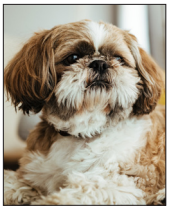
An SDMA case study: Sparkle



Patient: Sparkle, 11-year-old, spayed female shih tzu

Presenting reason and history: Since her last visit 8 months prior, Sparkle's owners noticed an increase in her drinking and urination. She tended to empty the entire bowl and went outside frequently. Although Sparkle spent her time primarily indoors, she did have free access to a small fenced yard through a doggie door. There were no other significant changes to her personality or playfulness.

Physical examination: Sparkle had a normal thoracic auscultation and abdominal palpation. Body temperature was 37.8° C, pulse was 100 beats per minute, and respiratory rate was 22 breaths per minute. Her bladder was small. Her rectal examination was normal. Her body weight was 5.17 kg with body condition score (BCS) of 3.5/9, and she had mild prominence to her spine and hips, suggesting mild to moderate muscle mass loss.[1] She had mild dental disease, grade 2/5.

Diagnostic plan

Previous laboratory testing for Sparkle had been normal. Possible clinical indications for her recent change in water consumption included possibly endocrine disease, liver disease, and/or kidney disease. In order to narrow the possible causes of her increased thirst and urination, her veterinarian suggested a complete blood count (CBC); chemistry panel, including the IDEXX SDMA® Test and electrolytes; complete urinalysis; and yearly vector-borne disease testing.

Diagnostic review—29th of October 2016

CBC

Haematology — Click to view Differentials

	29.10.16 08:05	
RBC	**9.59**	5.39 - 8.70 x10^12/L
Haematocrit	**0.59**	0.383 - 0.565 L/L
Haemoglobin	207	134 - 207 g/L
MCV	62	59 - 76 fL
MCH	**21.6**	21.9 - 26.1 pg
MCHC	351	326 - 392 g/L
% Reticulocyte	2.4	%
Reticulocytes	**230**	10 - 110 K/µL
Reticulocyte Comment	In nonanemic dogs, a reticulocyte count of greater than 110 K/uL of blood may be a transient physiologic response or evidence of bone marrow response to an increased peripheral demand. A persistent reticulocyte count >110 K/uL may indicate occult blood loss, underlying hemolytic disease or disorder that causes an absolute erythrocytosis. Serial monitoring of the erythrogram and reticulocyte count may help determine the significance of this finding. The following chart can be used as a guideline to determine the degree of regenerative response. Degree of bone marrow response (K/uL): Mild 110-150 Moderate 150-300 Marked >300	
WBC	10.0	4.9 - 17.6 x10^9/L
% Neutrophils	78.2	%
% Lymphocytes	14.7	%
% Monocytes	2.6	%
% Eosinophils	4.4	%
% Basophils	0.1	%
Neutrophils	7.82	2.94 - 12.67 x10^9/L
Lymphocytes	1.47	1.06 - 4.95 x10^9/L
Monocytes	0.26	0.13 - 1.15 x10^9/L
Eosinophils	0.44	0.07 - 1.49 x10^9/L
Basophils	0.01	0 - 0.1 x10^9/L
Platelets	**516**	143 - 448 x10^9/L
Polychromasia	SLIGHT	
Remarks	SLIDE REVIEWED MICROSCOPICALLY. NO PARASITES SEEN	

