug name”
Questions?