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LOGICAL APPROACH TO POLYURIA AND POLYDIPSIA

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Polyuria/polydipsia is a relatively frequent presenting complaint in small animal medicine. A variety of disorders may cause polydipsia or polyuria and an ordered, rational diagnostic approach to the problem is important.

IDENTIFY THE PROBLEM
The initial step is to ensure that true polyuria/polydipsia is present.

Physiological response?
Animals with profuse watery diarrhoea will often drink more than usual to maintain their hydration status – an appropriate physiological response. In addition, animals with gastritis will often drink large amounts of water but will vomit immediately hence are not truly polydipsic. Exercise and high ambient temperatures may also induce an animal to drink more than usual – another appropriate physiological response.

However, those animals that drink excessively and subsequently urinate excessively (or vice versa) require investigation to determine the cause of their disordered water intake.

Beware of the incontinent animal!
It is important to be aware that a polyuric animal may present for urinary incontinence and the owner may not be aware or may not volunteer that the animal is drinking more than usual. On the other hand, owners will often confuse pollakiuria with polyuria.

Urinary tract infections
Animals with lower urinary tract infections can present with polydipsia. Some of these patients probably do have pyelonephritis in addition to their lower urinary tract infection but in other patients it does not appear to be due to a urinary concentrating defect – i.e. it may be a primary polydipsia. Do these animals know in some way that if they drink more they will dilute their urine and perhaps ameliorate the discomfort of the UTI? Whatever the reason, it is advisable always to ensure that a UTI is not present before embarking on a more complex workup for PU/PD.

HOW CAN I CONFIRM POLYDIPSIA
Polydipsia is usually defined as a water intake that is twice maintenance requirements i.e. approximately 100 mls / kg day. (However, note that, in cats, ingestion of greater than 50 mls / kg day is probably excessive and indicative of PU/PD). It may be necessary to measure the animal's water intake to ensure that it is polydipsic. However, particularly in the stressful hospital environment, a polydipsic animal may reduce its water intake for a period of time and it is therefore desirable, if possible, to get the owner to measure intake at home.

If the owner has noticed that the dog or cat is drinking substantially more (especially cats), they can estimate roughly what the patient is drinking (e.g. "I normally only have to fill the ice cream container once per day but now I have to fill it three times per day") and the urine is not well concentrated, you can usually be fairly comfortable that the patient is polydipsic, without having to accurately measure water intake.

CLASSIFYING THE MECHANISMS OF POLYURIA/POLYDIPSIA
The mechanisms that result in polyuria and polydipsia can be classified according to the primary defect. Thus polyuria/polydipsia can be due to:

1. Primary polydipsia
a. Psychogenic
b. Hyperadrenocorticism (partly)
c. Hepatic encephalopathy (partly)
d. Hypothalamic lesion affect thirst receptors (extremely rare)

2. Absence or interference with ADH function
   a. Diabetes insipidus
   b. Hyperadrenocorticism
   c. Hypercalcaemia
   d. Hypokalaemia
   e. Pyometra

3. Increased metabolism and renal blood flow rate
   a. Hyperthyroidism

4. Osmotic diuresis
   a. Glucosuria

5. Reduced medullary hypertonicity
   a. Hyponatraemia
      i. Hypoadrenocorticism
      ii. Profound gut sodium loss
   b. Liver disease? (possibly due to decreased urea?)

6. Structural renal tubule damage

   DIAGNOSTIC APPROACH TO THE POLYURIC/POLYDIPSIC PATIENT

Determine urine SG

Having confirmed that an animal is truly polydipsic or polyuric, the initial and most important diagnostic step is to determine the urine specific gravity (SG) - without this information, appropriate interpretation of other pathology results can be difficult.

- Urine with an **SG of < 1.008**, (1.006 in cats) has been actively diluted
- Urine with an **SG of 1.008 - 1.012** has neither been diluted or concentrated
- Urine with an **SG of >1.012** has been concentrated to some degree - however whether the degree of concentration is appropriate must now be determined for the patient.