Chemistry

Chemistry — Click to view Differentials

	29.10.16 08:05	
Glucose	4.44	3.5 - 6.33 mmol/L
IDEXX SDMA (Learn More)	ak **18**	0 - 14 µg/dL
Creatinine	97.24	44.2 - 132.6 µmol/L
Urea	3.93	3.21 - 11.07 mmol/L
BUN: Creatinine Ratio	10.0	
Phosphorus	1.03	0.81 - 1.97 mmol/L
Calcium	2.45	2.1 - 2.94 mmol/L
Sodium	144	142 - 152 mmol/L
Potassium	5.4	4.0 - 5.4 mmol/L
Na: K Ratio	**27**	28 - 37
Chloride	**106**	108 - 119 mmol/L
Total Protein	64	55 - 75 g/L
Albumin	**26**	27 - 39 g/L
Globulin	38	24 - 40 g/L
Albumin: Globulin Ratio	0.7	0.7 - 1.5
ALT	59	18 - 121 U/L
AST	22	16 - 55 U/L
ALP	**312**	5 - 160 U/L
GGT	5	0 - 13 U/L
Bilirubin - Total	3.42	0 - 5.13 µmol/L
Bilirubin - Unconjugated	1.71	0 - 3.42 µmol/L
Bilirubin - Conjugated	<1.71	0 - 1.71 µmol/L
Cholesterol	**11.69**	3.39 - 8.92 mmol/L
Amylase	992	337 - 1,469 U/L
Lipase	156	138 - 755 U/L
Creatine Kinase	102	10 - 200 U/L

Diagnostic review—29th of October 2016, continued

Urinalysis

Urinalysis (Click to view Differentials)	29.10.16 08:05
Collection	h CYSTOCENTESIS
Colour	STRAW
Clarity	CLEAR
Specific Gravity	1.005
pH	6.5
Urine Protein	i 2+ (200-300 mg/dL)
Glucose	NEGATIVE
Ketones	NEGATIVE
Blood / Haemoglobin	TRACE
Bilirubin	NEGATIVE
Urobilinogen	NORMAL
White Blood Cells	0-2
Red Blood Cells	0-2
Bacteria	NONE SEEN
Epithelial Cells	RARE (0-1)
Mucus	NONE SEEN
Casts	NONE SEEN
Crystals	NONE SEEN

Vector-borne disease testing

Serology (Click to view Differentials)	29.10.16 08:05
Heartworm Antigen	NEGATIVE
Ehrlichia canis / ewingii	NEGATIVE
Lyme (Borrelia C6 Antibody)	NEGATIVE
Anaplasma phagocytophilum / platys	h NEGATIVE

Several findings of concern were present on Sparkle's laboratory testing. Sparkle did have some mild changes on her CBC—she has had a historical pattern of a slight increase in her hematocrit and reticulocytes. While this could be associated with splenic contraction or absolute erythrocytosis, the two-year history made breed-related changes or individual variation more likely.

Sparkle also had an increased SDMA* of 18 µg/dL. This indicated that there was likely impairment of her glomerular filtration rate (GFR), representing a decrease in normal kidney function. Her creatinine (CREA) and urea remained normal at 97.24 µmol/L and 3.93 mmol/L, respectively. Since this was her first occurrence of an increased kidney biomarker, and she had clinical signs of polyuria and polydipsia (PU/PD), further investigation was warranted. The first step is always to evaluate a urinalysis. Sparkle's urinalysis had two major indications that kidney disease was possibly present: an inappropriate urine specific gravity (less than 1.030 for dogs) and proteinuria. The urine sediment showed no pyuria, bacteriuria, or hematuria that would have suggested urinary tract inflammation or infection. A great tool to reference here is the IDEXX SDMA® Test Algorithm. Following the algorithm in Sparkle's case would lead to the concern for GFR impairment and kidney dysfunction that needs more immediate investigation.

Sparkle's veterinarian suggested adding a urine protein:creatinine (UPC) ratio to quantify the amount of protein she was losing in her urine. The UPC ratio was especially important as Sparkle appeared to have a slightly low albumin (26 g/L), an indication that she might have been losing a significant amount of protein through her kidneys. The negative Lab 4Dx® Plus Test suggested that neither Lyme disease nor ehrlichiosis was the cause of secondary insult and impairment of GFR. The veterinarian could have reasonably performed a urine culture and MIC (due to low urine specific gravity and presence of protein) to rule out urinary tract infection, or screening for leptospirosis based on the poor urine quality (insufficiently concentrated and proteinuria), but this was not elected because of other laboratory findings and patient history.

