MANAGEMENT OF METHICILLIN-RESISTANT STAPHYLOCOCCAL SKIN INFECTIONS

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Normal Cutaneous Flora

- Resident Bacteria
  - have the ability to live and multiply on the skin
  - persist for long periods of time
  - May overgrow and cause infection when conditions are favorable

- Dogs
  - *Staphylococcus pseudintermedius*
  - *Staphylococcus schleiferi*
  - Other *Staphylococcus* spp

- Cats
  - *Pasteurella multocida*
  - *Staphylococcus aureus*
  - *Staphylococcus pseudintermedius*
  - Other *Staphylococcus* spp
Infection vs. colonization?

• Signs of infection include:
  • consistent skin lesions
  • cocci in intact pustules
  • intracellular cocci
  • degenerate neutrophils
Pyoderma

• “pus in the skin”
• Most common organisms for dogs
  • *Staphylococcus pseudintermedius*
  • Other *Staphylococci*
  • Occasionally *Proteus* or *Pseudomonas*
• Cats
  • *Pasteurella multocida* (abscesses)
  • *S. aureus*
  • *S. pseudintermedius*
Pathogenesis: Predisposing Factors
These need to be looked for in ALL cases

- Trauma
- Xerosis (dry skin/coat)
- Ectoparasites
- Poor grooming
- Endocrine diseases
- Allergies
- Poor nutrition
- Underlying systemic disease
- Impaired immunity
- Anatomical defects
- Medications
Principles of Treatment: Bacterial Pyoderma

• Systemic Antibiotics
  • Effective against specific bacteria
  • Tissue distribution to the skin
  • Minimum side effects
  • Easy to give, reasonable cost
  • Continue treatment 1-2 weeks beyond clinical cure (THIS IS VERY IMPORTANT to minimize risk of reoccurrence)

• Cultures
  • Cases that do not improve with empirical treatment
  • Reoccurrences within 6 months
  • Immunocompromised pet or family member
What to culture

• Pustules
• Under epidermal collarettes or crusts (sterile blade to scrape)
• FNA of cellulitis or deep infections
• Material expressed from tracts after cleaning surface
• Skin biopsies
Review of Beta-Lactam Antibiotics

- Antibiotics that contain a beta-lactam ring
  - Penicillins
  - Beta-lactamase inhibitors
  - Cephalosporins
  - Carbapenems
- Bacteriocidal
  - Inhibit synthesis of peptidoglycans in bacterial cell wall
Penicillins
Oxacillin

- Bactericidal
- Binds to penicillin-binding proteins in bacterial cell wall
- Time dependent drug (time above MIC)
- Is resistant to beta-lactamase, therefore effective for most species of *Staphylococcus* + many Gram negative organisms
- Food interferes with absorption (give on empty stomach)
- Dogs and Cats
  - 22-40 mg/kg q 8 hr PO
Cephalosporins

• 1st isolated from cultures of *Cephalosporin acremonium*

• Bacteriocidal, disrupt the synthesis of peptidoglycan layer of bacterial cell walls

• Bind to bacterial penicillin-binding proteins (transpeptidase & carboxypeptidase)
Beta-Lactam Antibiotics

- Bacterial resistance
  - Bacterial production of Beta-lactamase or penicillinase
  - Bacteria with alterations in penicillin-binding protein
    - MecA gene transmits this form of resistance
“History of Staphylococcal infections in dogs”

- Prior to mid-70’s coagulase positive staphylococci were presumed to be S. aureus
- *S. intermedius* first described in 1976 as most common isolate from canine pyoderma
- Molecular techniques in 2006 reported the SIG group contains
  - *S. intermedius*
  - *S. pseudointermedius*
  - *S. delphini*
**S. pseudintermedius** in normal dogs

- **S. pseudintermedius**
  - Normal flora of nares, mouth, pharynx, forehead, groin and anus of dogs
  - Nares and anus have largest #s
Virulence factors of *S. pseudintermedius*

- Produces many enzymes
  - Coagulase
  - Proteases
  - Thermonuclease
  - Haemolysins
  - Exfoliative toxins
  - Enterotoxins
  - Leukotoxin (Luk-1)

- Binds to
  - Fibrinogen
  - Fibronectin
  - Cytokeratin

- Produces staphylococcal protein A (spa) binds to Iggs

- Some strains produce biofilms
Methicillin - Resistance

• mecA gene
  • encodes production of modified PBP
  • Located on Staphylococcal chromosomal cassette

