Diagnostic update

IDEXX Cystatin B Test

Cystatin B is a kidney injury biomarker. Unlike the functional biomarkers creatinine and SDMA that reflect changes in glomerular filtration rate, cystatin B concentrations increase when there is acute and/or active injury to renal tubular epithelial cells.

Background

Acute kidney injury is associated with high morbidity and mortality in veterinary patients. Despite advances in medical management, including renal dialysis, case fatality rates can be as high as 60%.[1,2,3] The diagnosis of kidney injury in companion animals has historically relied upon rapid or unexpected changes in functional markers, such as creatinine, urea, and more recently, SDMA. Functional markers reflect glomerular filtration rate (GFR) and may take hours to days to increase, during which time acute kidney injury may remain unrecognised. Identifying kidney injury before functional markers increase provides veterinarians with an opportunity for intervention, which has the potential to change otherwise poor outcomes.

Acute kidney injury (AKI) is characterised by four phases: initiation, which occurs during or immediately after the insult; extension, where cellular injury caused by hypoxia, ischaemia, and inflammation leads to necrosis and apoptosis of kidney cells; maintenance, which is characterised by azotaemia, uraemia, or both; and recovery, when azotaemia improves and tubular epithelial cells undergo repair. During the first two phases of initiation and extension, clinical signs may be inapparent to owners as well as veterinarians.[4] There is strong clinical evidence that novel urinary biomarkers that reflect injury to renal tubular epithelial cells may allow veterinarians to address potentially reversible damage to the kidney.[5–8]

Previously, chronic kidney disease (CKD) and AKI were considered separate, distinct conditions. However, in recent years, investigation into novel biomarkers of injury suggests that they share some common characteristics.[5,9,10] The understanding of kidney injury has evolved as well, with relatively mild injury or changes in renal function suggesting more severe underlying disease. Consider the relationship between the function of the kidneys and how that function is reflected in biochemical markers; substantial changes in GFR must occur before the increase in markers is recognised in laboratory results. The compensatory ability of remaining nephrons may understate the degree of decline in GFR, making an injury marker all the more valuable in assessing the overall health of the kidneys.[11,12]

Kidney injury may result from any number of causes, including a primary renal insult or injury secondary to nonrenal conditions.[5] The epithelial cells of the renal proximal tubule and the thick ascending loop of Henle are the most metabolically active segment of the nephron, and they are particularly susceptible to damage.[13] Cystatin B is a small (approximately 11 kDa) intracellular protein that is released into the urine when there is injury to or destruction of renal tubular epithelial cells.[5]

Biology of cystatin B

Cystatin B is found in many mammalian cells but is not found in large concentrations in systemic circulation. It is a member of the cystatin family of protease inhibitors that help protect against leakage of proteolytic enzymes from lysosomes. Cystatin B has been shown to be sensitive for the detection of renal proximal tubular toxicity secondary to gentamicin administration, and has been purified from ruptured kidney cells, but not from stressed kidney cells. This suggests that cystatin B found in the urine likely originates from apoptosis or necrosis of renal tubular epithelial cells.[5]

Clinical utility

The IDEXX Cystatin B Test is indicated for use in dogs and cats where kidney injury is suspected or possible, including nonrenal conditions that may secondarily affect renal perfusion. It is also indicated for use in patients with previously diagnosed renal disease as it may aid in distinguishing stable from progressive chronic kidney disease.[14] Increased cystatin B concentration in the urine suggests that active and/or acute injury is possible.[6,7,14,15] In patients with known or suspected toxin exposure or patients receiving potentially nephrotoxic medications, cystatin B may provide insight into tubular injury even in the absence of changes in functional markers like SDMA and creatinine. Tubular injury may also occur as a result of nonrenal conditions, including but not limited to hypotension, hypovolaemia, fever, and vasculitis, to name a few.[16]

Cystatin B and SDMA

Cystatin B complements SDMA in assessing the renal health of patients with known or suspected kidney disease or injury. While SDMA is recommended as part of every chemistry panel, including during screening or routine wellness visits, cystatin B is not recommended for use in healthy animals where no concern for kidney injury exists. Increased cystatin B concentration in the absence of changes in kidney function or indication of potential kidney injury should be interpreted in the context of the clinical presentation. Healthy dogs or cats without known underlying disease or risk of kidney injury are not expected to have increased concentrations of cystatin B.

IDEXX Cystatin B Test and interpretation of results

The IDEXX Cystatin B Test measures cystatin B concentration in the urine with agglutination technology, which involves the use of antibody-coated particles combined with buffered reagent in solution. When cystatin B is present in the specimen, the coated particles agglutinate and the subsequent change in opacity of the solution is converted to a numerical value, which is then reported in ng/mL. The test was validated in canine and feline urine by evaluating precision, accuracy, potential specimen interferents, and specimen stability.[17]

The reportable range for cystatin B is 50–500 ng/mL. Urine concentration of cystatin B < 100 ng/mL indicates that there is a decreased potential of kidney injury, while results ≥ 100 ng/mL suggest there is an increased risk of kidney injury. Results within the reportable range will receive a numerical value. Results less than 50 ng/mL and greater than 500 ng/mL will be reported out as < 50 ng/mL and > 500 ng/mL, respectively.