Urinalysis (Click to view Differentials)	29.10.16 08:05	
Urine Creatinine	3,261.96	µmol/L
Urine Protein	150.7	mg/dL
Urine Protein: Creatinine Ratio	4.1	
Color	an STRAW	

Sparkle had a significant increase in her UPC ratio of 4.1 (UPC ratio greater than 0.5 is concerning), likely renal in origin. A UPC ratio of 4.1 suggests significant loss of protein through the glomerulus, an increased risk for blood clots due hypercoagulability, and of concern, continued worsening of kidney function due to ongoing damage.

Review of her laboratory testing also suggested hyperadrenocorticism (Cushing's disease) as the possible primary cause of her condition based on increased ALP, increased red blood cell mass and platelets, proteinuria, and inadequate urine concentration. This endocrinopathy can cause secondary kidney damage due to hypertension and proteinuria. Other than PU/PD, however, Sparkle had no clinical signs to suggest Cushing's disease.

Sparkle's veterinarian decided it was also important to check her systolic blood pressure, which was normal at 135 mm Hg. It was recommended that Sparkle have a follow-up UPC ratio and chemistry panel with the IDEXX SDMA® Test in 2–4 weeks.

Recheck visit—6th of December 2016

Chemistry (Click to view Differentials)	06.12.16 07:18		
Glucose		5.61	3.5 - 6.33 mmol/L
IDEXX SDMA (Learn More)	af	22	0 - 14 µg/dL
Creatinine		106.08	44.2 - 132.6 µmol/L
Urea		4.64	3.21 - 11.07 mmol/L
BUN: Creatinine Ratio		10.8	
Total Protein		64	55 - 75 g/L
Albumin		26	27 - 39 g/L
Globulin		38	24 - 40 g/L
Albumin: Globulin Ratio		0.7	0.7 - 1.5
ALT		51	18 - 121 U/L
ALP		308	5 - 160 U/L
Bilirubin - Total		1.71	0 - 5.13 µmol/L
Haemolysis Index	ag	N	
Lipaemia Index	ah	1+	
Urine Creatinine		3,854.24	µmol/L
Urine Protein		175.7	mg/dL
Urine Protein: Creatinine Ratio		4.0	

Sparkle appeared to have a persistent increase in her SDMA. This is an important indicator of ongoing decline in GFR and kidney dysfunction. While her CREA and urea remained well within the reference interval, there was a mild upward trend. She continued to have significant proteinuria, with UPC ratio of 4.0, as well as mild hypoalbuminemia. Given that Sparkle had a negative vector-borne disease screen and no other evidence of major systemic disease, it was likely that she had primary kidney disease with proteinuria, a probable glomerulopathy.

The findings of a persistent stable increase in SDMA with inappropriate urine specific gravity would support a diagnosis of chronic kidney disease (CKD) and encourage staging according to the International Renal Interest Society (IRIS) Chronic Kidney Disease (CKD) guidelines.[2] The disparity between her SDMA and CREA suggested that SDMA was proving to be a more reliable marker of early impairment of GFR and kidney dysfunction. The most likely reason for the disparity in CREA was that Sparkle was a dog of small stature with some additional muscle wasting. When her veterinarian palpated her spine, there was notable muscle loss as well as loss of the pelvic musculature.[1] The IRIS CKD staging guidelines offered a method to classify the severity of CKD present using her SDMA concentration. Once CKD was established, further diagnostic tests as well as appropriate treatment were suggested. In Sparkle's case, imaging with radiographs or ultrasound of the abdomen specifically looking at her renal parenchyma was to be recommended along with a urine culture and MIC susceptibility, despite a negative urine sediment.

Sparkle was considered IRIS CKD Stage 2, substage proteinuric, normotensive. At this point, a diet change to a kidney therapeutic diet with restricted phosphorus and protein, increased omega-3 fatty acids, and a neutralizing effect on pH was indicated. In addition, a low dose of an angiotensin-converting enzyme (ACE) inhibitor, such as enalapril or benazepril was suggested to treat her proteinuria.[3] Sparkle was started on 0.5 mg/kg of benazepril once daily. A recheck at 10–14 days after instituting therapy with an ACE inhibitor was suggested to evaluate if this dose was effective in reducing her proteinuria and to ensure she had no side effects, such as hypotension, onset of azotemia (increased CREA), or hyperkalemia. Sparkle was seen 1 month after starting her medications.

