Diagnosis and Therapy of Renal Disease in Dairy Cattle

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There are a large number of diseases that may primarily affect the kidneys of dairy cattle.[1] The majority of these cattle with renal disease will be first identified by the clinician because of gross abnormalities observed during the cow's urination, abnormal rectal examination findings involving the urinary system or clinical laboratory data suggestive of renal dysfunction. Marked abnormalities, some of which are peculiar to ruminants, are frequently present in the blood chemistry findings of cattle with severe renal dysfunction.[2,3,4] These clinical pathological findings are often an unexpected finding on routine chemistry screens of cattle with an apparent occult disease.

Except for renal toxicities which may involve multiple animals in a herd, the incidence of any one particular renal disease is most likely to be sporadic in a bovine population. The sporadic incidence of many of these diseases may make the diagnostic, therapeutic and prognostic approaches more difficult than more familiar diseases of other systems. It is the intent of this presentation to provide a review and update on the causes, clinical signs, laboratory finding, methods of diagnosis, therapy an prognosis in cattle with renal disease.

Causes and Clinical Signs

Pyelonephritis frequently occurs in dairy cattle as a subacute or chronic condition. Cattle appear to be predisposed to this condition because of the large number of obstetrical manipulations required. The mechanical damage to the urethra may cause urine stasis and allow bacterial invasion and colonization of the urinary system. If vesicoureteral reflux follows, an infection of the upper urinary tract is likely.[5] The renal medulla is prone to ascending or bacteremic infections because of its anatomical location and decreased defense mechanism.[6] The hyperosmolality of the medullary interstitium may reduce neutrophil function and inactivate complement permitting bacterial invasion of the renal pelvis and medulla.[6]

Corynebacterium renale is the most frequent cause of subacute ascending pyelonephritis in cattle and results in fever, sepsis, dysuria and gross hematuria and pyuria. Cattle with subacute pyelonephritis are usually gaunt and depressed and because of stranguria may stand "hunched up." *Corynebacterium renale* and *Escherichia coli* are both frequent causes of chronic pyelonephritis in cattle. The most common clinical finding in these cases is chronic weight loss and/or decreased milk production. Gross pyuria may be seen but gross hematuria is rare. Calculi and/or crystals may be found in the urine or on the genital hairs and are occasionally palpated in the bladder. It is unusual for there to be symmetrical involvement of both kidneys in cattle with pyelonephritis. In some cases one kidney may be completely spared. An enlarged ureter(s) is usually felt during rectal examination of cattle with either subacute or chronic pyelonephritis. If the left kidney is grossly involved, renal enlargement and loss of normal lobations is usually appreciated on rectal examination. The examiner may also be able to elicit a painful response from affected cattle and to detect increased strength of pulsation of the renal artery while performing a rectal examination. In cattle with chronic pyelonephritis an enlarged left kidney may feel similar on rectal examination to hydronephrotic or congenital polycystic kidneys. Hydronephrosis and congenital polycystic kidney diseases are uncommon in cattle but are occasionally discovered as an abdominal mass during routine rectal examinations.

Bovine renal amyloidosis, although not a common disease, is diagnosed sporadically in most dairy practices. The history and clinical signs of bovine amyloidosis are sufficiently distinct to allow the clinician to make a tentative diagnosis. Bovine renal amyloidosis usually affects a single cow in a herd; and clinical signs do not occur until cattle are 4 years of age or older. The earliest clinical signs of amyloidosis in cattle are ventral edema, diarrhea and weight loss which result from the physical presence of amyloid in the kidneys and gastrointestinal.[7,8] The amyloid deposition in the kidney glomeruli result in increased loss of protein in the urine, decreased plasma oncotic pressure and inpending edema. Diarrhea and weight loss occur because of amyloid infiltration into the small intestine with resulting gastrointestinal lymphangiectasis and edema; intestinal malabsorption and gastrointestinal motility dysfunction. In bovine renal amyloidosis the kidneys are uniformly enlarged. This can usually be readily appreciated during rectal examination. Although amyloid kidneys are enlarged they retain their normal shape, lobation and firmness which differentiates them from the enlarged kidneys that occur with hydronephrosis, pyelonephritis, renal lymphosarcoma, renal cortical necrosis or polycystic disease. The amyloid in cattle is reported to be reactive systemic (AA protein fibrils) produced as a result of various acute, recurrent or chronic

inflammatory disorders.[7,9]

