Outcome Prediction of Acute Kidney Injury in Dogs and Cats

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ABSTRACT

Acute kidney injury, resulting in acute uremia, is associated with high morbidity and mortality. It requires intensive treatment, which is accompanied by high treatment costs. To date, there is no available tool to forecast the outcome of dogs and cats with acute kidney injury. Nonetheless this information is always requested by the owners, both to know the prognosis in order to make rational decisions as whether to pursue medical treatment or dialytic intervention and for how long. There are multiple factors that determine the outcome and long term prognosis of dogs and cats with acute kidney injury. These include the severity of the injury, comorbid disorders, concurrent complications, the underlying cause, and the medical management available. The reversibility of the kidney injury depends mostly on the severity of the injury and the underlying cause. It determines, among other things, the short term outcome, and will be the major factor determining the long term result. This review briefly discusses the terminology, pathophysiology and treatment of acute kidney injury, but it primarily focuses on the available information in the veterinary literature that can aid the clinician with prognostication of acute kidney injury in dogs and cats.

Keywords: acute renal failure, outcome, canine, feline, prognosis, chronic kidney disease

TERMINOLOGY

Acute renal failure is defined as a rapid decline in renal function, resulting in retention of uremic toxins, as well as fluid, acid-base and electrolyte imbalances (1). The terminology of acute renal failure has recently been modified in the human literature from 'acute renal failure' to 'acute kidney injury' (AKI). A similar modification is expected to occur in the veterinary literature as well, similar to the change made in the terminology of chronic kidney diseases (CKD), both in the human and the veterinary literature. One of the reasons for the modified terminology is to better describe the disorder (i.e., not every kidney injury is associated with a measurable failure), and to sensitize clinicians to early identification of the disease. Early identification will prompt early intervention, aimed to decrease further kidney damage, and thus may prevent overt renal failure. Early identification is extremely important in veterinary medicine, in which dialysis in not readily available, and thus the medical management is limited in its capability to manage patients with severe uremia.

PATHOPHYSIOLOGY

The disease course can be categorized into four phases (2). The first phase, the initiation, is typically a short phase in which the inciting cause is present and causing direct renal damage. At this stage clinical signs are absent and a decrease in renal function is usually not documented, when using the routine markers of kidney function (e.g., serum creatinine, urea, urine specific gravity). The second phase is the extension phase, in which kidney function further declines due to ischemic and inflammatory events that are a consequence of the initial injury, even if the inciting cause is no longer present. The third phase is the maintenance phase, in which there is an established and measurable decrease in kidney function. Many of the veterinary patients present for medical care in this phase of the disease, which may last from days to weeks. The fourth phase is the recovery phase, which does not occur in all patients. This phase may take weeks to months, it may be complete or partial, and will determine the long term outcome of the patient. Patients may regain complete or partial kidney function. In the latter scenario it may, or may not be enough to maintain the patient with a good quality of life for a substantial period of time, with the aid of medical management.

ETIOLOGY

There are numerous causes of AKI in dogs and cats. These can be categorized into few major categories including ischemia (e.g., hypotension), nephrotoxicity (e.g., ethylene glycol, gentamicin) and infectious causes (e.g., leptospirosis, pyelonephritis). The proportion of each etiology varies among different geographical locations. The initial diagnostic worked up, performed in AKI patients, is aimed also to identify the underlying cause, so the latter can be eliminated, and further kidney injury can be minimized. As will be discussed below, this information is also extremely valuable for outcome prediction.

MEDICAL AND DIALYTIC MANAGEMENT OF AKI

Acute kidney injury is a multi-systemic disease involving usually more than one organ (3). Thus, each patient should be assessed for concurrent complications. Successful management of all emerging complications is vital for complete recovery and better short and long term outcome.

