Interpreting raised urea and and creatinine- Is it all bad news?

Azotaemia is the laboratory finding of increased concentrations of serum urea and creatinine. Advanced renal failure and other causes of severe azotaemia may be associated with a set of unpleasant clinical features termed uraemia. To interpret a blood parameter it is important to remember the following:

- increase means: increased production or decreased excretion
- decrease means: decreased production or increased elimination.

In order to interpret renal parameters accurately, a basic understanding of the origins, metabolism and excretion of urea and creatinine is necessary.

1. Components of azotaemia

**Urea**

Urea is the major nitrogenous waste product of mammals and is ultimately excreted almost exclusively in urine. It is synthesized in the liver from carbon dioxide and ammonia via the urea cycle. The urea formation permits elimination of excess ammonia, most of which is being produced during deamination of amino-acids. Urea is a small, uncharged molecule that is not protein bound. Therefore it diffuses rapidly throughout all body fluid compartments and is freely filtered at the glomerular basement membrane. When the overall glomerular filtration rate (GFR) falls below 25% of normal, serum urea exceeds the upper limit of the reference range. Most of the ammonia incorporated into urea comes from protein breakdown. Thus the rate of urea formation is highly dependent on the protein dietary intake and the rate of endogenous protein catabolism. High protein diets of low biological value and gastro-intestinal haemorrhage increase the serum urea concentration even in animals with normal renal function. Anything that increases endogenous protein catabolism can increase serum urea concentration, independent of diet and renal excretory function. Some specific causes of increased endogenous protein catabolism include:

- fever
- starvation
- vigorous, prolonged exercise
- recent glucocorticoid administration
- burns
- sepsis.

Conversely, the following will reduce serum urea:

- anabolic steroids
- severe hepatic dysfunction
- feeding of a protein restricted, high quality protein diet that meets calorific needs.

As well as being freely filtered at the glomerular basement membrane, urea is reabsorbed in the tubules and collecting ducts. During intense diuresis only 40% of the filtered urea is being reabsorbed. However when the flow of fluid
through the renal tubules is reduced, much more urea is being reabsorbed. Retention of urea in the renal medullary interstitium is indeed one of the mechanisms by which the kidney is able to concentrate urine. From a diagnostic point of view, serum urea will tend to underestimate the GFR in dehydrated patients and overestimate the renal excretory function in hydrated polydipsic animals or those receiving vigorous fluid therapy. In the situation of a patient with CRF that have been receiving 2-3 times maintenance fluid therapy for several days creatinine is a more reliable indicator of GFR.

**Creatinine**

Small quantities of creatinine are ingested by dogs and cats in the animal tissues they eat, but the vast majority of creatinine is produced from their own skeletal muscle by breakdown of creatine. The amount of creatinine formed daily depends upon the total body creatine, which in turn depends on dietary intake, rate of synthesis and total skeletal muscle mass. Muscular dogs or cats would be expected to have higher serum creatinine concentration than less muscular ones, other factors (such as renal function) being equal. It is a small molecule that is not protein bound and is freely filtered by the glomerular basal membrane. Unlike urea, creatinine is not reabsorbed by the renal tubules or collecting ducts. In male dogs a very small amount of creatinine is actively secreted into the tubular filtrate by the proximal renal tubules. This is of limited clinical significance. More significantly, creatinine diffuses into the gastro-intestinal lumen and is subsequently metabolised by intestinal bacteria. This represents a substantial pathway for creatinine removal in azotaemic patients. Although some of the creatinine broken down by the intestinal bacteria may be recycled to produce more creatinine, most creatinine metabolised through this pathway is permanently removed from the body. The intestinal catabolism of creatinine becomes increasingly significant in severely azotaemic animals.

**Diagnostic value of serum creatinine and serum urea**

Both creatinine and urea are insensitive measures of renal excretory dysfunction. Up to 75% of total renal filtering capacity can be lost without these blood parameters exceeding their reference ranges. As creatinine is not reabsorbed by the renal tubules, it is a more reliable indicator of GFR than urea. However, creatinine does not increase precisely in proportion to a decrease in GFR. A modest deviation occurs as a result of extrarenal creatinine loss increasing in a non-linear unpredictable fashion as azotaemia worsens. However one study in humans has shown that serum urea correlates more directly with symptoms of uraemia than serum creatinine concentration does.

**2. Localisation of azotaemia in dogs and cats**

Information from a thorough history and physical examination, results of routine laboratory tests, and findings from diagnostic imaging usually allows for the distinction between pre-renal, renal, and post-renal disorders. In some patients, additional diagnostic tests (e.g. ACTH stimulation test, abdominal fluid analysis, contrast radiography) may be needed. Occasionally, renal
biopsy is needed to definitely differentiate between acute and chronic renal failure.

One of the most useful tests for distinguishing between pre-renal and renal azotaemia is analysis of urine obtained before treatment has commenced. Azotaemic patients with evidence of adequate urinary concentration (specific gravity above 1.030 in dogs and above 1.040 in cats) have pre-renal azotaemia. The clinician must first determine if the patient has received any treatment susceptible to interfere with urine concentrating ability such as intravenous fluids, corticosteroids, diuretics. Also disorders that may cause pre-renal azotaemia but may concomitantly decrease urine specific gravity must be excluded. This includes hypoadrenocorticism, diabetic ketoacidosis, hypercalcaemia, hepatic disease and pyometra. In fact hypoadrenocorticism may be the greatest imitator and most easily misdiagnosed as acute renal failure because these patients have similar clinical signs and clinicopathological abnormalities.

