Review of Bladder Defense Mechanisms and Urinary Tract Infections

Dr. Maura Duffy | DVM, DACVIM
OUTLINE

- Review of bladder defenses
- Urinary tract infection management
  - Predisposing diseases
  - Diagnostic options
  - Treatment strategies
  - Prevention
Bladder Defenses

- Micturition
  - 99% pathogen clearance
- Physical barriers
  - Urothelium
- Host responses
  - Antibacterial substances
  - Immune responses
- Basal layer
- Intermediate layer
- Apical layer
  - Cells connected by tight junction
  - Apical surface:
    - Crystalline proteins
    - Sulfated polysaccharide glycosaminoglycans

Urothelium
Urothelium

(Lavelle 2002)
Glycosaminoglycans (GAGs)

- Prevent bacterial adherence
- Without GAG layer – adherence increased 55 fold
Glycosaminoglycans (GAGs)

• Importance:
  • Prevent crystal adhesion to urothelium
  • Prevent bacterial adherence
    • Without GAG layer – adherence increased 55 fold

(Bojanic 2012, Gill 1982, Hurst 1996)
Host Responses

- Antimicrobial substances
  - High urea concentrations
  - Defensins
    - Regulators of local inflammation
    - Triggered by bacteria contact with epithelium

- Secondary defenses
  - Cytokines
  - Immunoglobulins
    - Mainly IgA – noted to increase with inflammation in the lower urinary tract

(Gantz 2001)
Host Responses

- Tamm-Horsfall protein (THP)
  - Renal protein
  - Functions:
    - Binds E.coli and increases clearance
    - Neutralizes urinary toxic factor which can damage uro-epithelium
    - Chelates calcium in urine

(Bates 2004, Parsons 2007)
Dysfunction in Micturition

- Prevents voiding of bacteria
- Increases residual urine volume
- Overdistension leads to ischemic injury to urothelium
- Diseases leading to abnormal urine flow:
  - Urethral Incontinence
  - Ectopic ureters and other congenital abnormalities
  - Neurogenic bladders (back dogs, trauma)
  - Lower urinary neoplasia

(Truzzi 2008)
Dysfunction in GAG Layer

- Results in colonization of bacteria
- Solutes penetrate and can be toxic to smooth muscle
- Diseases leading to GAG and barrier disruption:
  - FIC and urethral obstructions
  - Some chemotherapy agents
  - Any catheterization or urogenital surgery
  - Bladder stones
  - Bladder neoplasia

(Moskowitz 1994, Parsons 2001)
Dysfunction of Host Responses

- Tamm – Horsfall Protein –
  - Some diseases reduce production
  - Others reduce function of the protein
- Diseases leading to host dysfunction:
  - Chronic kidney disease
  - Diabetes mellitus
  - Cushing’s disease
Urinary Tract Infection Management
Different types of UTI

- Uncomplicated
  - First time offender
- Complicated
  - Has had antibiotics in past 30 days
  - Known systemic or local predisposing factor
  - Recurrent vs Relapse UTI
  - Superinfection
  - Any intact male dog UTI
Predisposing diseases

- Dogs with ectopic ureters = 80% positive cultures
- Dogs with Cushing’s – 40% positive cultures
- Dogs with IVDD – 40% positive cultures
  - 60% of those were asymptomatic
- Cats with CKD – 13% positive cultures
- Cats with hyperthyroid – 20% positive cultures
- Diabetes mellitus patients
  - Dogs = 30% positive cultures
  - Cats = 13% positive cultures
• Urinalysis with sediment evaluation
  • Goal to identify bacteria AND white blood cells
  • Easier to find rods >> cocci
    • Rods reliably be detected if >10,000CFU/ml
    • Cocci need >100,000CFU/ml
  • Gram stain increases sensitivity of urine sediment

Comparison of routine urinalysis and urine
Gram stain for detection of bacteriuria in dogs

Leilani Ireland Way, DVM; Lauren A. Sullivan, DVM, MS, DACVECC; Valerie Johnson, DVM, DACVECC and Paul S. Morley, DVM, DACVIM, PhD
Diagnosis Gold Standard

- Urine culture
  - Dilute urine makes sediment less sensitive and culture more indicated
  - Keep in mind diseases or medications leading to a false negative sediment
Other testing

- Dipstick for WBC and nitrite for bacteria
  - Poor sensitivity dogs

- Urine dipstick paddle system
  - + result was reliable
  - Bacterial ID was not reliably