Acute kidney injury leading to severe uremia is associated with high morbidity and mortality (4-6). The medical management of acute uremia is limited to elimination of known causes of the renal injury, and supportive therapies directed to the clinical and clinicopathologic consequences of uremia. The treatment goals are to keep the animal alive for a sufficient period of time, while maintaining homeostasis, and providing optimal conditions for the kidneys to recover, until the kidneys can regain function. Nevertheless, if the injury is severe, patients may die from the consequences of uremia before kidney function has been regained. Hemodialysis is an advanced extracorporeal renal replacement therapy for uremic patients with the capability to remove uremic toxins, correct fluid and electrolyte disorders, and restore acid-base balance (7). Hemodialysis extends the life expectancy of patients with severe uremia and expands the window of opportunity for recovery of the renal injury (7). Without hemodialysis, this window may be as short as hours to days in severe injuries, and patients may die from uremia before recovery had occurred, despite the potential for reversal of the renal damage in some of these cases. Despite its advantages, hemodialysis is a costly therapy, and usually is applied at a late stage of the disease, when medical management has failed. In many patients it may not be applied in a timely manner due to the uncertainty of the prognosis.

OUTCOME

There are multiple factors which determine the outcome and long term prognosis of dogs and cats with AKI. These include the severity of the injury, comorbid disorders, concurrent complications, the underlying cause, and the medical management available. The reversibility of the kidney injury depends mostly on its severity and the underlying cause.

The overall mortality of dogs with AKI was 56% in one study when the dogs were managed medically, and 53% in another study of dogs managed with hemodialysis (3-5). In cats the reported mortality was 42% in a study of medically managed cats, and 40-48% in cats managed with hemodialysis (6, 8, 9). Seemingly, the survival rate of dogs and cats managed medically or with hemodialysis is not substantially different; however, one should take into consideration that in veterinary medicine dogs and cats that are managed with hemodialysis are those that failed medical management, and were expected not to survive without the dialytic intervention.

It is thus clear that the prognosis of AKI is not determined only by the severity of the disease, but also from the medical management available in each facility. Most studies reporting survival rates of dogs and cats with AKI originate from veterinary teaching hospitals, where management is usually intensive. Therefore it is expected that the mortality rate will be even higher in facilities that cannot provide such an intensive management. On the other hand one may argue that veterinary teaching hospitals receive the most severe cases of AKI, a factor that increases the reported mortality rates in those facilities.

Euthanasia is a factor that influences the reported mortality rate in veterinary medicine as well. Most studies of AKI in dogs and cats report patients that were euthanized as non-survivors, even if no significant attempt for intervention was made. Therefore the reported survival rates may be an underestimation of the true survival rate of patients that are managed intensively. For example in one study of 99 dogs with AKI, 57 dogs (57.6%) did not survive, of those, 34 dogs (34.3%) were euthanized. It is likely that some of the dogs were euthanized due to poor prognosis, but others might have been euthanized due to other reasons (e.g., financial constrains), and thus had the potential to recover had euthanasia not elected. Based on the aforementioned data the prognosis of dogs and cats with AKI should be individualized to each patient based on the severity of the injury, comorbid conditions, complications, the facilities available to manage the patients and the owners' compliance.

The long term outcome of patients with AKI depends mostly on the degree of reversibility. In two studies, 57% and 53% of dogs and cats, respectively, that survived the AKI episode, sustained CKD (5, 6). Thus when providing an owner with a prognosis it would be fair to say that half of the patients will be discharged from the hospital, and of those half will recover completely and half will sustain CKD at variable degrees.

OUTCOME OF SPECIFIC COMMON ETIOLOGIES

Although the overall mortality of patients with AKI is around 50%, it is highly dependent on the inciting cause. It has been shown that different etiologies convey different prognoses. Hence, identifying the etiology is the first most important step, not only for managing patients with AKI, but also for determining the prognosis.

Leptospirosis is usually associated with a reversible injury and high survival rates, even when the injury is severe enough to necessitate dialytic intervention. Most studies of dogs with AKI due to leptospirosis report survival rates close to 80% (10-14). In a recent study, only 3 of 56 dogs diagnosed with leptospirosis, and managed with hemodialysis, died or were euthanized due to lack of renal improvement (15). These data suggest that the vast majority of patients with AKI due to leptospirosis sustain a reversible injury. Therefore, if these patients can be managed successfully for a sufficient period of time, the kidneys will eventually recover in most of the cases. Nonetheless some patients with leptospirosis may not survive due to complications of the disease, which are not related directly to uremia *per se*. It has been shown that patients with leptospirosis that have respiratory involvement are at a higher risk of death, compared to patients that do not have respiratory involvement [odds ratio, 5.23 (1.13-24.07), $P<0.05$] (15). It has also been suggested that the infecting serogroup may play a role in the severity of the disease and the outcome (11). In this study, infection with *Leptospira* serogroup *pomona* caused more severe renal disease, and was associated with a worse outcome compared with disease caused by other serogroups (11).