Dogs and cats with renal azotaemia usually have isosthenuria (USG 1.008-1.013) or minimally concentrated urine (USG<1.025). However some cats with CRF have USG values up to 1.035.

In animals with post-renal azotaemia, USG is rarely useful because urinary obstruction may cause tubular dysfunction and interfere with urine concentrating ability. However the history and physical examination are usually sufficient to make a diagnosis.

One pitfall that should be avoided is using the magnitude of azotaemia for diagnostic or prognostic information. First, remember that serum urea and creatinine concentrations are very crude indicators of renal dysfunction that do not increase before at least 75% of nephrons have been destroyed. This means that mild azotaemia may indicate significant and advanced renal disease. Secondly while serum urea and creatinine concentrations increase while GFR decrease, this relationship is not linear, therefore small changes in GFR in advanced renal disease may be associated with large changes in urea and creatinine serum concentrations.

The magnitude of a single measurement of urea and creatinine concentrations cannot be used to:
- distinguish between pre-renal, renal and post-renal azotaemia
- distinguish between acute renal failure and chronic renal failure
- determine if the disease is progressive or not
- predict the cause or reversibility of renal disease

3. Distinction between acute and chronic renal failure:

Once pre- and post-renal disorders have been excluded and renal failure has been diagnosed, additional evaluation is indicated to distinguish between acute renal failure (ARF) and chronic renal failure (CRF). The distinction is important because ARF has a very different short- and long-term prognosis but requires aggressive and expensive treatment. It is more likely that an animal with ARF will recover than an animal with CRF. Careful review of
history, physical examination findings, and results of laboratory evaluation is helpful.

<table>
<thead>
<tr>
<th>Acute renal failure</th>
<th>Chronic renal failure</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical findings</strong></td>
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</tr>
<tr>
<td>• Acute onset of clinical signs (usually less than a week)</td>
<td>• Vague onset of clinical signs (weeks to months)</td>
</tr>
<tr>
<td>• Usually moderately to severely depressed</td>
<td>• Alert, responsive, only slightly depressed</td>
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<tr>
<td>• Urine volume often decreased</td>
<td>• PUPD common</td>
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<tr>
<td>• Good body condition</td>
<td>• May be thin</td>
</tr>
<tr>
<td>• Kidneys enlarged, painful or may be normal</td>
<td>• Kidneys small, irregular or may be normal</td>
</tr>
<tr>
<td>• Bone density always normal</td>
<td>• Bone density may be reduced</td>
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<thead>
<tr>
<th>Lab Findings</th>
<th>Lab Findings</th>
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</thead>
<tbody>
<tr>
<td>• Normal or increased haematocrit but anaemia may be present</td>
<td>• Non regenerative anaemia but haematocrit may be normal</td>
</tr>
<tr>
<td>• Urea and creatinine previously normal but increase progressively</td>
<td>• Urea and creatinine previously increased and typically stable</td>
</tr>
<tr>
<td>• Normal to increased serum potassium</td>
<td>• Normal to decreased serum potassium</td>
</tr>
<tr>
<td>• Moderate to severe metabolic acidosis</td>
<td>• Mild to moderate metabolic acidosis</td>
</tr>
<tr>
<td>• Urinary casts in some patients</td>
<td>• Usually no urinary casts</td>
</tr>
<tr>
<td>• Proteinuria or glucosuria may result from acute tubular necrosis</td>
<td>• Proteinuria often present but usually due to glomerular disease</td>
</tr>
</tbody>
</table>

Even after careful questioning of owners and performing a thorough diagnostic evaluation, it may be difficult to distinguish between ARF and acute exacerbation of CRF. In such cases, a renal biopsy can provide important diagnostic and prognostic information. Alternatively, treatment of renal failure can be instituted and some idea of prognosis can be made on the basis of initial response to treatment.

4. Examples:
(These will be treated during the oral presentation)

A. Chronic and acute renal failure:
Example 1: acute on chronic renal failure, congenital renal dysplasia
Example 2: paraquat poisoning or ethylene glycol

B. Hypoadrenocorticism: why it is often mistaken for severe primary renal disease

As with all hypovolemic conditions, animals with primary hypoadrenocorticism develop azotaemia as a consequence of renal underperfusion and sometimes urea is also elevated as a result of gastro-intestinal bleeding (typical of glucocorticoid deficiency). However, unlike other hypovolaemic conditions where renal concentrating ability is maintained, dogs with primary hypoadrenocorticism are generally unable to concentrate their urine effectively. Impaired urine concentrating ability is due to:
- mineralocorticoid deficiency and resultant chronic renal sodium loss
- depletion of the normal renal medullary sodium concentration gradient
- impaired water resorption from the renal collecting ducts

Other common abnormalities to both hypoadrenocorticism and renal disease:
  - Non regenerative anaemia
  - Hyponatraemia, hyperkalaemia
  - Hypercalcaemia
  - Identical or very similar clinical signs

C. Infectious renal disease
   Example: Leptospirosis

D. Post-renal: cat with urolithiasis

E. Congestive heart failure, diuretic therapy and azotaemia