- Point of care culture set
  - Reliably ruled out UTI but not reliably diagnose
• More sensitive for identifying UTI compared to sediment evaluation (90% vs 78% sensitive)
• Positive test still indicates need for urine culture
Treatment

- When to begin therapy while waiting for culture results:
  - Complicating factors
  - Clinical signs of lower urinary tract infection
- Empirical antibiotic selection:
  - Somewhat based on history
Most Common Bugs

- **E. coli**
  - 30-50% of all + urine cultures
- **Gram + cocci**
  - *Staphylococcus* spp
  - *Streptococcus* spp
  - 25-30% of + urine cultures
- **Remainder:**
  - *Proteus*
  - *Klebsiella*
  - *Pseudomonas*
Antibiotic selection

- Uncomplicated
  - Amoxicillin
  - TMS
- Complicated
  - Based on culture

### TABLE 90-5

<table>
<thead>
<tr>
<th>Identified Organisma</th>
<th>Antimicrobials Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>Trimethoprim-sulfonamide, amoxicillin-clavulanate, quinolone, chloramphenicol</td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>Amoxicillin-clavulanate, first-generation cephalosporins</td>
</tr>
<tr>
<td><em>Streptococcus or Enterococcus</em></td>
<td>Ampicillin, amoxicillin</td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td>Ampicillin, amoxicillin</td>
</tr>
<tr>
<td><em>Pseudomonas</em>b</td>
<td>Tetracycline, quinolone</td>
</tr>
<tr>
<td><em>Klebsiella</em>b</td>
<td>First-generation cephalosporins, trimethoprim-sulfonamide, amoxicillin-clavulanate, quinolone</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>Trimethoprim-sulfonamide, quinolone</td>
</tr>
<tr>
<td><em>Corynebacterium urealyticum</em></td>
<td>Doxycycline, tetracycline</td>
</tr>
</tbody>
</table>

(Green 2012)
Positive Culture

- True infection?
- Do we need to treat it?
- What do I treat it with?
- How long do I treat?
- What monitoring should the family be prepared for?
- Any other diagnostics or therapies needed beyond this UTI management?
Cystocentesis is ideal to avoid contamination
Can interpret quantitative culture on collection method

TABLE 90-3

<table>
<thead>
<tr>
<th>Culture Method</th>
<th>Contamination (Bacteria/mL)</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midstream voided</td>
<td>&lt;10^5</td>
<td>Cannot distinguish in dogs &gt;10^5 in cats^a</td>
</tr>
<tr>
<td>Catheterization</td>
<td>&lt;10^3 in male dogs, any number in female dogs &lt;10^3 in cats</td>
<td>&gt;10^4 in male dogs &gt;10^3 in cats any number with indwelling catheters</td>
</tr>
<tr>
<td>Cystocentesis</td>
<td>&lt;1000^b</td>
<td>&gt;10^3</td>
</tr>
</tbody>
</table>

(Green 2012)
Should We Always Treat??

• Asymptomatic bacteriuria
  • Lack of signs or evidence of inflammation
  • Mainly Mycoplasma, E coli, or Enterococcus
  • No treatment required unless performing urogenital surgery or symptomatic

Prevalence and clinical outcome of subclinical bacteriuria in female dogs

Stephanie Y. Wan, DVM; Faye A. Hartmann, MS; Michelle K. Jooss; Katrina R. Viviano, DVM, PhD

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Treatment – Antibiotic Selection

- Antibiotic selection tailored to culture susceptibility
- Keep in mind:
  - Dosing regiment and owner compliance
  - Cost and length of needed therapy
  - Accessibility (clinic or owner)
  - Adverse reactions or contraindications of drug
  - Past use
Comparison of fluoroquinolone pharmacokinetic parameters after treatment with marbofloxacin, enrofloxacin, and difloxacin in dogs

D. L. Frazier, L. Thompson, A. Trettien, E. I. Evans

First published: October 2000  Full publication history

• Urine concentrations of Marbofloxacin did not differ from urine Enrofloxacin concentrations
Multi-drug resistant bacteria
MIC – least amount of drug to inhibit growth
“Intermediate” sensitivity drug can still be used
  • If concentration is 4x the MIC = 90-95% effective