Pyelonephritis is another potential cause for AKI. To date, there is a limited amount of data regarding the prognosis of dogs and cats with pyelonephritis. Based on the current data, pyelonephritis is another etiology that is associated with a favorable outcome, as the underlying cause can be eliminated, based on culture and sensitivity results, and the injury is potentially reversible. In a study of cats with AKI managed with hemodialysis, the survival rate of cats with pyelonephritis was 100% compared to an overall survival rate of 40% (8), but in another study, the survival rate of 7 cats with pyelonephritis and severe uremia, management with hemodialysis was only 58% (9). Obviously more data are required before the prognosis of pyelonephritis can be determined more accurately.

Nephrotoxicity is a common cause of AKI in companion animals, and the prognosis is highly dependent on the type of injury. Toxins that induce ischemia (e.g., NSAIDs, angiotensin converting enzyme inhibitors) usually cause reversible injury whereas toxins that cause a direct kidney damage may induce irreversible injury (14). Ethylene glycol, for example, has a poor outcome once AKI has been established, even when dialytic intervention is employed (3, 16). The prognosis of ethylene glycol intoxication is favorable only when treatment is initiated before the ethylene glycol has been metabolized to its nephrotoxic metabolites.

Grapes and raisins ingestion is a recently recognized cause of AKI (17, 18). Grapes and raisin toxicity may result in degeneration and/or necrosis of proximal renal tubules. Recovery has been reported to occur in approximately half of the patients with grapes and raising toxicity (17, 18). Few risk factors for mortality have been identified in this intoxication, and can aid in prognostic projections. These include decreased urine output, ataxia, weakness, high initial and peak total calcium concentration, as well as initial and peak Ca x P product (17).

Lily toxicity is another severe and often irreversible intoxication in cats, resulting in a high mortality rate and residual kidney damage in the survivors. In a report of 6 cats with lily intoxication, 2 of which were managed with hemodialysis, the survival rate was 50%. Moreover, all the cats that survived sustained CKD (19). Nevertheless complete clinical recovery following lily ingestion and severe AKI has been described in a cat managed with hemodialysis (20). Thus, despite the severe injury, owners should not be discouraged from perusing medical care.

Ureteral obstruction has become one of the most common causes of acute uremia in cats in North America (9), and its prevalence is likely increasing worldwide. The pathophysiology of naturally occurring ureteral obstruction is not well documented. Intraluminal obstruction is the most common cause for ureteral obstruction in dogs and cats. It is usually caused by ureteral calculi, which are, in cats, almost exclusively composed of calcium oxalate (21). Most cats with ureteral obstruction present for medical care when the disease is advanced and both kidneys are affected. Ureteral obstruction may lead to a rapid accumulation of uremic toxins and progressive renal damage. The severity of azotemia present in most cats with ureteral obstruction attests for a compromised contralateral kidney, which in many cases was previously obstructed and underwent chronic changes and progressive decline in kidney function. Management of ureteral obstruction is challenging, often necessitates advanced diagnostic and therapeutic modalities, and special surgical skills. With all these present the survival rate of cats with aggressive medical and surgical intervention are as high as 75% (22.). Nonetheless, the majority of survivors sustain chronic kidney damage (22). In facilities that do not have access to advanced diagnostics (e.g., CT) and therapeutic (e.g., hemodialysis) options, such a high survival rate cannot be expected.

Acute kidney injury is also a potential complication of hospitalized patients. In a study of hospital acquired renal failure in dogs the most common etiology was exposure to a nephrotoxicant (23). In this study old dogs were more prone to develop hospital acquired renal failure. The overall survival rate in this study was only 38%, suggesting that hospital acquired renal failure is associated with an unfavorable outcome. Risk factors for mortality in this study included old age, initial low urine output, initial high anion gap, and high serum phosphorus concentration (23).