Acute Tubular Necrosis

Acute tubular necrosis (ATN) may result from hemodynamically mediated renal ischemia, nephrotoxic drug administration or ingestion of poisonous plants. Any condition which predisposes cattle to marked hypotension and/or release of pressor drugs has the potential of initiating hemodynamically mediated subacute renal failure.[10,11] Cattle with sepsis resulting from mastitis, metritis, right abomasal torsion or salmonellosis seem to be at greatest risk. This systemic hypotension may result in release of renin and activation of angiotensin II, and release of other potent constrictors of afferent glomerular arterioles.[10] Endothelial cell swelling, deficiency of intrarenal vasocilatory mechanisms or continued angiotension activation may prevent restoration of normal function.[11] Drug induced acute tubular nephrosis may occur in cattle following the administration of aminoglycosides, tetracyclines or sulfonamides.[2] Aminoglycoside nephrotoxicity is most commonly found in cattle with concurrent gastrointestinal disease and/or fluid and electrolyte deficits.[2,12] Sodium, potassium and volume depletion are thought to enhance aminoglycoside nephrotoxicity in other species.[13,14] There is no proof that calves are most susceptible to aminoglycoside toxicity than adult cattle. Without concurrent volume or electrolyte depletion and when given at recommended dosages, kanamycin, gentamicin and streptomycin rarely cause clinically detectable nephrotoxicity in cattle. Neomycin may produce nephrotoxicity and renal failure in cattle if administered for extended periods of time.[12] Tetracyclines and sulfonamides may also produce ATN if given to cattle with volume contraction or when given in excessive dosages.[2] Toxic plant ingestion is a frequent cause of ATN in pastured cattle. These plants include Rumes (sorrels and docks), *Amaranthus spp.* (pigweed), *Quercus spp.* (oak).[2,15,16]

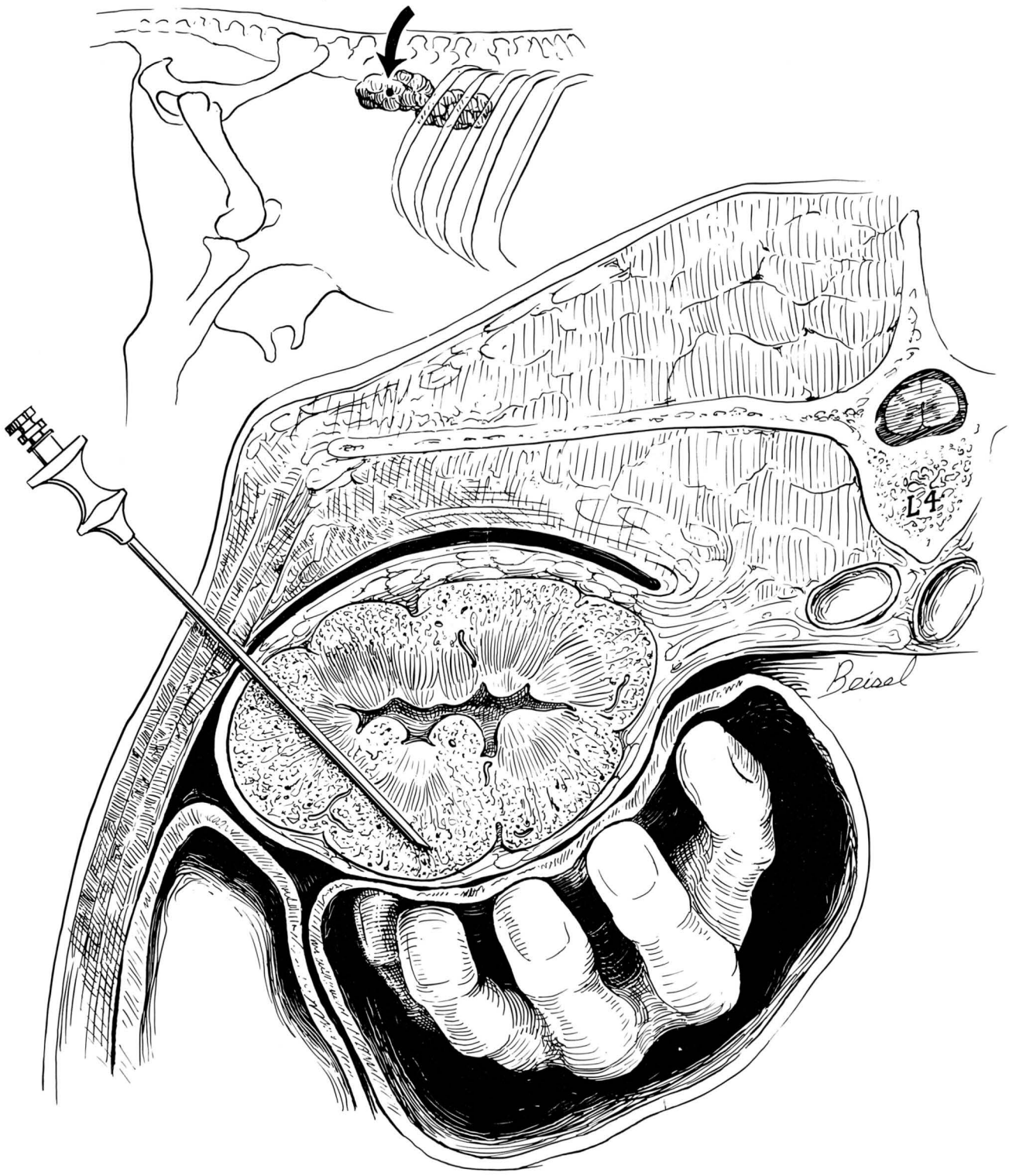
The clinical signs of ATN in cattle are relatively nonspecific. In many cases a pre-existing disorder (diarrhea, abomasal torsion, septic mastitis, etc.) is present which may have more pronounced clinical signs than the renal failure. Marked depression, anorexia, bleeding diathesis, recumbency, polyuria and dehydration are the most frequently observed signs of ATN.[2] The kidneys may be slightly enlarged and have palpable perirenal edema in some cases.