### TABLE 90-4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/kg)</th>
<th>Route</th>
<th>Interval (hours)</th>
<th>Mean Urine Concentration (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>22</td>
<td>PO</td>
<td>8</td>
<td>309</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>11</td>
<td>PO</td>
<td>8</td>
<td>201.5</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>33</td>
<td>PO</td>
<td>8</td>
<td>124</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>4.4</td>
<td>PO</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Trimethoprim-sulfonamide²</td>
<td>13</td>
<td>PO</td>
<td>12</td>
<td>26/79²</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
<td>SC</td>
<td>8</td>
<td>107</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5</td>
<td>SC</td>
<td>8</td>
<td>342</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>2.5</td>
<td>PO</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>18</td>
<td>PO</td>
<td>8</td>
<td>138</td>
</tr>
</tbody>
</table>

(Green 2012)
Treatment – Antibiotic Selection

- Extended culture panels
  - Any other antibiotic options?
  - Imipenem or Meropenem
  - Nitrofurantoin

- Kirby Bauer plates

- What does “NI” mean
Length of treatment:

- Uncomplicated – 5-10 days
- Complicated – 4-6 weeks
  - Will depend on monitoring
Evaluation of the Efficacy and Safety of High Dose Short Duration Enrofloxacin Treatment Regimen for Uncomplicated Urinary Tract Infections in Dogs

J.L. Westropp, J.E. Sykes, S. Irom, J.B. Daniels, A. Smith, D. Keil, T. Settje, Y. Wang, and D.J. Chew

- 3 days of Baytril = 14 days of Clavamox

Short- and Long-Term Cure Rates of Short-Duration Trimethoprim-Sulfamethoxazole Treatment in Female Dogs with Uncomplicated Bacterial Cystitis

S. Clare, F.A. Hartmann, M. Jooss, E. Bachar, Y.Y. Wong, L.A. Trepanier, and K.R. Viviano

- 3 days of TMS = 10 days of Cephalexin
• Complicated UTIs
• Three cultures
  • One at diagnosis
  • One during the 4-6 weeks of therapy
  • One 1 week following antibiotic therapy
Prevention

- Urinary antiseptics
- Urinary acidification
- Supplements
- Antibiotic techniques
Prevention

- **Methenamine**
  - Turns into formaldehyde
  - Best with urine pH <6.0
  - 10-20mg/kg PO q8hr
- **Urinary acidification**
  - Methionine, ammonium chloride
    - Caution with hepatic insufficiency due to metabolism
    - 0.2-1 gram per dog PO q8hr
  - Diets with lower protein content and acidifiers added
• Cranberry products
  • Fructose and proanthocyanidins (PAC) are found in Cranberries – inhibit pili
  • Many studies but unclear how effective with dogs
Pulse therapy of antibiotics
  • 3-5 days every 3-4 weeks

Preventative evening antibiotics
  • Concentrates in urine overnight
  • Usually a fluoroquinolone or cephalosporine

Biggest risks = antibiotic resistance
When do we need more testing?

- Cannot clear UTI
- Recurrent or Relapse UTI with no evident reason
- Normal AXR (including urethra)

Next testing:
- AUS
- +/- Contrast cystourethrogram
- Cystoscopy
QUESTIONS??
Diagnostic accuracy of a point-of-care urine bacteriologic culture test in dogs

Shelly J. Olin, DVM; Joseph W. Bartges, DVM, PhD, DACVIM, DACVN; Rebekah D. Jones; David A. Bemis, PhD, DACVM

- Compartmented bacteriologic culture and antimicrobial susceptibility plate (CCSP) – was human product now marketed for veterinary use
- 18-24 hours to see results
- Reliable to RULE OUT a UTI but was less reliable for diagnosis of UTI
Performance of a veterinary urine dipstick paddle system for diagnosis and identification of urinary tract infections in dogs and cats

Winnie L. Ybarra, DVM; Jane E. Sykes, BVSc, PhD; Yenlie Wang, DVM; Barbara A. Byrne, DVM, PhD; Jodi L. Westropp, DVM, PhD

+ result was reliable
Bacterial ID was not reliable
Effects of oral administration of N-acetyl-D-glucosamine on plasma and urine concentrations of glycosaminoglycans in cats with idiopathic cystitis

Jinnapat Panchaphanpong, DVM; Tanong Asawakarn, DVM, PhD; Rosama Pusonthornthum, DVM, PhD

- NAG oral supplementation did improve GAG to Crt ratio in bladder of FIC cats after 21 days
- No clinical parameters were recorded or improved
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