OUTCOME PREDICTION

Although the etiology is a major determinant of the prognosis, it is often unknown at presentation and remains unknown in a substantial portion of patients throughout the course of the disease, thus often cannot facilitate prognostic projections (4). On the basis of limited studies, risk factors for mortality have been identified, including the degree of azotemia, hypocalcemia, hyperkalemia, anemia, proteinuria, hyperphosphatemia, decreased urine production, increased anion gap, presence of disseminated intravascular coagulation, and respiratory and neurological involvement (24). In one study, dogs that survived in the hospital for more than 5 days were more likely to recover and to be discharged from the hospital (5). The most consistent negative prognostic indicator among the different studies is decreased urine output. In anuric and oliguric patients accumulation of uremic toxins is likely more rapid, and thus the consequences of the uremia are more pronounced. Urine production may also be a marker of the severity of the injury and the likelihood for recovery. Counterintuitive, the degree of azotemia, which also attests for the severity of the injury, is not a consistent negative prognostic indicator, especially in patients that are managed with hemodialysis (4, 8). In the latter, death due to acute uremia is prevented by the use of dialysis, and the main determinate of the prognosis is the reversibility of the damage.

Presence of risk factors for mortality can probably aid in the overall assessment. A patient that presents with many of the negative risk factors is less likely to survive compared to a patient that does not present any of the risk factors. Nevertheless, presence or absence of prognostic indicators cannot be translated to an accurate prognosis. Therefore, there is a need for additional tools that can aid clinicians to provide owners of dogs and cats with AKI a more accurate prognosis.

Since the early 1980s a number of scoring systems have evolved in human medicine to forecast outcome for emergency and critical care patients. Many of the scoring system are merely based on expert opinions, who decide which variables should be included in such scoring systems. Conversely, other scoring systems are more statistically based, and include only variables that were shown statistically to be associated with the outcome. Typically, in these scoring systems, variables are selected, and a score is assigned for each deviation from the reference range, for each one of the selected variables. Once the scoring system is completed, it can be used to assess the severity of a disease and the outcome associated with it. To do so, values of a specific patient are compared to the ranges that were established for each one of the variables included in the scoring system, and subsequently a score is assigned for each one of the variables. Finally all the scores assigned for all the variables are summed to a final predictive score for the patient. One of the most common scoring systems developed for human patients is the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE), which underwent few modifications during the years (25-27). Similar scoring systems have been developed in veterinary medicine, to assess trauma, critically ill, and surgery patients (28-30). Recently, a scoring system was developed to aid in outcome prediction for dogs with AKI that are managed with hemodialysis, (4) and a similar scoring system is under development for cats. The scoring system for dogs was based on statistical analysis of 182 dogs managed with hemodialysis in the University of California, Davis. Causes for AKI of dogs in this study included leptospirosis (56 dogs), ethylene glycol intoxication (50 dogs), hemodynamic (18 dogs), and toxicoses other than ethylene glycol (e.g., NSAID) (11 dogs). The remaining 47 dogs had different (n=7) or uncharacterized etiologies (n=40) (4).

In the development of this scoring system, variables available at presentation were screened initially for a possible relationship with survival. It was important to incorporate those variables that are routinely available during the initial first 24 hours from presentation, so the scoring system could be used early in the course of the disease, when clinical decisions need to be taken. In the second stage continuous variables identified to be detrimental for survival based on the initial analysis were partitioned into normal and abnormal ranges. The abnormal range for each variable was further partitioned into quartiles (which represent the degree of deviation from the reference range). Additional analysis was then performed to yield odds ratio for survival for each one of the quartiles. The odds ratio were used to assign a score for each quartile (4).

In order to assess the models' performance a final predictive score was calculated for each one of the dogs in the study as follows: the clinical value of each dog was compared to each variable ranges, for score assignment for the variable. Scores for all variables were summed to produce a final predictive score for each dog. Logistic regression was then used to assess the accuracy of each model's relationship to the probability of survival 30 day post discharge. Receiver operating curve (ROC) analysis was performed to determine sensitivities and specificities for outcome prediction for different cutoff scores. The optimal cutoff score was chosen as the score that produced the least number of misclassification

The overall mortality rate for dogs with AKI in this study was 53% (4). Four models were generated. In some of the models the etiologies are assumed to be unknown at presentation, but in others additional variables were added for the etiology, when the latter is known, to increase accuracy and decreased the number of misclassifications. Thus, these models can be used both for patients in which the etiology in known, and for patients in which the etiology is unknown at presentation.