• Oxacillin susceptibility correlates well with mecA status

• Oxacillin is more stable than methicillin
Methicillin Resistance

• Prevalence of MRSP
  • 0-4.5% general population
  • 0-7% of dogs with skin disease
  • 15-17% of dogs cultured for skin infections
  • As high as 30% of cases submitted to some laboratories (2008 – UT)
  • 2010 Japanese study – 67% of dogs with pyoderma
Methicillin Resistance

- Most North American MRSP are of ST68 clonal lineage
- Most European MRSP are of ST71 clonal lineage
- Multidrug resistance varies with location
  - USA – 50% susceptible to chloramphenicol
  - Europe – 10% susceptible to chloramphenicol
Methicillin Resistance

- Risk factors for MRSP (dogs)
  - Urban dogs
  - Systemic antibiotics within past year
- Risk factors for MRSA (dogs)
  - Recent treatment with FQs or B-lactams
  - Multiple courses of antibiotics
  - Multiple-day hospitalization
  - Surgical implants
  - Intravenous catheters
  - Contact with people who are sick or who have been hospitalized
Methicillin Resistance

• *Staphylococcus schleiferi*
  • Subspecies *schleiferi* (coagulase negative)
  • Subspecies *coagulans* (coagulase positive)
  • MR > 50%
  • Risk factor for MRSS—recent (30 d to 6 month prior) treatment with a B-lactam antibiotic
## Other resistance genes

<table>
<thead>
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<th>Antibiotic</th>
<th>Resistance breakpoint</th>
<th>% of resistant isolates</th>
<th>Resistance genes involved</th>
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<tbody>
<tr>
<td>Erythromycin</td>
<td>≥ 8</td>
<td>89</td>
<td>erm (B)</td>
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<tr>
<td>Clindamycin</td>
<td>≥ 4</td>
<td>89</td>
<td>Erm (b), Inu (A)</td>
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<tr>
<td>Trimethoprim</td>
<td>≥ 16</td>
<td>90</td>
<td>dfrG</td>
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<tr>
<td>Ciprofloxacin</td>
<td>≥ 4</td>
<td>87</td>
<td>ND</td>
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<tr>
<td>Gentamicin</td>
<td>≥ 16</td>
<td>70</td>
<td>aac(6’)-le-aph(2’)-Ia</td>
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<tr>
<td>Tetracycline</td>
<td>≥ 16</td>
<td>70</td>
<td>tet(M); tet (K)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>≥ 32</td>
<td>57</td>
<td>cat</td>
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</table>

J Antimicrob Chemother 2011; 66: 2705 –2714
Risk for humans

- Carriage of MRSP in people
  - 1/242 humans + living with a dog
  - 1/20 staff members + in a veterinary clinic
  - 7.9% of staff in a veterinary academic hospital + in 2008
  - 2/25 owners + during time dog culture positive, all negative following successful treatment of their dogs
  - 5.3% of staff in veterinary dermatology practices +
Methicillin-resistant *Staphylococcus aureus* (MRSA) in Veterinarians

- Emerging as a problem in vet med
- MRSA carriage 1.3% in US population
- Human health care workers ↑ risk
- 13% of veterinary personal working with USA strain
  500 infected horses identified as carriers
- 6.5% of veterinarians screened at 2005 ACVIM Forum identified as carriers
  - 15.6% of large animal vets were carriers
  - 4.4% of small animal vets were carriers
Superficial Bacterial Folliculitis

- ** *S. pseudintermedius***
  - different strains may be present on one animal
  - produce enterotoxins (A, B, C, D), toxic shock protein, Protein A, hemolysins, and slime
  - not very virulent, so cutaneous infection is usually DUE TO AN UNDERLYING DISORDER
  - Methicillin resistant strains are increasing
    - Culture recurrent cases
- Other bacteria sometimes involved
  - *S. aureus (may be a reverse zoonosis)*
  - *S. schelferi*
Superficial Bacterial Folliculitis

• Generally are secondary infections:
  Underlying causes may include
  • hypersensitivity disorders
  • keratinization disorders
  • metabolic diseases
  • immune deficiency
  • follicular diseases
  • miscellaneous:
    trauma, dry skin, poor grooming...
Methicillin Resistant Staphylococcus aureus in dogs