Recheck visit—12th of January 2017

Chemistry (Click to view Differentials)	12.01.17 07:57		
Glucose		5.77	3.5 - 6.33 mmol/L
IDEXX SDMA (Learn More)	ab	25	0 - 14 µg/dL
Creatinine		97.24	44.2 - 132.6 µmol/L
Urea		6.78	3.21 - 11.07 mmol/L
BUN: Creatinine Ratio		17.3	
Total Protein		64	55 - 75 g/L
Albumin		24	27 - 39 g/L
Globulin		40	24 - 40 g/L
Albumin: Globulin Ratio		0.6	0.7 - 1.5
ALT		38	18 - 121 U/L
ALP		158	5 - 160 U/L
Bilirubin - Total		1.71	0 - 5.13 µmol/L
Haemolysis Index	ac	N	
Lipaemia Index	ad	N	
Urine Protein: Creatinine Ratio If Indicated		A urine protein-to-creatinine ratio (UPC) has been ordered to evaluate renal damage, as indicated by a positive SSA protein result and inactive urine sediment.	
Urine Creatinine		7,911.8	µmol/L
Urine Protein		149.4	mg/dL
Urine Protein: Creatinine Ratio		1.7	

Upon recheck, Sparkle's owners reported that she was handling the diet change and medications well, and they noted a slight reduction in drinking and urination. Her urinary protein (UPC ratio) had decreased by 50%, which is often a reasonable goal for initial response. However, she continued to have mild hypoalbuminemia, and her SDMA had increased slightly from 22 to 25 µg/dL. Since SDMA is highly correlated to GFR, it is possible that Sparkle had progressive kidney disease or that benazepril had further reduced her GFR and her current SDMA was reflecting that change. Since her CREA and BUN remained stable and her blood pressure was normal at 130 mm Hg, her ACE inhibitor dose was not changed. Her IRIS stage was unchanged at IRIS CKD Stage 2, substage proteinuric, normotensive.

Sparkle was to be rechecked in 3–6 months on a maintenance schedule appropriate for her current level of disease. The best method to determine how each individual dog's kidney disease progresses is regular monitoring with a chemistry panel, including the IDEXX SDMA® Test; CBC; urinalysis; UPC ratio; and blood pressure.

Recheck visit—17th of May 2017

Haematology

Click to view Differentials

	17.05.17 08:10	
RBC	7.85	5.39 - 8.70 x10^12/L
Haematocrit	0.496	0.383 - 0.565 L/L
Haemoglobin	171	134 - 207 g/L
MCV	63	59 - 76 fL
MCH	**21.8**	21.9 - 26.1 pg
MCHC	345	326 - 392 g/L
% Reticulocyte	1.2	%
Reticulocytes	94	10 - 110 K/µL
WBC	7.6	4.9 - 17.6 x10^9/L
% Neutrophils	75.0	%
% Lymphocytes	15.0	%
% Monocytes	3.0	%
% Eosinophils	7.0	%
% Basophils	0.0	%
Neutrophils	5.7	2.94 - 12.67 x10^9/L
Lymphocytes	1.14	1.06 - 4.95 x10^9/L
Monocytes	0.228	0.13 - 1.15 x10^9/L
Eosinophils	0.532	0.07 - 1.49 x10^9/L
Basophils	0	0 - 0.1 x10^9/L
Platelets	**633**	143 - 448 x10^9/L
Remarks	SLIDE REVIEWED MICROSCOPICALLY. NO PARASITES SEEN	

