METHICILLIN-RESISTANT STAPHYLOCOCCUS INFECTIONS

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OUTLINE

• Brief overview of recognizing pyoderma
• Introduction to methicillin resistance (MR) and multi-drug resistance (MDR)
• When do I suspect MR and MDR infections?
• Diagnostics for pyoderma
• Topical treatment options
• Systemic treatment options
• Prevention

WHAT IS THE PURPOSE OF THIS LECTURE?

• What is the principal reason for antimicrobial use in small animal practice?
  • Superficial bacterial pyoderma
    • A study in 2014 in the UK showed that 92% of 480 dogs with pyoderma, either suspected or confirmed, received systemic antibiotics.
    • With the continuing emergence of methicillin-resistant staphylococci, it is necessary to reduce antimicrobial usage which is the principal driver of multidrug resistance.
    • Pyoderma provides excellent opportunities for good antimicrobial stewardship.

PYODERMA

• Pyogenic bacterial infection of the skin
  • One of the most common canine skin diseases
  • Less common in cats but we do see it
  • The vast majority of cases are secondary to an underlying disease
  • Etiology: allergies, endocrinopathies
  • Usually haired skin, pressure points, body folds, and symmetrically distributed
  • +/- pruritus

Classification is based on depth of infection
• Surface, superficial, deep
• Superficial bacterial folliculitis = most common
• Type of pyoderma + cytology ➔ diagnosis and treatment plan
• Topical and/or systemic therapy when possible
• Empiric systemic antibiotics for most first-time infections

WHAT BACTERIAL SPECIES DO WE SEE?

• Staphylococcus pseudintermedius ➔ most commonly isolated
  • Normal flora of dog and cat skin
  • S. schleiferi
  • Coagulase variable
  • S. aureus
  • Uncommon in pets but possible especially with healthcare worker pets
TWO IMPORTANT PAPERS

- Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of International Society for Companion Animal Infectious Diseases)
  - Journal of Veterinary Dermatology
- Recommendations for approaches to methicillin-resistant staphylococcal infections of small animals: diagnostic considerations, therapeutic considerations, and preventative measures
  - Clinical Consensus Guidelines of the World Association of Veterinary Dermatology

ANTIMICROBIAL RESISTANCE

- Staphylococcus harbors resistance to all available antimicrobials
- In human medicine, MRSA since early 1960s
- In veterinary medicine, methicillin resistance a serious and widespread problem in past 10-15 years
- Methicillin resistance (MR) = mecA gene is carried by a large mobile genetic element, the staphylococcal cassette chromosome (SCC)
- Only 3 genetic steps are required for rapid evolution to multidrug resistance (MDR) (resistance to 3 or more drug classes)
- Percentages of MRSP vary based on region (30% of isolates in UK, up to 70% of isolates in Japan)

- Biofilm production
  - Can promote resistance to host defense mechanisms
  - Enhances antimicrobial resistance
- Fluoroquinolones usage
  - Major risk factor for selecting for MRSA
- Fluoroquinolone resistance also travels with the SCC mobile element
- Promotes development of MDR
- When used, it is important to dose as high as possible.
- Should NOT be used without a culture

WHAT IS CONTRIBUTING TO ANTIMICROBIAL RESISTANCE?

- Previous, repeated courses of antibiotics
  - Especially fluoroquinolones
- Biofilm production
  - Can promote resistance to host defense mechanisms
  - Enhances antimicrobial resistance
- Unfinished courses
  - Owner noncompliance
- Treatment of non-bacterial infections
  - Exposure to animals or people with resistant Staph

WHEN DO I SUSPECT MR AND MDR INFECTIONS?

- Clinical signs – erythema, scaling, crust or pustules, moist-wet papules, epidermal collarettes
- **Clinically, MRS infections in animals are no different from infections involving less resistant staphylococci.

- Clinical outcome is the same for MSS vs. MRS if safe tx option is available
- History
  - Previous course(s) of antibiotics
  - Previous course of subtherapeutic dosing
- Lack of resolution to an appropriate length and dosage of antibiotics
- They come to me on cephalexin “but it’s not working!”
WHAT IS MY NEXT STEP?

