Pyoderma - treatment options

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Disclosures

- Grant/Research Support:
  - Merial

- Consultant:
  - Elanco
  - Zoetis

- Major Shareholder:
  - None
Pyoderma

- Staphylococcus pseudintermedius which represents over 90% of infections in dogs (normal flora)
- Common sequela to allergic, parasitic, endocrine and immune mediated disease
  - Do not forget to look for underlying cause!
- Cytology is key to diagnosis
  - First line treatment is empirical
  - If suspect MRSP/MRSA, then consider culture and sensitivity (see later)
- Pyoderma contributes significantly to pruritus, resulting in self-trauma and continuation of itch-scratch cycle
  - Need to address infections quickly and effectively
Before using antibiotics ask:

**Site of infection?**
(Barriers to penetration/ activity: abscess, purulent debris, biofilm?)

**What class of antibiotic is best?**
(ex. beta lactam, lincosamide, fluoroquinolone?)

**What is the “most appropriate choice” antibiotic?**
(efficacy, PK/PD activity, safety, compliance)

**What dose, frequency, duration, route?**
# Treating Pyoderma

<table>
<thead>
<tr>
<th>Empirical First Choice</th>
<th>Alternative Choice</th>
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<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
<td><strong>Fluoroquinolones ??</strong></td>
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<tr>
<td>Convenia® (cefovecin sodium)</td>
<td>Zeniquin® (marbofloxacin)</td>
</tr>
<tr>
<td>Simplicef® (cefpodoxime proxetil)</td>
<td>Baytril® (enrofloxacin)</td>
</tr>
<tr>
<td>Rilexine®, human generic (cephalexin)</td>
<td>Orbax® (orbifloxacin)</td>
</tr>
<tr>
<td>Cefatabs® (cefadroxil)</td>
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<tr>
<td><strong>Potentiated penicillins</strong></td>
<td><strong>Lincosamides</strong></td>
</tr>
<tr>
<td>Clavamox® (amoxicillin/clavulanic acid)</td>
<td>Lincomycin® (lincomycin hydrochloride)</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
<td><strong>Macrolides</strong></td>
</tr>
<tr>
<td>Antirobe® (clindamycin)</td>
<td>Human generic erythromycin, azithromycin</td>
</tr>
<tr>
<td><strong>Sulfonamides</strong></td>
<td><strong>Mupirocin ointment</strong></td>
</tr>
<tr>
<td>Primor® (ormetoprim/sulfadamethoxine)</td>
<td><strong>Antibacterial shampoos, other topicals</strong></td>
</tr>
<tr>
<td>Human generic trimethoprim/sulfonamides</td>
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</table>

What influences our antibiotic choice?

- Efficacy
- Compliance
- Side effect profile of the antibiotic (including drug interactions)
- Speed of action
- Dosing strategies
- Cost
- Potential to induce bacterial resistance
  - Regional variation in bacterial resistance patterns
- Human (last-line) drug?
Superficial pyoderma - in practice

First line:
- Cephalexin (22 mg/kg q12h or 30 mg/kg q24h) - vomiting may occur at higher doses
- Cefovecin 8 mg/kg q14d for 21-28 days
  - Particularly useful in cats and animals difficult to medicate, or where compliance is a concern

Second line:
- Clindamycin 11 mg/kg q12h
- Fluoroquinolones should be avoided for Staphylococcal pyodermas unless bacterial resistance has been demonstrate\(^1\)

\(^1\) Antibiotic prescribing detailed guidelines, Australian Infectious Diseases Advisory Panel. 2013 Zoetis Australia
How does Convenia measure up?

- **Efficacy**
  - Comparable to other cephalosporins

- **Compliance**
  - Obvious advantages

- **Side effect profile of the antibiotic (including drug interactions)**
  - Comparable to other cephalosporins

- **Speed of action**
  - In tissues in 30 mins
  - Bactericidal within 4 hrs
  - Impact on cytokine and other inflammatory mediator production (e.g. bacterial exotoxins)
How does Convenia measure up?

- Dosing strategies
  - q 14 days
- Cost
  - Sliding scale?
- Potential to induce bacterial resistance
  - Would seem to be at same rate as for cephalexin
  - First generation cephalosporins (cephalexin etc.) do this too\(^2\)
- Regional variation in bacterial resistance patterns
  - Not noted with Convenia
- Human (last-line) drug?
  - No

So let’s talk about bacterial resistance

- Popular misconception that synthetic antibiotics cause resistance

- For millions of years bacteria have been producing natural antibiotics, expressing antibiotic resistance genes for “self protection”
  - Ex. Resistant bacteria isolated in 4 million year old cave in New Mexico; in deep terrestrial subsurface (500-700 feet below surface); permafrost; in remote isolated communities (Peruvian Amazon, Nepal, Bolivia), wild animals

- Bacteria have adapted natural resistance genes to protect against synthetic antibiotics

Use of *any* antibiotic has potential to select for resistant bacteria
What is Methicillin Resistant Staphylococcus (MRS)?