<table>
<thead>
<tr>
<th>Normal animals may have a urine SG of any value depending on the physiological circumstances</th>
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<tbody>
<tr>
<td>Always interpret urine SG in relation to the hydration status of the patient</td>
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</table>

Although urine with a SG greater than 1.012 has been concentrated, the degree of concentration may not be appropriate.

If an animal is **dehydrated** or **hypovolaemic**, the appropriate renal response is to produce urine that is concentrated to at least a SG of 1.030 (dogs) or 1.035 (cats).

If a **dehydrated** animal has a urine SG less than 1.030, it has by definition **inadequate urine concentration** and it must have some degree of renal dysfunction (primary structural renal dysfunction or extra-renal dysfunction).
If an azotaemic animal has a urine SG less than 1.030, then the patient must have impaired urine concentrating ability because if the azotaemia was due to prerenal factors only and the patient had normal renal concentrating ability the urine SG would be >1.030 or 1.035.

IDENTIFY THE SYSTEM – PRIMARY RENAL (STRUCTURAL) OR EXTRA-RENAL (FUNCTIONAL)?

Structural vs Functional
Persistent polyuria (primary or secondary to polydipsia) or failure to concentrate urine appropriately in the presence of dehydration or azotaemia may be the result of a structural renal abnormality (i.e. primary renal disease) or a functional renal abnormality (extra-renal disease).

A functional (extra-renal) abnormality occurs when the kidney is structurally normal but urine concentration is impaired as a result of alterations in, for example, medullary hypertonicity (e.g. hyponatraemia) or ADH function (ADH deficiency, impaired ADH function secondary to hypercalcaemia).

If the urine is very dilute (hyposthenuria) there are a limited number of diagnostic possibilities (see Table 1) and differentiation of the possible causes is relatively simple.

If the urine SG is between 1.008 and 1.030 the first consideration is whether the urine is inappropriately dilute. If a patient is dehydrated and renal function is normal, the urine SG should be greater then 1.030 (dog) or 1.035 (cat). If it is not, then renal dysfunction must be present - this can either be due to a structural or functional renal abnormality.

If the urine is concentrated the patient is either not polyuric or if it is definitely polyuric then there must be an osmotic solute in the urine that is creating polyuria - the most common of these would be glucose.

Table 1 outlines the differential diagnoses for polyuria/polydipsia.

TABLE 1: DIFFERENTIAL DIAGNOSIS OF POLYURIA/POLYDIPSIA

<table>
<thead>
<tr>
<th>Urine concentration</th>
<th>Differential diagnosis</th>
<th>Useful tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOSTHENURIA&lt;br&gt;Urine SG &lt;1.008</td>
<td>Psychogenic polydipsia</td>
<td>Water deprivation</td>
</tr>
<tr>
<td></td>
<td>Diabetes insipidus*</td>
<td>Water deprivation/ADH response test</td>
</tr>
<tr>
<td></td>
<td>Hypercalcaemia</td>
<td>Serum Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hyperadrenocorticism</td>
<td>WBC, ALP, cholesterol&lt;br&gt;Low-dose dexamethasone suppression</td>
</tr>
<tr>
<td></td>
<td>Pyometra</td>
<td>WBC</td>
</tr>
<tr>
<td></td>
<td>Hepatic disease</td>
<td>ALT, ALP, bile acids</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td>Serum K&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hypoadrenocorticism (usually associated with isosthenuria or hypersthenuria but very</td>
<td>Serum Na&lt;sup&gt;2+&lt;/sup&gt;, Na&lt;sup&gt;+&lt;/sup&gt;:K&lt;sup&gt;+&lt;/sup&gt; ratio, resting cortisol, ACTH stim test</td>
</tr>
</tbody>
</table>
occasionally can cause hyposthenuria)

