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INTRODUCTION

Three unique mechanisms of bacterial renal infections will be highlighted in this presentation:

1. The most common – pyelonephritis or ascending infection from the lower urinary tract, most commonly the urinary bladder.
2. Canine Leptospirosis an example of hematogenously spread infection of the kidney by bacteria with a specific tropism for renal tissue.
3. Canine Lyme nephritis as an example of immune complex disease, an infectious disease of the kidney without actual invasion of the renal tissue by the bacteria.

ASCENDING INFECTIONS AND PYELONEPHRITIS

Urinary tract infections (UTIs) are the most common cause of lower urinary tract signs in dogs. Although rare in young cats, UTIs are being diagnosed with a much higher frequency today in older cats and cats with underlying urinary and non-urinary diseases. The incidence of pyelonephritis is unknown in companion animals but is thought to be a common cause of acute renal failure and of deterioration of more stable chronic renal disease.

Defense Mechanisms

Ascending urinary tract infections do not occur with even higher frequency due to the normal defense mechanisms of the canine and feline lower urinary tract. These include:

1. The antibacterial properties of urine including those of urea as well as those of increased urine osmolality and urine acidity. (Likely important especially in cats).
2. The normal host defenses of the bladder and urethra include complete and normal voiding or hydrokinetic washout, inherent antimicrobial properties of the normal urothelium and a high pressure zone in the mid urethra. This area is more effective in males than females. Local secretion of IgA provides humoral immunity.
3. The unidirectional flow of urine in the ureters may play a role in preventing ascending bacterial infections. There are no ureteral valves in dogs and cats, like in human ureters. Vesicoureteral reflux can be normal in dogs.
4. If bacteria do arrive at the renal pelvis there are poorly understood defense mechanisms to prevent nephritis.

Anatomical abnormalities, urolithiasis, incontinence, low urine osmolality, increased urinary glucose or decreased immunity would increase the likelihood of a UTI. Urinary catheterization also thought to increase the likelihood of a UTI. A recent study in the ICU unit at UC Davis, though, showed that when managed properly indwelling catheters only caused UTIs in approximately 5% of the cases if left in for 1 day and close to 40% if left in for 4 days. Interestingly, the positive predictive value for catheter tip culture in that study was only 25 %. Much has been published about underlying disease as a predisposing factor for UTIs and pyelonephritis in dogs. In a recent retrospective study we determined the incidence of UTIs in cats with chronic renal disease (22%), diabetes mellitus (12%) and hyperthyroidism (12%) all much higher than cats presenting with otherwise unexplained signs of lower urinary tract disease (3%). Although bacteria and white blood cells were recognized in the urine of the majority of cats with positive urine cultures, there were quite a few cats with UTIs despite an inactive sediment. This observation is true in dogs as well and therefore justifies culturing the urine of any dog or cat thought to be at risk for a UTI even if the sediment is benign.

Bacterial virulence factors and renal damage

These have been studied extensively over the last 5-10 years including many studies involving common bacteria of the canine (very little feline) urinary tract. Most of the studies are on factors effecting adhesion, penetration and virulence of E. coli, the most common canine urogenital pathogen. Uropathogenic virulence Factors (UVFs) have been identified that appear to differentiate uropathogenic E. coli from commensal intestinal E. coli. These strains are more likely to possess operons for pap (encoding for P
fimbriae), fim (type 1 fimbriae), sfa (S fimbriae), hlyA (α-hemolysin), and cnf1 (cytotoxic necrotizing factor 1). The mechanisms of renal damage caused by ascending UTIs have not been well studied in dogs or cats. In humans it has been shown that 55-75% of children that develop febrile UTIs have concurrent renal parenchymal damage, and 20-40% of these children will suffer permanent renal cell damage (5). The possible pathogeneses of renal damage from UTIs that has been studied in humans include:

- Vesicoureteral reflux
- Direct effects of uropathogenic bacteria on renal cells via above mentioned virulence factors (fimbriae, LPS, HlyA) Causing:
  - Local inflammatory response (cytokine and chemokine production)
  - Infiltration of inflammatory cells
  - Liberation of proteolytic enzymes and free radicals
- Eventually leading to cell death, and if sub-lethal then ultimately to fibrosis and renal scarring (6). It is unknown how similar the processes are in companion animal medicine.