- *Staphylococci* that has lost its sensitivity to most β-lactam antibiotics
  - Ampicillin, amoxicillin
  - Amoxicillin / clavulanate
  - Most cephalosporins (all veterinary approved ceph’s)
  - Oxacillin
  - Ticarcillin

- Oxacillin is used as the C/S “marker” for methicillin
- May be multi-drug class resistant- often resistant to fluoroquinolones
How often is MRS seen in veterinary practice?

**Source:** PAH 2011 Companion Animal Surveillance Program Data- general practices, dogs/cats

*Staphylococcus pseudintermedius*
SSTI cultures (n=199)

- Mec A +: 32.2%
- Mec A -:
Species of Staphylococcus is important MRSP ≠ MRSA

- **MRSP - dog, cat source**
  - Most common cause of MR pyoderma in dogs and cats
  - Unlikely to cause zoonotic infection unless owner immunosuppressed
  - Pet owners uncommonly colonized
  - Infected cases can colonize contact animals; hospital, home environment often contaminated
  - Multi-drug resistant to multiple drug classes

When to Suspect MRS and Perform a Culture?\textsuperscript{7,8}

- Cocci on cytology, poor response to cephalosporins, amoxillin-clavulanic acid, fluoroquinolones
- Previous antibiotics in the past 12 months
- Pet recently hospitalized
- Non-healing post-surgical infection
- Owner works in healthcare field, MRSA infection in household
- Therapy dog with pyoderma

Antibiotics Used to Treat MRSP Infections

- MRSP not more pathogenic, just more difficult to treat
- Sometimes: sulfas, clindamycin, doxycycline, minocycline
- Many cases only:
  - Chloramphenicol 40-50 mg/kg q 8 h
  - Amikacin 15 mg/kg SQ inj q 24 h
  - Rifampin 5-10 mg/kg q 24 h
- Combine with antibacterial topical therapy, environmental disinfection

Do we need to treat MRSP systemically?

- Many cases can be resolved with topical therapy alone
  - Chlorhexidine
  - Dakin’s solution (dilute bleach)
  - SSD
  - Mupirocin ointment
Topical Treatment for MRS Pyoderma

► Shampoo daily to twice weekly
  ► 3 - 4% chlorhexidine (Hexadene-Virbac) w/ phytosphingosine (Douxo), TrisEDTA (TrizChlor 4)
  ► Chlorhexidine more effective in vitro for MSSP/MRSP then benzoyl peroxide, ethyl lactate, chloroxylenol, acetic acid-boric acid\(^\text{11}\)
  ► Offer weekly “bathing packages” for pet owners

Topical Treatment for MR Pyoderma

- Chlorhexidine spray, mousse or wipes (Douxo, TrizChlor 4)
- Zymox spray
- 2% Mupirocin ointment
Topical Treatment for MR Pyoderma

- **Bleach baths**\textsuperscript{12,13}
  - 2 tsp/ gallon
  - 1/2 cup per ¼-full tub of water
  - Effective in human MRSA cases, anecdotal reports of success by vet dermatologists

Proper Antibiotic Use- Summary

► All antibiotics can select for resistant bacteria

► Use antibiotics appropriately when a bacterial infection is present and not “just in case”

► USE TOPICALS!!!!
  ► This is becoming the mainstay of treatment for superficial infections, not parenteral antibiotics

► Culture more often
  ► With resistance on the rise don’t wait for treatment failure e.g., recent antibiotic use is indication for culture

► Don’t play antibiotic roulette
Questions?
Factors that may contribute to resistance

▶ What if antibiotics are used without veterinary supervision?

▶ Two year study of 2 breeding kennels

▶ Kennel A- judicious antibiotic use only with veterinary prescription

▶ Kennel B- excessive use of cephalosporins, fluoroquinolones, macrolides without veterinary supervision

▶ Results: 16 MRSP strains isolated from dogs in Kennel B, 0 from Kennel A at end of 2 year period

▶ Conclusion: Use of antibiotics without veterinary supervision can increase risk of colonization with MRSP

Do Certain Antibiotics Contribute to Resistance?

- **What about fluoroquinololones?**
  - Studies in human medicine: hospitalized patients more likely to develop nosocomial MRSA if received ciprofloxacin or levofloxacin\(^{16-18}\)
  - Fluoroquinolones, beta lactams in past 90 days risk factor for MRSA infection in dogs: **author recommends restrict use of FQ’s as empirical or first-line therapy**\(^{19}\)
  - Enrofloxacin treatment in laboratory dogs resulted in development of persistent MDR fecal E.coli\(^{20}\)

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\(^{18}\)Nseir S et al. Crit Care Med 33:283-89, 2005
Do Certain Antibiotics Contribute to Resistance?