| LACK OF APPROPRIATE CONCENTRATION (if patient is not normally hydrated) | Renal disease | Urea, creatinine, PO^4^- |
| Renal disease | Hypercalcaemia | Serum Ca^{2+} |
| Renal disease | Hyperadrenocorticism | WBC, ALP, cholesterol |
| Renal disease | Low-dose dexamethasone suppression |
| Renal disease | Hepatic disease | ALT, ALP, GGT bile acids |
| Renal disease | Diabetes mellitus | Blood and urine glucose |
| Renal disease | Pyometra | WBC |
| Renal disease | Hyponatraemia (often but not always due to hypoadrenocorticism) | Na^+:K^+, cortisol, ACTH response test |
| Renal disease | Hypokalaemia | Serum K^+ |

| CONCENTRATED | Diabetes mellitus | Urine and blood glucose |
| Renal glucosuria | Urine and blood glucose |

Further comments related to Table 1
- Animals with partial central diabetes insipidus (low but not total lack of ADH) can have isosthenuric urine if they are dehydrated.
- Animals with partial diabetes insipidus (central or nephrogenic) may on occasions have both hypostenuria and isosthenuria.
- Other disorders that may be associated with polyuria/polydipsia, and SG values ranging from hypostenuria to concentrated, include hyperthyroidism, polycythaemia and pheochromocytoma.

Having ascertained the urine concentration of the patient, the clinician can now concentrate on differentiating disorders that may be associated with each category.

IDENTIFY THE SYSTEM OR ORGAN INVOLVED

Hypostenuria

Animals with persistent hypostenuria cannot have primary renal disease. Hypostenuric urine has been actively diluted, a function that animals with renal disease cannot perform. However, it is my observation that cats with renal failure can occasionally have urine concentration values of between 1.006 and 1.008.

Persistent hypostenuria is a consistent feature of diabetes insipidus and psychogenic polydipsia. Note however, that a patient with partial central diabetes insipidus may present with urine in the isosthenuric range if, but only if, they are dehydrated.

Hyperadrenocorticism, liver disease, pyometra, hyperthyroidism, hyponatraemia and hypercalcaemia may all be associated with hypostenuria but, as Table 1 illustrates, can also be associated with isosthenuria or minimally concentrated urine.

Dogs with internal haemorrhage e.g. due to splenic haemangiosarcoma, can present with profound PU/PD and hypostenuria. This is paradoxical because haemorrhage is a potent stimulus for ADH release as ADH at high doses has a vasopressor function (hence its other name, vasopressin). This should cause increased urine concentration and haemodilution due to water retention. Perhaps the observed polyuria and hypostenuria are a compensatory measure: the
initial hemodilution may result in excretion of excess water, and profound blood loss may stimulate the thirst mechanism.

Water-deprivation useful?
A water-deprivation test should not be the first procedure performed once hyposthenuria is confirmed. Animals with hepatic disease, hypercalcaemia, hyperadrenocorticism, hyperthyroidism, hyponatraemia and pyometra may or may not be able to concentrate urine, to a certain extent, and a water-deprivation test will be of little discriminative value. In addition, water deprivation and delay in diagnosis may be detrimental, particularly to animals with hypercalcaemia (we can probably assume that an animal with pyometra will have sufficient other clinical signs to ensure a diagnosis is made relatively easily). Therefore, the first step should be directed at determining whether hepatic disease, hyperadrenocorticism, pyometra, hyperthyroidism or hypercalcaemia exist.

Note that azotaemia is an ABSOLUTE contraindication to doing a water deprivation test - if the patient is azotaemic, it has in essence failed this test.

A diagnosis of polydipsia/polyuria associated with hepatic disease (most often hepatic encephalopathy), hypercalcaemia, hyperthyroidism, hyperadrenocorticism or pyometra can be made relatively easily, based on the history, physical examination and selected tests.

If you are considering a water deprivation test to rule out psychogenic polydipsia it is often a good idea to get the owner to collect multiple urine samples from different times of day. Often these dogs will only have low urine SGs some of the time (because they can concentrate their urine if they are not drinking excessively). For example, after a long walk is a good time to get a concentrated sample. Then you have no need to do a water deprivation test.