This dog was successfully treated with the combination of rifampin + Ciprofloxacin for 16 weeks
Treatment of Methicillin Resistant Infections

• Antibiotic options MAY include (culture STRONGLY recommended)
  • Potentiated sulfonamides
  • Clindamycin
  • Fluoroquinolones
  • Chloramphenicol
  • Rifampin
  • Amikacin
Potentiated Sulfanomides

• Synergistic inhibition of folic acid synthesis in bacteria and protozoa

• Side effects may include keratoconjunctivitis sicca, iatrogenic hypothyroidism, drug hypersensitivity reactions (polyarthritis), anemia, thrombocytopenia, vomiting, diarrhea

• Are effective in some animals with MRSA
Potentiated Sulfanomides

- Ormetoprim-sulfadimethoxine and Baquiloprim-sulfadimethoxine
  - Dogs 27.5 mg/kg q 24 hr (double dose the first day)
- Trimethoprim-sulfadiazine and Trimethoprim-sulfamethoxazole
  - Dogs 30 mg/kg q 24 (or 15 mg/kg q 12 hr)
  - Cats 15 mg/kg q 12 hr (give with 2.5 mg/kg/day folinic acid to prevent anemia)
- Monitor tear production and blood counts
- If giving long-term consider giving thyroid hormone supplements
Clindamycin

• Dogs and Cats
  • 11 mg/kg q 12 hr
• Penetrates well into areas of fibrosis
• *Staphylococci* may be resistant; culture recommended
Fluoroquinolones

- Bacteriocidal antibiotics
  - Inhibit DNA gyrase or topoisomerase IV enzymes thereby preventing DNA transcription
- Examples
  - Ciprofloxacin
  - Enrofloxacin
  - Marbofloxacin
  - Orbifloxacin
  - Difloxacin
  - Sarafloxacin
- Contraindicated in young animals (cartilage damage)
Ciprofloxacin

- Variable absorption in dogs and low absorption in cats
  - Avoid giving with food
  - Do not give with antacids or sucralfate
- Dogs 10-40 mg/kg q 24 hours
- Cats 20 mg/kg q 24 hours
Enrofloxacin

- Well absorbed and converted into ciprofloxacin
- Concentrates in phagocytes which carry to sites of inflammation
- Cats treated at doses above 5 mg/kg may have damage to retinas
- Dogs 5 mg/kg q 24 hours for *Staphylococci*, 11-20 mg/kg for *Pseudomonas*
Marbofloxacin

- Concentrates intracellularly
- Poor activity against *Streptococci* and anaerobes
- Dogs and Cats
  - 2.75-5.5 mg/kg q 24 h
Orbifloxacin

- High absorption
- Effective against many Gram positive and Gram negative organisms, NOT for anaerobes
- May predispose to seizures
- High doses may cause retinal damage in cats
- Dogs and Cats
  - 5.0 -7.5 mg/kg q 24 hrs
Doxycycline

- High absorption especially when given with food
- Good tissue distribution
- Good activity against many intracellular pathogens including some mycobacteria
- Many staphylococci are resistant
- May cause esophageal irritations and strictures (especially in cats)
- Dogs 3-5 mg/kg q 12 hr
- Cats 5-10 mg/kg q 12 hr
Chloramphenicol

- Bacteriostatic
  - Binds to 50S ribosomes of bacteria inhibiting protein synthesis
- Lipid soluble with wide tissue distribution
- Good activity against many staphylococci (including many MRSA) and also against Gram negative, anaerobes, rickettsia and others
Chloramphenicol

- Cytochrome P-450 inhibitor (potential for drug interactions)
- Side effects: possible bone marrow suppression (do not use if FIV or FeLV cats, monitor CBCs in cats)
- GI upsets
- Rear limb weakness
- Contraindicated in pregnancy and in neonates
- Dogs 25-50 mg/kg q 8 hr
- Cats 50 mg/cat q 12 hr
Rifampin

• Binds to bacterial DNA-dependent RNA polymerase
• Excellent absorption
• Excellent tissue distribution
• Effective against *Staphylococci*, *Bartonella*, *Brucella*, and some *Mycobacterium* spp
• Resistance may develop rapidly; ideal to give with another antibiotic
• May cause reddish color to urine, saliva, tears and feces; possible hepatotoxicity –MONITOR LIVER PANEL every week!!!! Give with SAMe
• Dogs 10 mg/kg q 12 hr
• Cats 5-10 mg/kg q 24 hr
Aminoglycosides