Renal cortical necrosis and renal vein thrombosis[2] are sporadically seen in dairy cattle. Bilateral renal cortical necrosis has been seen in cattle with septicemia and/or bacteremia.[a] A similar pathologic lesion has been described in other domestic animals believed to be due to the generalized Schwartzman reaction.[17] The Schwartzman reaction results in stagnation of red blood cells and platelets in the glomerular capillaries with formation of fibrinoid thrombi and followed by thrombosis of interlobular and afferent capillaries.[17] The initiating factor is believed to be an endotoxemia or bacteremia which overwhelms the reticuloendothelial system and activates the complement cascade causing vasodilation and activated intravasuclar coagulation.[18] The renal medulla is usually spared. Renal vein thrombosis has been reported in cattle and may not be as sporadic as previous literature would suggest.[2] Renal vein thrombosis in human patients may be associated with severe proteinuria and a deficiency of antithrombin III due to urinary excretion of this protein.[19] Antithrombin III is an $alpha_2$ globulin and in man is the primary inhibitor of thrombin formation; with massive proteinuria, plasma concentrations of antithrombin III can be reduced to such an extent that inactivation of procoagulent factors is not sufficient to prevent the development of thrombosis.[19] One cow with amyloidosis and massive proteinuria died from RVT which might suggest a similar pathogenesis in cattle.[20] Severe dehydration and plasma volume contraction have also been associated with RVT in man and cattle.[2,18] The predominant clinical signs of RCN and RVT are severe and progressive depression and weakness. There may also be a clinically appreciable decline in urine volume. Renal cortical necrosis or RVT should be suspected in any cattle with marked proteinuria, severe dehydration and/or spesis which have a marked worsening in clinical signs associated with a progressing azotemia. Rectal examination of the left kidney usually reveals renal enlargement; much of which may be perirenal edema.

Diagnosis

The tentative diagnosis of renal dysfunction in cattle is based on history and clinical and laboratory findings. Renal disease may be confirmed and valuable information regarding prognosis may be acquired by renal biposy (Fig. 1) and microscopic examination of renal tissue. Most cattle with easily detectable clinical signs resulting from ATN or renal vascular disease have >75% of nephrons damaged and are azotemic. These cattle also have urine specific gravity <1.022 in spite of azotemia and/or dehydration.[2] Serum urea nitrogen appears to be comparable with serum creatinine content as an index of glomerular filtration rate in cattle.[2] Cattle with marked azotemia frequently have biochemical findings of hypochloremia, hypocalcemia, hypokalemia, hyponatremia, hyperphosphatemia and hypermagnesemia.[2,3,4] The hypochloremia may be so marked that right abomasal torsion or upper gastrointestinal obstruction is presumed. Cattle with RVT and acute pyelonephritis may have gross hematuria. Microscopic hematuria is present with RCN and may be found with ATN.[2] Cattle with renal amyloidosis have marked proteinemia without hematuria.[20] Pyuria and bacteruria ($>10^4$ organisms/ml) are found in cattle with pyelonephritis. Renal tubular and granular casts, while blood cell casts (pyelonephritis) and renal epithelial cells may be present in the urine of cattle with renal disease.