CANINE LEPTOSPIROSIS

The Leptospira organisms are maintained in the renal tubules of the reservoir host and excreted in the urine. These hosts are typically non-symptomatic and may be able to shed bacteria for their entire life. This may also be true for dogs secreting L. canicola. It is unknown whether such a carrier state exists in dogs infected with other serovars. Transmission can occur via direct or indirect contact with an infected host, urine or other body excretions.

Pathogenesis

Understanding the molecular basis for Leptospiral virulence is crucial in the effort to produce more effective vaccines. Identifying surface antigens that are expressed during active infection in vivo may also facilitate distinction between active infection and vaccination or exposure. For example, Leptospira immunoglobulin-like protein A (LigA) contains domains homologous to proteins with attachment and invasion functions and is expressed in vivo but not in vitro. Leptospira organisms penetrate abraded skin or mucus membranes and replicate rapidly in the bloodstream. The sequence of events after infection likely depends on:

1. Virulence. Important questions include: Is there a difference between serovars?
2. Immune response. Questions: Has the dog been vaccinated or previously exposed? How well does the vaccine protect from natural infection and is there acquired immunity after being infected with a specific serovar? Many of the commercially available vaccines have been shown to provide good short term immunity but the length of that immunity is unknown. A recent study comparing different commercially available vaccines showed only a mild serological response to a series of 2 vaccinations but good immunity when challenged 1 month and 1 year after the second vaccine.
3. Gender – Some studies show males as being more likely to be clinically affected than females.

After infection the following organs may be affected:

1. Blood endothelium, inducing an acute febrile and often thrombocytopenic state. More common than we think!
2. Kidneys: Renal colonization. Organisms persist and multiply in the renal tubular epithelial cells causing acute nephritis. If not fatal and not treated appropriately this MAY lead (info is mostly experimental from L. canicola) to chronic interstitial nephritis and a persistent carrier state.
3. Liver: Liver damage. Centrilobular necrosis and sub cellular damage, bile canaliculi and duct occlusion may cause icterus. This is not seen as commonly today as with ictero.
4. Lungs: Pulmonary hemorrhage. This is common in severe cases in people. The incidence of canine cases is unknown.
7. Brain: Meningitis and encephalitis have been documented in severe cases in humans. The incidence of canine cases is unknown.
8. Immune system: Secondary immune mediated disease (poly-arthritis, hemolytic anemia etc...). The incidence of canine cases is unknown.

LYME NEPHRITIS
This condition was first described in a large histopathological study (Dambach et al Vet Pathol. 1997). This study described a common pathological lesion noted in 49 dogs. The common finding in all of those dogs (these are the criteria that were used to search their data base) were glomerulonephritis (GN) (usually membranoproliferative) uncharacteristically accompanied by tubular necrosis with severe tubular dilation. There was also marked interstitial inflammation. Approximately 50% of these samples were obtained at necropsy and 50% were biopsies of dogs alive at the time. The clinical syndrome of severe glomerular disease progressing to acute renal failure and death, with severe uremia, within a short time appeared to be common to all dogs in the study. 21 dogs were shown to have immune complex GN with IgG, IgM and basement membrane complement (C3) deposition. All dogs evaluated with urinalyses were proteinuric. Eighteen of 18 dogs that were tested serologically for Lyme were positive. What were the affected breeds? Labrador Retrievers: 14/49 or 29%, Golden Retrievers: 10/49 or 20%, 15 other breeds were represented.

Age and Gender? Younger dogs were affected (mean 5.6 ±0.48 years) with no gender predilection.

So What Do We Know?
A unique lesion in the kidneys of dogs with a devastating glomerular-tubular disease is described with relatively good circumstantial evidence for a Lyme connection. Today we know that although there are no Borrelia burgdorferi (Bb) organisms in the kidneys of dogs that died of Lyme nephritis, there are Bb specific immune complexes in those kidneys. This is a somewhat unique finding in dogs although a similar phenomenon may occur in other rapidly progressive canine GN diseases such as canine Leishmaniasis in parts of Europe and Asia.

Studies will be presented showing that:
There is no invasion of Bb bacteria in the kidneys of dogs with Lyme nephritis
There are immune complexes lodged in those kidneys that include Lyme specific antibodies.
A monitoring and treatment protocol for the diagnosis and treatment of Lyme nephritis will be presented.

References available upon request