Increased cystatin B concentration in appropriately concentrated urine with serum SDMA and creatinine within reference intervals suggests possible active (ongoing) kidney injury. Similarly, patients with early IRIS* AKI Grade I or II may not exhibit clinical signs or changes in functional markers while still experiencing subclinical kidney injury. Patients with increased cystatin B concentrations (≥ 100 ng/mL) should have a complete urinalysis and cystatin B along with functional kidney markers rechecked within 24–48 hours.

Increased cystatin B concentration in urine that is inappropriately concentrated with serum SDMA and creatinine outside of reference intervals suggests that active/acute kidney injury is likely. Address current renal deficits and monitor patients closely for biochemical disturbances and urine output, and consider additional diagnostics, such as imaging, urine protein:creatinine ratio, and urine culture and MIC susceptibility. Cystatin B concentration < 100 ng/mL indicates that kidney injury is not present at the time of testing. If you suspect kidney injury despite results within the expected range, you may wish to recheck urinalysis with cystatin B within 5–7 days.

Under experimental conditions, doxycycline hyclate has been shown to interfere with urine cystatin B recovery when spiked into urine specimens with urine cystatin B concentrations below 250 ng/mL.[17]

Specimen requirements

Only domestic canine and feline urine specimens in a sterile container with no additives will be accepted for the IDEXX Cystatin B Test. Specimen collection may include cystocentesis, catheterisation, or voided (ideally midstream). Refrigeration is required; freezing is not recommended.

References

1. Vaden SL, Levine J, Breitschwerdt EB. A retrospective case-control of acute renal failure in 99 dogs. *J Vet Intern Med.* 1997;11(2):58–64. doi:10.1111/j.1939-1676.1997.tb00074.x
2. Segev G, Kass PH, Francey T, Cowgill LD. A novel clinical scoring system for outcome prediction in dogs with acute kidney injury managed by hemodialysis. *J Vet Intern Med.* 2008;22(2):301–308. doi:10.1111/j.1939-1676.2008.0063.x
3. Rimer D, Chen H, Bar-Nathan M, Segev G. Acute kidney injury in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and outcome. *J Vet Intern Med.* 2022;36(2):609–618. doi:10.1111/jvim.16375
4. Ross L. Acute kidney injury in dogs and cats. *Vet Clin North Am Small Anim Pract.* 2011;41(1):1–14. doi:10.1016/j.cvsm.2010.09.003
5. Yerramilli M, Farace G, Quinn J, Yerramilli M. Kidney disease and the nexus of chronic kidney disease and acute kidney injury: the role of novel biomarkers as early and accurate diagnostics. *Vet Clin North Am Small Anim Pract.* 2016;46(6):961–993. doi:10.1016/j.cvsm.2016.06.011
6. Gordin E, Gordin D, Viitanen S, et al. Urinary clusterin and cystatin B as biomarkers of tubular injury in dogs following envenomation by the European adder. *Res Vet Sci.* 2021;134:12–18. doi:10.1016/j.rvsc.2020.11.019
7. Harjen HJ, Anfinsen KP, Hultman J, et al. Evaluation of urinary clusterin and cystatin B as biomarkers for renal injury in dogs envenomated by the European adder (*Vipera berus*). *Top Companion Anim Med.* 2022;46:100586. doi:10.1016/j.tcam.2021.100586
8. Bar-Nathan M, Chen H, Rimer D, Segev G. Long-term outcome of dogs recovering from acute kidney injury: 132 cases. *J Vet Intern Med.* 2022;36(3):1024–1031. doi:10.1111/jvim.16435
9. Cowgill LD, Polzin DJ, Elliott J, et al. Is progressive chronic kidney disease a slow acute kidney injury? *Vet Clin North Am Small Anim Pract.* 2016;46(6):995–1013. doi:10.1016/j.cvsm.2016.06.001
10. Cowgill L. Grading of acute kidney injury. International Renal Interest Society. 2016. Accessed September 28, 2023. www.iris-kidney.com/education/pdf/4_Idc-revised-grading-of-acute-kidney-injury.pdf
11. Syme H. CKD early diagnostis. International Renal Interest Society. 2019. Accessed September 28, 2023. www.iris-kidney.com/education/education/early_diagnosis.html
12. Fattah H, Layton A, Vallon V. How do kidneys adapt to a deficit or loss in nephron number? *Physiology.* 2019;34(3):189–197. doi:10.1152/physiol.00052.2018
13. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney. *Nat Rev Nephrol.* 2017;13(10):629–646. doi:10.1038/nrneph.2017.107
14. Segev G, Vaden S, Ross S, et al. Urinary cystatin B differentiates progressive versus stable stage I chronic kidney disease in dogs [ACVIM Abstract NU27]. *J Vet Intern Med.* 2022;36(6):2433–2434. doi:10.1111/jvim.16541
15. Hezzell MJ, Foster JD, Oyama MA, et al. Measurements of echocardiographic indices and biomarkers of kidney injury in dogs with chronic kidney disease. *Vet J.* 2020;255:105420. doi:10.1016/j.tvjl.2019.105420
16. Dunaevich A, Chen H, Musseri D, et al. Acute on chronic kidney disease in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and survival. *J Vet Intern Med.* 2020;34(6):2507–2515. doi:10.1111/jvim.15931
17. Data on file at IDEXX Reference Laboratories, Inc. Westbrook, Maine USA.

*IRIS is the International Renal Interest Society.

Published October 2023