[a] *Unpublished data. University of Pennsylvania, New Bolton Center, 1982.*



Percutaneous renal biopsy technique in the cow from the right paralumbar area. The needle tip can be directed toward the pole of the kidney by digital palpation through the rectum.

Therapy and Prognosis

Pyelonephritis

Cattle with subacute pyelonephritis resulting from *Corynebacterium renale* infection require intensive antimicrobial therapy. Intravenous fluid therapy and electrolyte replacement are also required to combat hypovolemic and associated metabolic abnormalities. Diuresis, provided early in the disease by isotonic fluids, may "wash out" plugged tubules and allow more rapid urine flow. If diuresis does not begin after seemingly appropriate volume replacement, furosemide or osmotic diuretics should be administered. *Corynebacterium renale* is sensitive to penicillin in vitro; the high concentrations of penicillin found in bovine urine and effectiveness in a wide range of pH makes penicillin the drug of choice.[22] When the expense of the cow allows, intravenous penicillin should be used initially in the therapy in order to provide higher serum and renal parenchymal levels. Procaine penicillin should then be continued for up to 4 weeks. Free choice salt and water will be required since animals with pyelonephritis may not be able to adequately conserve water and solutes.

In chronic pyelonephritis, antimicrobial therapy is based on culture and sensitivity and minimum inhibitory concentrations of the offending organism, pH of the animal's urine, percent excretion and activity in the urine and parenchymal concentration of the antimicrobial agents. Expense, withdrawal time, toxicity, rumen inactivation and ease of administration are all important considerations in bovine practice. *Corynebacterium renale* would best be treated with procaine penicillin while *Escherichia coli* may often be successfully treated with ampicillin or penicillin. Therapy should be continued for at least 4 weeks. One week after the end of treatment, a catheterized urine sample should be evaluated cytologically and culture and colony counts determined. As with subacute pyelonephritis, free choice water and salt are necessary. Those with unilateral pyelonephritis, gross reneal enlargement and abscessation may be best treated by nephrectomy.[22] Accurate assessment of renal function in the opposite kidney is imperative prior to surgery. This should include careful rectal examination, measurement of serum creatinine and preferably microscopic examination of a biopsy specimen of the opposite kidney. If treated adequately, the prognosis for life and return to production is usually good in most cattle with pyelonephritis.

The basis of therapy in cattle with ATN is discontinuation of the nephrotoxic substance and the administration of fluids and electrolytes to restore blood volume and renal blood flow.[2] Fluids containing isotonic amounts of sodium, chloride, potassium and calcium are preferred. The use of sodium bicarbonate seems unnecessary except in cattle with complicating diarrhea. The use of magnesium cathartics, which are frequently administered when orally ingested toxins are suspected, should be avoided in the presence of hypermagnesemia. The cause and duration of the ATN dictates prognosis more accurately than degree of azotemia. The prognosis of those cattle with aminoglycoside or poisonous plant ATN is good with early diagnosis and adequate therapy. Those cattle with ATN associated with sepsis have a guarded prognosis in spite of intensive therapy.

Cattle with RVT or RCN have a very poor prognosis and only valuable cattle warrant attempted therapy. Fluid and electrolyte replacement are the basis of treatment. Furosemide may be used if increased urine production has not developed after the replacement of any fluid and electrolyte deficiencies. Aspirin or other prostaglandin synthetase inhibitors should be administered to septic animals in hopes of diminishing clinical signs of endotoxemia. If RVT is thought to have resulted from massive proteinuria, compatible plasma should be administered at the same time as heparinization (40-80 IU/kg, t.i.d.).

Bovine renal amyloidosis has always proved fatal. Salvage is therefore usually recommended. Clinical recovery from systemic amyloidosis has been documented in humans when the underlying disease is controlled. Massive doses of dimethyl sulfoxide (80 mg/dl) given intravenously have proved useful in some human cases and experimental animals with systemic reactive amyloidosis.[23] Experiences with dimethyl sulfoxide therapy for amyloidosis in dogs were unsuccessful.[24]

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