Hepatic disease: Hepatic disease is usually associated with other clinical signs in addition to polydipsia/polyuria and can be investigated by measurement of serum enzymes, and of bile acids if serum enzymology is only slightly abnormal.

Hypercalcaemia: Hypercalcaemia can be diagnosed by a serum calcium level. It is usually associated with systematic signs such as inappetence and/or GI signs.

Pyometra: Patients with pyometra will have other clinical signs as well as polyuria/polydipsia and should not pose a diagnostic dilemma.

Hyperthyroidism: Hyperthyroidism is primarily of consideration in cats and will usually be associated with other clinical signs and increased serum T4 values.

Hyperadrenocorticism: Diagnosis of hyperadrenocorticism may prove more problematical as animals may not have any other clinical signs (although many will have characteristic signs such as alopecia, thin skin, pot belly and hepatomegaly).

Although a low-dose dexamethasone suppression test is necessary to definitively diagnose or exclude hyperadrenocorticism, the vast majority of animals with the disorder will have increased ALP and/or cholesterol and/or stress leukogram. Thus a polydipsic animal which has no other clinical signs and no changes in these haematological or biochemical parameters is unlikely to have hyperadrenocorticism although the diagnosis cannot be completely excluded without provocative testing of the adrenal gland.

Dogs with hyperadrenocorticism are usually systematically well (i.e. they eat well and are bright and alert). If the dog is systematically unwell then non-adrenal illness should be suspected (even if there is also concurrent hyper A).

The low-dose dexamethasone suppression test and ACTH stimulation test can be abnormal in systematically unwell animals with non-adrenal disease hence it is very important to interpret these tests light of the dog’s overall well-being. If there is concurrent illness but you still suspect that hyperA may be present, delay provocative testing of the adrenal gland until the concurrent disease has been resolved and the dog appears systematically well.

What if all tests are normal?
If an animal with hyposthenuria and no other clinical signs has a normal white blood cell count, serum calcium, serum ALP, serum T4 and serum cholesterol then closed pyometra,
Hypercalcaemia, hyperthyroidism and hepatic disease can be eliminated from the differential diagnosis. Hyperadrenocorticism is unlikely but is theoretically possible and should be investigated by a low-dose dexamethasone suppression test or ACTH stimulation test.

*Diabetes insipidus vs psychogenic polydipsia*

The clinician can now concentrate on differentiating diabetes insipidus from psychogenic polydipsia. If other clinical signs suggest the possibility of hyperadrenocorticism or hepatic encephalopathy, further tests may be required such as: a low-dose dexamethasone suppression test; fasting and postprandial bile acids; or blood ammonia concentrations.

Diabetes insipidus and psychogenic polydipsia may be differentiated by a water-deprivation test. It is important to recognise that the end point must be detectable dehydration, which may take many hours in an animal with normal urine concentrating capacity.

**BEWARE!**

In contrast, the animal with diabetes insipidus has no capacity to concentrate urine in the face of water deprivation and, hence, can become dehydrated extremely quickly (within hours). Close monitoring of body weight, PCV, plasma protein and blood urea is essential to prevent catastrophic hypernatraemia occurring. It is not acceptable, for example, to deprive the animal of water overnight and see what its urine SG is in the morning - the chances are you’ll have a moribund patient with a brain as dry as a crisp if it does have diabetes insipidus. Animals with psychogenic polydipsia will usually be able to concentrate urine appropriately although occasionally medullary washout secondary to profound polyuria may impair concentration. A partial water-deprivation test with or without salt administration may be necessary in some cases.

**ADH response test**

If the patient has been water-deprived for sufficient time to induce dehydration, its urine SG remains in the hyposthenuric range, and hyperadrenocorticism, hypercalcaemia, hepatic disease, hyperthyroidism and pyometra have been ruled out by appropriate testing, diabetes insipidus is the most probable diagnosis and response to ADH should be assessed.