In this study, dogs with higher predictive scores had a decreased probability of survival. A ROC analysis was performed for each one of the models to select a cutoff score below which AKI patients will be predicted to survive, and above which not to survive. The areas under the ROC curve, which is a measurement of the accuracy of the models, ranged in this study from 0.88-0.91 (4). In general an area under an ROC curve <0.5 is considered non-predictive, while area under the ROC curve around 0.75 is considered to be moderately predictive, and an area under the ROC curve of >0.9 is considered to be highly predicative. It thus can be seen that the aforementioned models have a relatively high area under the curve, and can potentially aid in outcome prediction of dogs with AKI.

For each model an optimal cutoff score, which is the score associated with the least number of misclassifications, was selected. The optimal cutoff score, of the best performing model, yielded sensitivity and specificity for outcome prediction of 83% and 90%. Using these models and the optimal cutoff score correctly classified 85-90% of dogs as survivor or non-survivors (4).

The scoring systems developed also permit flexibility of clinician preference to either maximize sensitivity or specificity through individualized selection of cutoff scores. Increasing the cutoff score will result in higher sensitivity and lower specificity, whereas decreasing the cutoff point will lower sensitivity but raise specificity of the prediction. By increasing the cutoff score more patients with the actual outcome of survival would be classified correctly by the models (lower false negative); however, more dogs with the actual outcome of not surviving will be erroneously predicted to survive by the model (higher false positive) (4). Conversely, by decreasing the cutoff score, more patients with the actual outcome of survival will be predicted to not survive (higher false negative); but, more dogs with the actual outcome of not surviving will be correctly classified (fewer false positive) (4). Specific cutoff score also can be used to establish a "gray zone" for scores in which predictions will not be made due to the risk of misclassification. Only scores outside the "grey zone" are accepted to maximize sensitivity or specificity (4). This approach is also accepted in other diagnostic tests.

It is expected that such scoring systems will perform superiorly in dogs with acute uremia compared to cats with acute uremia. While all dogs in the aforementioned study had acute intrinsic kidney injury due to various etiologies, the most common etiology in cats with acute uremia is ureteral obstruction. As previously described, these cats sustain variable degrees of previous kidney damage of the obstructed and the contralateral kidney. Thus, this patient population represents a more heterogeneous group of patients with variable underlying CKD and therefore is more difficult for prediction.

Another use of scoring systems as presented here is the ability to objectively compare and classify the severity of a disease among different patient populations. Severity classification would facilitate comparison of reported outcomes in clinical trials with multiple patient groups or between centers. For example, if two medical centers compare the mortality rate of AKI patients in order to assess the usefulness of a therapeutic intervention, differences in baseline characteristics of the patients may account for at least some of the differences in mortality between the centers. Scoring system can accurately and objectively compare the two populations, to assure that both have the same disease severity, and thus to allow reliable conclusions to be drawn.

LIMITATION OF SCORING SYSTEMS

Scoring systems have limitations and should be used with caution. They main limitation of the scoring system described in this review is that the accuracy of the models was assessed in the same patients used to generate the models. Developing and testing the model on the same group of patients might have resulted in overestimation of the true performance of the models. It would be ideal to develop the models on half of the patients and to determine their accuracy on the other half. However this approach would have resulted in a significant decrease in the power of the statistical analysis, and the ability to correctly identify variables for the models, and determining the scores assigned to each deviation from the reference range. Therefore, the models need to be prospectively validated in independent group of dogs with AKI and managed with hemodialysis, before their true accuracy can be assessed. It is also difficult to speculate if these scoring system, which has been tailored for dogs requiring hemodialysis, can be applied reliably to dogs with less severe AKI that do not require hemodialysis for their management. Thus models should be validated for this purpose as well.

It is also important to emphasize that no model can ever replace proper clinical assessment or should serve as a sole prognostic tool. Models should be applied judiciously and with caution in the individual patient, and should be viewed as an additional diagnostic tool.

SUMMARY

Acute kidney injury is associated with high morbidity and mortality. Early intervention and close attention to all organs involved in the disease are essential for a favorable outcome. The overall survival rate of dogs and cats with AKI is close to 50%. Of the survivors, around 50% recover completely and 50% sustain variable degrees of chronic CKD. The etiology is a major determinant of the prognosis; some are associated with a good outcome and others with poor outcome. Scoring systems can objectively assess the severity of the disease and have the potential to assess the outcome, but they should be used with caution.

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