Urinalysis

Click to view Differentials

	17.05.17 08:10	
Collection	CYSTOCENTESIS	
Colour	STRAW	
Clarity	CLEAR	
Specific Gravity	1.011	
pH	6.0	
Urine Protein	d	1+ (100-200 mg/dL)
Glucose		NEGATIVE
Ketones		NEGATIVE
Blood / Haemoglobin		NEGATIVE
Bilirubin		NEGATIVE
Urobilinogen	e	NORMAL
White Blood Cells		0-2
Red Blood Cells		NONE SEEN
Bacteria		NONE SEEN
Epithelial Cells		1+ (1-2)/HPF
Mucus		PRESENT
Casts		NONE SEEN
Crystals		NONE SEEN

Chemistry

Click to view Differentials

	17.05.17 08:10	
Glucose	5.44	3.5 - 6.33 mmol/L
IDEXX SDMA Learn More	y **27**	0 - 14 µg/dL
Creatinine	132.6	44.2 - 132.6 µmol/L
Urea	**11.42**	3.21 - 11.07 mmol/L
BUN: Creatinine Ratio	21.3	
Phosphorus	1.39	0.81 - 1.97 mmol/L
Calcium	2.74	2.1 - 2.94 mmol/L
Sodium	145	142 - 152 mmol/L
Potassium	**5.8**	4.0 - 5.4 mmol/L
Na: K Ratio	**25**	28 - 37
Chloride	112	108 - 119 mmol/L
Total Protein	65	55 - 75 g/L
Albumin	28	27 - 39 g/L
Globulin	37	24 - 40 g/L
Albumin: Globulin Ratio	0.8	0.7 - 1.5
ALT	50	18 - 121 U/L
AST	17	16 - 55 U/L
ALP	**225**	5 - 160 U/L
GGT	4	0 - 13 U/L
Bilirubin - Total	1.71	0 - 5.13 µmol/L
Bilirubin - Unconjugated	0	0 - 3.42 µmol/L
Bilirubin - Conjugated	<1.71	0 - 1.71 µmol/L
Cholesterol	**10.03**	3.39 - 8.92 mmol/L
Amylase	998	337 - 1,469 U/L
Lipase	173	138 - 755 U/L
Creatine Kinase	78	10 - 200 U/L
Haemolysis Index	z N	
Lipaemia Index	aa N	
Urine Protein: Creatinine Ratio If Indicated	A urine protein-to-creatinine ratio (UPC) has been ordered to evaluate renal damage, as indicated by a positive SSA protein result and inactive urine sediment.	
Urine Creatinine	4,579.12	µmol/L
Urine Protein	100.8	mg/dL
Urine Protein: Creatinine Ratio	1.9	
Color	ab STRAW	

At Sparkle's recheck 4 months later (17th of May 2017), her proteinuria was still well controlled with a stable UPC ratio. The most concerning finding was an increase in severity of SDMA and now concurrently increased CREA and BUN. This suggested a subtle worsening of her GFR and loss of kidney function. Her mild hyperkalemia was likely a side effect of her long-term ACE-inhibitor therapy. There continued to be no evidence of other systemic disease and no suggestion of infection in her urinary tract. Her veterinarian rechecked her blood pressure, which was 170 mm Hg, consistent with hypertension. It was very likely her hypertension was secondary to her previously diagnosed CKD. If left untreated, Sparkle's hypertension could have led to continued kidney damage and worsening kidney function, so it was very important to institute additional therapy. Since Sparkle was already being treated with an ACE inhibitor, a calcium channel blocker, amlodipine, was added to play an additional role in reducing her blood pressure.

Sparkle's blood pressure was rechecked by a Doppler method after 48 hours on the new medication regimen. Her blood pressure had decreased to 145 mm Hg. Based on IRIS guidelines, she remained prehypertensive, but with a documented 25 mm Hg reduction in blood pressure in the face of significant anxiety in the clinic environment, Sparkle's blood pressure was deemed adequately controlled.

In order to best manage Sparkle's kidney disease long-term, she was to be monitored for worsening of renal biomarkers, specifically her SDMA, CREA, BUN, and UPC ratio, every 4–6 months. At that time, blood pressure was also to be checked. Other considerations for her care included monitoring her electrolytes, given that her potassium concentration could continue to increase with chronic administration of ACE inhibitors, as well as monitoring her red blood cell count for development of anemia, given the downward trend in her hematocrit.