A positive response to ADH (2.5-5.0 units Pitressin tannate i.m. or 0.5 U/kg aqueous ADH i.m) confirms central diabetes insipidus. If pitressin tannate is unavailable, desmopressin acetate (Minirin) drops can be instilled in the eye. A negative response suggests a diagnosis of nephrogenic diabetes insipidus (a very rare and controversial diagnosis).

**Impaired Urine Concentrating Ability**

<table>
<thead>
<tr>
<th>A urine specific gravity from 1.008-1.035 is only evidence of a urine concentrating defect if the patient is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• definitely PU/PD</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• dehydrated or azotaemic</td>
</tr>
</tbody>
</table>

As Table 1 illustrates, the differential diagnoses for the animal with inappropriately dilute urine when the urine concentration is 1.008-1.035 includes renal disease, hyperadrenocorticism, diabetes mellitus, hypercalcaemia, pyometra, hyperthyroidism, hypokalaemia, hypoadrenocorticism and hepatic disease (or very occasionally consider diabetes insipidus if the patient is dehydrated).

**What tests are required?**

As discussed in the previous section, hepatic disease, pyometra, hypercalcaemia, hyperthyroidism and hyperadrenocorticism can be excluded relatively easily from the list of differential diagnoses. Animals with hypoadrenocorticism rarely present with PU/PD as their major clinical sign.
Diabetes mellitus is also easily investigated utilising urine and/or blood glucose levels. (Note that cats may have substantial hyperglycaemia associated with stress and other disease and animals with proximal renal tubular defects may have glucosuria without hyperglycaemia). Hypokalaemia may be investigated by measuring serum potassium concentrations.

Are all animals with renal disease azotaemic? Animals with impaired urine concentration due to renal disease may or may not be azotaemic depending on the percentage of nephron loss – loss of 67% of nephron function results in impaired concentration ability, loss of 75% results in azotaemia.

Is a water-deprivation test useful? Although it is often assumed that a water-deprivation test is useful in diagnosing compensated renal disease, it should be remembered that the animal with compensated renal disease may become seriously azotaemic if water is deprived and dehydration ensues.

As previously mentioned, disorders such as hyperadrenocorticism may also impair the animal’s ability to concentrate urine in the face of dehydration and hence the test may not be particularly discriminatory. It is preferable to rule out other possible disorders with appropriate tests (urea, creatinine, liver enzymes, calcium, electrolytes, T4 and WBC).

If these tests are all normal and there are no other clinical signs, compensated renal disease is the probable diagnosis. Confirmation requires more sophisticated tests to measure glomerular filtration rate such as endogenous or exogenous creatinine clearance (not usually feasible in practice).

It is important to recognise that hypercalcaemia and hypoadrenocorticism (or hyponatraemia due to other causes) as well as renal disease may be associated with impaired urine concentration and azotaemia (see Table 2).

Concentrated Urine
The most common diagnosis in this category is diabetes mellitus.

Note that polyuria in diabetes mellitus is due to the osmotic effect of glucose in the renal tubules, which decreases water reabsorption from, for example, the thin loop of Henle. Urine concentration per se however is not impaired as the extra water excreted is accompanied by a solute (glucose) and there is no disturbance to medullary hypertonicity.

This is in contrast to drugs/disorders causing sodium wasting which as well as causing increased water loss to accompany the sodium, result in reduced medullary hypertonicity.

Renal glucosuria vs diabetes
Renal tubular defects causing glucosuria should also be considered and differentiated from diabetes mellitus by measuring blood glucose.

Cats with stress-related hyperglycaemia may also have glucosuria that could conceivably be of sufficient magnitude to cause polyuria. Diagnosis of the underlying disorder can present a diagnostic challenge in these patients. However, measurement of serum fructosamine levels appears to be useful in differentiating most cases of stress hyperglycaemia from true diabetes mellitus.

Animals with hyperadrenocorticism, hypercalcaemia and hypoadrenocorticism may not be consistently polyuric and therefore may have concentrated urine at certain times.