1. CYTOLOGY
   - This step is non-negotiable.
   - Powerful adjunctive diagnostic test (93% diagnostic sensitivity), strongly encouraged for proper diagnosis.
   - Underused in general practice.
   - Teach your technicians.
   - Different methods: smear vs. clear tape.
   - Differentiate culture from cytology.

2. AEROBIC CULTURE AND SUSCEPTIBILITY
   - Cytology is MANDATORY before this step.
   - Cytology ensures concordance between the two tests.
   - Positive cytology + negative culture = repeat culture.
   - Negative cytology = don't culture!!
   - Helps sort through the kitchen sink cultures.

CULTURE AND SUSCEPTIBILITY TESTING

- Five situations that may indicate the likelihood of resistance:
  - Less than 50% reduction in extent of lesions within 2 weeks of appropriate systemic antimicrobial therapy.
  - Emergence of new lesions 2 weeks or more after the initiation of appropriate antimicrobial therapy.
  - Presence of residual lesions after 4 weeks of appropriate therapy (and presence of cocci on cytology).
  - Intracellular rod-shaped bacteria detected on cytology.
  - Prior history of MDR infection in the dog or in a household.

HOW SHOULD YOU TAKE A CULTURE?

- Swab (usually aseptic preparation is NOT recommended).
- Pustules are the preferred lesion for sampling.
- In the absence of pustules, sample pus beneath crusts.
- Epidermal collarettes.
- Papules.
- Deeppetemum cultures produce relevant pathogens in 38% of cases.
- Tissue culture via biopsy (intact papule or nodule).
- Local anesthesia.
- Clip hair with scissors.
- Clean skin with a single wipe of 70% alcohol, allow to dry.
- 4-6 mm punch, sterile instruments, sterile saline in tube.

WHAT ABOUT ACRAL LICK DERMATITIS?

- Acral lick dermatitis should be sampled by biopsy.
- Studies show that deep cultures do not correlate well with superficial cultures.
- Often show resistance to empiric drugs.
- Rinse skin with sterile saline or wipe with 70% alcohol.


IMPORTANT NOTES ABOUT LAB SELECTION

- Laboratories should be used that observe protocols such as those published by the Clinical and Laboratory Standards Institute (CLSI).
- The lab must perform tests to differentiate MRSA and MRSAP as well as coagulase- positive staph from coagulase-negative.
- You should not receive a result of "Staphylococcus species".
- S. schleiferi is coagulase variable, is associated with recurrent infections, shows a high rate of MR.
- Probably previously underreported.
- Different Staphs have different breakpoints for oxacillin.

- MRSA and MRSAP are public health risks if your patient truly has S. aureus.
INTERPRETING CULTURE RESULTS

- Always interpret in light of cytology findings
- Is the isolate reported as methicillin resistant?
- Oxacillin = methicillin
- Marker of methicillin resistance
- Methicillin-resistant staphylococci are resistant to all beta-lactam antibiotics*
- Cephalosporins, penicillins, carbapenems, and monobactams
- Regardless of apparent in-vitro susceptibility
- Methicillin-resistant Staph are commonly resistant to multiple antimicrobials in addition to beta-lactams
- Susceptibility in vitro does not always parallel clinical responses in infected animals!
- AKA what the lab says will work does not always work
- Gram-negative bacteria (Pseudomonas, E. coli) are uncommon agents in superficial pyoderma.

WHAT DO I DO IF MY CLIENT DECLINES A CULTURE?

HOW DO YOU DECIDE BETWEEN TOPICALS, SYSTEMICS, OR BOTH?

- Depth of infection
- Severity and extent of lesions
- Patient factors
- Hair coat, temperament, environment
- Concurrent diseases
- Owner’s ability to perform topical or systemic therapy
- Owner compliance

TOPICAL THERAPY

- Probably underused because of perception that clients will find it more difficult to apply and that compliance may be poor
- Many benefits to topical therapy
- More rapid lesion resolution
- Decrease in duration of antimicrobial administration when combined with systemic drugs
- Physical removal of organisms and debris from skin surface
- Minimal adverse effects
- Greatly reduced exposure to antibiotics of bystander organisms in other organ systems
- Helps to restore normal skin structure and function, moisturization, etc.