Haematology

Click to view Differentials

	30.05.19 08:27	17.01.19 08:29	25.05.18 08:10	10.11.17 08:27	17.05.17 08:10	12.01.17 07:57	06.12.16 07:18	29.10.16 08:05
RBC	6.73	6.92	6.84	7.03	7.85	8.53	**9.24**	**9.59**
Haematocrit	0.461	0.47	0.454	0.492	0.496	0.524	0.558	**0.59**
Haemoglobin	156	162	150	167	171	188	200	207
MCV	68	68	66	70	63	61	60	62
MCH	23.2	23.4	21.9	23.8	**21.8**	22.0	**21.6**	**21.6**
MCHC	338	345	330	339	345	359	358	351
% Reticulocyte	1.4	1.1	0.7	1.0	1.2	1.4	2.0	2.4
Reticulocytes	94	76	48	70	94	**119**	**185**	**230**

Chemistry

Click to view Differentials

	30.05.19 08:27	17.01.19 08:29	25.05.18 08:10	10.01.18 08:17	10.11.17 08:27	17.05.17 08:10	12.01.17 07:57	06.12.16 07:18	29.10.16 08:05
IDEXX SDMA (Learn More)	g **34**	j **29**	m **29**		q **26**	t **27**	w **25**	z **22**	ac **18**
Creatinine	**176.8**	**159.12**	**159.12**		**150.28**	132.6	97.24	106.08	97.24
Urea	**18.21**	**17.49**	**13.92**	**16.06**	**13.57**	**11.42**	6.78	4.64	3.93

Chemistry

Click to view Differentials

	02.06.19 04:22	17.01.19 08:29	25.05.18 08:10	10.11.17 08:27	17.05.17 08:10	12.01.17 07:57	06.12.16 07:18	29.10.16 08:05
Urine Protein: Creatinine Ratio If Indicated	A urine prot...	A urine prot...	A urine prot...	A urine prot...	A urine prot...	A urine prot...		A urine prot...
Urine Creatinine	4,260.88	5,304	3,969.16	7,133.88	4,579.12	7,911.8	3,854.24	3,261.96
Urine Protein	87.2	97.5	81.9	134.2	100.8	149.4	175.7	150.7
Urine Protein: Creatinine Ratio	1.8	1.6	1.8	1.7	1.9	1.7	4.0	4.1
Color	STRAW	YELLOW	YELLOW	YELLOW	STRAW	YELLOW	STRAW	STRAW

In Sparkle's case, SDMA was the earliest biochemical marker of impairment in GFR. SDMA was able to alert her veterinarian over a year earlier than CREA that she had a decline in kidney function leading to a diagnosis of CKD. Sparkle's kidney disease, despite appropriate care, appeared to be slowly progressive, with the development of increased CREA. By including an IDEXX SDMA® Test in her initial diagnostics, an earlier diagnosis of kidney disease was made. Additionally, continued inclusion of SDMA in monitoring provided evidence of progressive disease. The earlier discovery of her underlying kidney disease allowed for early, appropriate intervention, likely improving her long-term survival.

*Symmetric dimethylarginine.

References

1. WSAVA Nutritional Assessment Guidelines Task Force Members, Freeman L, Becvarova I, et al. WSAVA Nutritional Assessment Guidelines. *J Small Anim Pract*. 2011;52(7):385–396. doi:10.1111/j.1748-5827.2011.01079.x
2. International Renal Interest Society. IRIS CKD Staging Guidelines (modified 2019). www.iris-kidney.com/guidelines. Accessed June 17, 2020.
3. Lees GE, Brown SA, Elliott J, Grauer GE, Vaden SL; American College of Veterinary Internal Medicine. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). *J Vet Intern Med*. 2005;19(3): 377–385. doi:10.1892/0891-6640(2005)19[377:aamopi]2.0.co;2