• Derived from *Streptomyces*
• Bacteriocidal with multiple sites of action (bind 30S ribosomal unit, some also 50S subunit + 16S rRNA, inhibit protein synthesis and disrupt cell wall; also disrupt integrity of cell membranes)
• Have a post-antibiotic effect allowing prolonged intervals between doses
• Broad spectrum for Gram positive and negative organisms, not effective for anaerobes
• Must be given by injection
Aminoglycosides

- Nephrotoxic and ototoxic
- Not absorbed from intestines
- Synergistic with penicillins (however increased nephrotoxicity when given with cephalexin, increased ototoxicity when given with furosemide)
- Gentamicin
  - Dogs 4.4-6.6 mg/kg q 24 hr
  - Cats 2.2 mg/kg q 24 hr
- Amikacin
  - Dogs 7.5 mg/kg q 12 hr
  - Cats 5-10 mg/kg q 12 hr
- Monitor Urinalysis 1x-2x/week and renal panel
Adjuvants to Treating Infections

- Shampoos
  - Benzoyl peroxide
  - Chlorhexidine
  - Ethyl lactate
  - Monosaccharides

- Leave-on products
  - Chlorhexidine lotion or spray
  - Mupirocin cream
  - Benzoyl peroxide gel
Benzoyl peroxide

- Kills most bacteria and yeast
- Potent degreaser
- Suppresses sebaceous gland activity
- Oxidizer (bleaches fabrics, may be irritating)
- Follicle flusher (removes sebum, keratin and mites from hair follicles)
- Use with a moisturizer
Chlorhexidine

- Bactericidal through disruption of cell membranes
- Residual activity
  - 6 hours non-encapsulated
  - Up to 1 week with micro-emulsion spray
- Can cause corneal ulcers
- Ototoxic inside middle ear (do not use in ears if eardrum is ruptured!)
Mupiracin

- Bactericidal
- Binds to bacterial isoleucyl-tRNA synthetase
- Unique mechanism of action therefore no concern about cross-resistance with other antibiotics
- Only used topically
- Used in treatment of MRSA (including nasal treatment for human carriers)
Dakin’s Solution

• Start with ¼ strength solution
  • Final rinse after bath
  • Daily between baths

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<tr>
<th></th>
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<th>½ strength</th>
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<tr>
<td>Bleach</td>
<td>1.5 tablespoons</td>
<td>3 tablespoons</td>
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<tr>
<td>Water</td>
<td>1 quart</td>
<td>1 quart</td>
</tr>
<tr>
<td>Baking Soda</td>
<td>½ teaspoon</td>
<td>1 teaspoon</td>
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</table>
Immunostimulants

- Staphylococcal phage lysate
  - Stimulates production of interleukin-6 and interferon-gamma
  - Increases immune response against Staphylococci
  - Dogs 0.5 ml subcutaneous twice weekly for 10-12 weeks then every 1-2 weeks
Immunostimulants

• Alpha-interferon
  • May serve as a stimulus to improve immune responses
  • Low dose oral αIFN2a upregulates the production of interferon-γ, interleukin-12 (IL12), and IL18
  • enhances natural killer cell function & macrophage activity
  • upregulates MHC-1 & MHC-2 expression
  • upregulates cytotoxic T cell function and cellular immunity
  • increases production of immunoglobulins
  • Dose 1000 IU/dog q 24 hr (squirt directly in mouth)
Principles of Treatment

- systemic antibiotics for a minimum of 21 days
- treat 7-10 days past clinical cure
- avoid steroids
- Culture if suspect resistant bacteria may be present
- identify and treat underlying conditions
- topical medications: antiseptic shampoos, antimicrobial creams/gels
- MULTIMODAL TREATMENT
Methicillin-resistant *Staphylococcus* Infection Control Recommendations

- Implement infection control measures
  - Environmental hygiene
  - Hand washing
  - Barrier protection
  - Isolation facilities/procedures
  - Traffic pattern within hospital
  - Surveillance
  - Education
Preventing transmission of Methicillin Resistant Infections

• Contact—limit contact with infected individuals
• Contamination—minimize by use of disinfectants
• Compromised Skin—clean wounds promptly and cover open wounds
• Cleanliness—wash hands frequently
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(October 20-24, 2020)
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