- Are 3rd generation cephalosporins big guns that should be reserved and not used first line?
  - Cefpodoxime, cefovecin are not “big guns”
    - FDA approved as appropriate first line empirical therapies for superficial Staphylococcal pyoderma²¹
  - Acquiring the gene for methicillin resistance not linked to the generation of cephalosporin used
  - Not used IV in hospital setting for severe infections as in human medicine
  - Not effective against Enterococcus, Pseudomonas, MR Staphylococcus

Do Certain Antibiotics Contribute to Resistance?

- **Do first generation cephalosporins like cephalexin cause less resistance?**


  - **Objective:** To evaluate possible selection of *E. coli* resistant to extended spectrum cephalosporins after treatment with cephalexin

  - **Design:** Treated (cephalexin BID 25 mg/kg 14-28d) and control (no Ab in past 6 m) dogs screened for occurrence of *E. coli sp.* resistant to cefoxatime (human third generation cephalosporin)
Do Certain Antibiotics Contribute to Resistance?


  ▶ Results:
    - 8/13 (62%) of cephalexin treated dogs were positive for cefoxatime – resistant E.coli (CMY-2 β-lactamase positive)
    - No positive growth in control group
    - CMY-2 β-lactamase confers resistance to all β-lactams used in dogs

  ▶ Conclusions
    - Dogs receiving oral first generation cephalosporins may be an important reservoir for CMY-2 β-lactamases (ESBL’s)
    - Cephalexin administration impacts the intestinal E.coli population in favour of resistant strains
When to Use Convenia®?

- Empirical, *first choice* to treat common skin infections in dogs, cats
- Ideal PK/PD profile for time-dependent antibiotic
  - Sustained uninterrupted therapeutic drug concentrations
- Assures 100% compliance
- Excellent safety and efficacy profile

Time-Dependent Antibiotic Efficacy =
Time Above MIC (beta-lactam antibiotics)

Predictor of Efficacy: Time Above the MIC

**Treatment Goal**
Maximize bacterial killing time by maintaining drug concentration above the MIC for most of the dosing interval; at least 50% of the dosing interval

**MIC** (Minimum Inhibitory Concentration)
The lowest concentration of drug required to inhibit visible growth of the target organism in vitro
Time Dependent Drugs
“Twice Daily Dosing” vs. CONVENIA®

A Model of a Single Injection of CONVENIA Pharmacokinetics Contrasted with Twice Daily Oral Antibiotics
CONVENIA® is not for use in dogs or cats with a history of allergic reactions to penicillins or cephalosporins. Similar to other cephalosporins, side effects for both dogs and cats include vomiting, diarrhea, decreased appetite/anorexia, and lethargy. The safety of CONVENIA® has not been determined in lactating or breeding animals. Adverse event reporting or technical inquiries should be directed to Pfizer Animal Health Product Support, 1-800-366-5288 or 1-855-424-7349 (USA).

# Contemporary Classification

<table>
<thead>
<tr>
<th><strong>Group</strong> (Example)</th>
<th><strong>Characteristics</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>Group 1</strong> 1st Generation (cefa-zolin)</td>
<td>Parenteral, resistant to staphylococcal ( \beta )-lactamase, sensitive to enterobacterial ( \beta )-lactamase, moderately active</td>
</tr>
<tr>
<td><strong>Group 2</strong> 1st Generation (cefa-droxi)</td>
<td>Oral, resistant to staphylococcal ( \beta )-lactamase, moderately resistant to some enterobacterial ( \beta )-lactamase, moderately active</td>
</tr>
<tr>
<td><strong>Group 3</strong> 2nd Generation (cefa-clor)</td>
<td>Parenteral, resistant to many ( \beta )-lactamases, moderately active</td>
</tr>
<tr>
<td><strong>Group 4</strong> 3rd Generation (cefi-orur, cefovecin*)</td>
<td>Parenteral, resistant to many ( \beta )-lactamases, highly active</td>
</tr>
<tr>
<td><strong>Group 5</strong> 3rd Generation (cepo-do-xime)</td>
<td>Oral, resistant to many ( \beta )-lactamases, highly active</td>
</tr>
<tr>
<td><strong>Group 6</strong> 3rd Generation (cefo-per-azo, cefta-zidime)</td>
<td>Parenteral, resistant to many ( \beta )-lactamases, active against <em>Pseudomonas aeruginosa</em>, highly active</td>
</tr>
<tr>
<td><strong>Group 7</strong> 4th Generation (cefe-pilme)</td>
<td>Parenteral, resistant to staphylococcal, enterobacterial, and pseudomonal ( \beta )-lactamases, highly active</td>
</tr>
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