TOPICAL THERAPY RECOMMENDATIONS

- Lack of studies on optimal protocols
- Continue until 7 days beyond clinical resolution
- Contact time should be at least 10 minutes
- Hair coat should be kept short
- Other tips:
  - Client communication
  - Use an e-collar for 15-15 minutes after application
  - Feed a meal or give a Kong
  - Go for a walk
  - Play fetch

TOPICAL TREATMENT OPTIONS FOR MRSP

- Chlorhexidine (3-4%)%
- Chlorhexidine 2% + miconazole 2%
- Dilaute bleach solution
- Mupirocin 2% ointment (US)
- Fusidic acid (UK and Canada)
- Topical antibiotics (tetracycline, gentamicin, enrofloxacin)

*Should be reserved for cases that don’t respond to above options and have a culture showing susceptibility.
• 48 dogs with *Staphylococcus pseudintermedius* superficial pyoderma (8 MRSP)

  - Randomized controlled trial
  - Group T (n = 31) treated topically with 4% chlorhexidine digluconate shampoo (twice weekly) and solution (once daily) x 4 weeks
  - Group S (n = 20) treated orally with amoxicillin-clavulanic acid (25 mg/kg PO BID) x 4 weeks

  All topical therapy dogs showed resolution of clinical signs, including those with MRSP

**SAMPLE TOPICAL PLANS**

(REASSESS Q 2 WEEKS)

• Owner CAN bathe
  - Chlorhexidine 4% shampoo or 2% chlorhexidine/2% miconazole daily with 10 minute contact time
  - Shampoo 2-3 times weekly with sprays or mousse on non-bath days
  - Owner CANNOT bathe

  • Spray/mousse/wipes BID
  • Mupirocin ointment BID to focal lesions
  • Mupirocin spray (mupirocin + HB | 1020, mupirocin + dax + salin, mupirocin + saline) BID to multifocal lesions

**DO WE NEED TO WORRY ABOUT TOPICAL ANTIMICROBIAL RESISTANCE?**

• There is concern over resistance to topically used antibacterial agents.
  - No conclusive evidence of clinical treatment failure of topical anti-staphylococcal therapy
  - MICs for staph from animals are consistently low and likely to be substantially exceeded by achievable topical drug concentrations
  - Continual monitoring of resistance and clinical efficacy and further evaluation of alternatives (bleach, Manuka honey) is important

**DILUTE BLEACH SOLUTION**

• Excellent for meticillin resistant Sopgh
  - Can be used with or without oral antibiotics
  - 1-3 TBSP regular household bleach + 1 gallon of water
  - Pour, sponge, spray, soak
  - Let sit for 10 minutes then rinse

**IS MRSP CONTAGIOUS??**

• Yes, MRSP is zoonotic.
  - However, the risk of zoonotic transmission of MRSP is generally considered to be low.
  - There are low carriage rates of *S. pseudintermedius* in people regularly exposed to dogs.
  - The risk for zoonosis is greatly increased for immunocompromised people and animals.
  - Importance of good hygiene

**SYSTEMIC THERAPY FOR MRSP**

• Required for deep pyoderma and widespread or severe superficial infections
  - “As little as possible but as much as necessary”
  - Efficacy dependent upon the following
    - Bacterial susceptibility
    - Correct drug administration
    - Appropriate dosing
    - Owner compliance
    - Severity of infection
    - Concurrent diseases
ANTIMICROBIAL CLASSIFICATIONS

First tier
- Can be used empirically
- Cephalexin
- Clindamycin (use BID!)
- Amoxicillin-clavulanate
- Potentiated sulfonamides

Second tier
- Identification and without a culture
- Third generation cephalosporins (cefovecin, cefpodoxime)
- Fluoroquinolones
- Lincosamides
- Tetracyclines
- Chloramphenicol
- Rifampin
- Aminoglycosides

Third tier
- Reserved for life-threatening MRSA infections in humans
- Linezolid, teicoplanin, vancomycin

WHAT WILL MRSP USUALLY RESPOND TO?
- Fluoroquinolones (maybe)
- Amikacin
- Chloramphenicol
- Doxycycline
- Minocycline
- Rifampin
- Trimethoprim/sulfa
- Other options reported should not be used: linezolid, vancomycin

FLUOROQUINOLONES
- Enrofloxacin (Baytril):
  - 5 mg/kg is no longer appropriate
  - 10-20 mg/kg PO SID
  - Retinal degeneration in cats
  - Cartilage defects in growing large breed dogs
- Marbofloxacin (Zeniquin):
  - 5 mg/kg PO SID
- Pradofloxacin (Veraflox):
  - 7.5 mg/kg PO SID
  - 3rd generation, activity against anaerobes too

SULFONAMIDES
- TMS
- Tribrissen (veterinary approved)
- Sulfadiazine/Trimethoprim
- Bactrim (human, generic, cheaper)
- Sulfamethoxazole/Trimethoprim
  - 50 mg/kg SID-BID
- Primor
- Sulfadimethoxine/Ormetoprim
  - 55 mg/kg day 1, 27.5 mg/kg PO SID

CHLORAMPHENICOL
- 40-65 mg/kg PO TID
- Narrow range of efficacy
- Nausea, vomiting, diarrhea
- Hepatotoxicity

RIFAMPIN
- 5.9 mg/kg PO SID
- 150 mg and 300 mg capsules
- Activates p-glycoprotein and cytochrome P-450 CYP3A and CYP2C
- Causes faster metabolism of drugs like prednisolone, ketoconazole, and chloramphenicol
- Recent abstract
- Side effects include vomiting, diarrhea, lethargy, weight loss, death in 2%
- Hepatotoxicity
  - 20/94 (21%) had ALT increase
  - Significant association with > 19 day treatment
  - Chemistry panel as baseline
  - 2 weeks later
  - Then weekly thereafter
  - Stop if increased ALT, ALP, or bilirubin

RIFAMPIN
- Chemistry panel as baseline
- 2 weeks later
- Stop if increased ALT, ALP, or bilirubin
- Resistant orange-red discoloration to urine and stools
- AVOID if possible or refer
AMIKACIN

- Injectable only (or topical)
- 15-20 mg/kg SQ SID
- Diminished activity with pus or debris
- Nephrotoxicity:
  - Acute tubular necrosis
  - Otoxicity:
  - Monitoring
    - Urinalysis – glucose, casts, protein
    - Chemistry – BUN, creatinine
  - Expensive to use and monitor every side effects. AVOID USING

SIDE NOTES ABOUT DOSING

- Clindamycin 11 mg/kg PO BID
  - Potentially should not use if erythromycin R unless D-test is performed
- Dose per for MRSP should be close to 10 mg/kg PO BID
  - Consider monitoring liver values
- Cefovecin (Convenia):
  - Often need to repeat dose at least once
  - Always recheck your Convenia patients to make sure 100% resolved

CLINICAL RECOMMENDATIONS

- Expensive to use and monitor, scary side effects, AVOID USING

SAMPLE CASES

- To be provided

AVOIDANCE/PREVENTION

- Avoid systemic antibiotics when possible (topicals)
- High doses:
  - Cephalosporins 15-20 mg/kg PO BID, sulfadiazine
  - 15 mg/kg PO SID, Cephalexin 8 mg/kg SID
  - Please don’t use enrofloxacin at 5 mg/kg for MRSP
- Avoid using 3rd or 4th generation antibiotics without a culture. If client declines a culture, don’t start antibiotics.
- Don’t use fluoroquinolones empirically.
- Treat for 7 days past clinical resolution
  - Prescribe 30 day course and recheck on day 21.

WHAT HAPPENS IF A PREVIOUS MRSP CASE RELAPSES WITH ANOTHER PYODERMA?

- Ideally you should re-culture the patient since we know that any course of antibiotics can change the susceptibility pattern.
- If culture is not performed, the same antimicrobial should be used that successfully resolved the previous infection.

LAST BUT CERTAINLY NOT LEAST...

- What is the underlying trigger?
  - Allergies
    - ASIT over drugs
  - Ectoparasite infestations
    - ivermectin, moxiect, selamectin
  - Endocrinopathies
  - Adult-onset secondary infections
  - Ask about systemic signs, but not always present
PERTINENT REFERENCES


