Grading of acute kidney injury (2016)

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Acute kidney disease represents a spectrum of disease associated with a sudden onset of renal parenchymal injury most typically characterized by generalized failure of the kidneys to meet the excretory, metabolic, and endocrine demands of the body,

i.e. acute renal failure (ARF). Acute kidney disease typically is recognized clinically by its advanced and most overt manifestations, ARF. This convention and practice has relegated this syndrome to one of reactive rather than proactive intervention.

Acute renal failure is characterized by rapid hemodynamic, filtration, tubulointerstitial, or outflow injury to the kidneys and subsequent accumulation of metabolic toxins (uremia toxins) and dysregulation of fluid, electrolyte, and acid-base balance. However, ARF reflects only a subset of patients with kidney injury who have the highest morbidity and mortality (Figure 1). The term "acute kidney injury" (AKI) has been adopted in human medicine to better reflect the broad spectrum of acute diseases

of the kidney and to reinforce the concept that AKI encompasses a continuum of functional and parenchymal damage from its least to its most severe manifestations. Kidney injury may be imperceptible clinically at early stages and culminate with the requirement for renal replacement therapy (RRT, various forms of dialysis or renal transplantation) with the onset of overt failure of kidney function or death.
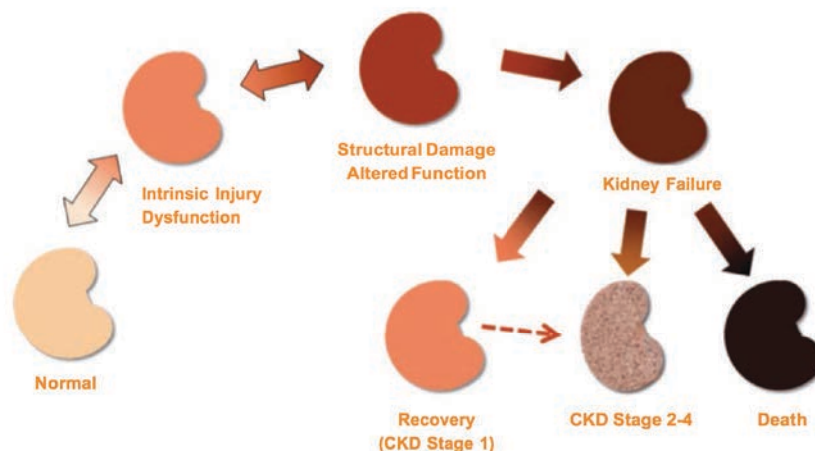
Figure 1 *Schematic illustration of the spectrum of acute kidney injury (AKI) from early kidney injury/dysfunction to kidney failure. Acute kidney failure is the most recognizable presentation of AKI, but identification of earlier stages of injury are critical for timely diagnosis and to facilitate more effective management.*

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The clinical presentation of AKI includes prerenal and postrenal conditions which may be independent or combined with intrinsic renal injury depending on the functional origin, extent, and duration of the conditions inciting the disease. Animal patients most often are recognized with an acute uremia which must be differentiated subsequently into its prerenal, intrinsic renal parenchymal, and/or postrenal components for proper diagnostic evaluation, management, and grading. Acute kidney injury typically affects intrinsically normal kidneys, but events predisposing
to AKI frequently are superimposed on preexisting chronic kidney disease (CKD) to produce a seemingly ¬acute uremia with similar clinical features. Currently, there are no markers to define or stratify the conditions that constitute AKI, although some discrete biomarkers are showing promise. Precise definitions for AKI have not been established in veterinary medicine. There also is no formal categorization of the spectrum of the functional deficiencies to standardize its classification, severity, grade, clinical course, response to therapy, or prognosis for recovery.

To better emphasize the concept that AKI represents a continuum of renal injury, three classification schemes (RIFLE, AKIN and KDIGO) have been proposed for human patients to stratify the extent and duration of renal injury and predict clinical outcomes. There is considerable overlap and integration between these classification systems, and criteria for each category are based ostensibly on insensitive markers of renal injury including abrupt changes in glomerular filtration rate (GFR), blood creatinine, urine output, and duration of signs. Unfortunately, the criteria which define these classification schemes in human patients are not as consistently applicable in animal patients with naturally occurring disease. In human medicine, AKI is a condition that manifests typically within the hospital setting. In animals, by contrast, AKI most commonly develops outside of the hospital setting and, as a consequence, the abruptness of the disease and the magnitude of changes in GFR, azotemia, and/or urine production are rarely known or quantitated.

The IRIS staging system for CKD was developed as a consensus scheme to promote more uniform characterization and recognition of CKD in animals with goals to promote understanding of its pathophysiology and to better facilitate its evaluation and rational management. IRIS has adapted this same schematic approach to classify and grade the severity of AKI in dogs and cat. Unlike IRIS staging for CKD, grading of AKI would not imply the kidney disease is stable or at steady-state.
On the contrary, the "grade" represents a moment in the course of the disease and is predicted to change as the condition worsens, improves, or transitions to CKD as illustrated schematically in Figure 1. Table 1 outlines the proposed IRIS AKI grading scheme for dogs and cats based on blood creatinine, urine formation, and the requirement for RRT which is intended to facilitate classification, functional stratification, and therapeutic decision making (Table 1).

IRIS AKI Grade I defines non azotemic animals with historical, clinical, laboratory (biomarkers such as: SDMA, glucosuria, cylinduria, proteinuria, inflammatory sediment, microalbuminuria, etc.), imaging evidence of AKI, and/or those with clinical oliguria/ anuria. IRIS AKI Grade I includes animals with progressive (hourly or daily) increases in blood creatinine of ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within the nonazotemic range during a 48 h interval. IRIS AKI Grade I also includes animals whose decreased urine production is readily fluid volume-responsive. Fluid volume responsiveness represents an increase in urine production to >1 ml/kg/h within 6 h; and/or decrease in blood creatinine to baseline over 48 h.

IRIS AKI Grade II defines animals with documented AKI characterized by mild azotemia in addition to other historical, biochemical, anatomic, or urine production characteristics of AKI (as above for Grade I), and similarly includes those whose oliguria and/or azotemia is readily fluid volume responsive. Fluid volume responsive represents an increase in urine production to >1 ml/kg/h within 6 h; and/or decrease in blood creatinine to baseline over 48 h. IRIS AKI Grade II also includes animals that have an increase from their baseline creatinine concentration of ≥ 0.3mg/dl (≥ 26.4 µmol/l) during a 48 h interval associated with pre-existing CKD (see Table 1).

IRIS AKI Grades III, IV, and V define animals with documented AKI and progressively greater degrees of parenchymal damage and functional failure (uremia).

Each grade of AKI is further subgraded on the basis of current urine production as oligoanuric (O; oliguria, <1 ml/kg/h, or anuria, no urine produced, over 6 h) or nonoliguric (NO; >1 ml/kg/h), and on the requirement for RRT. The inclusion of subgrading by urine production is based on the importance of the interrelationship of urine production to the pathological or functional contributions to the kidney injury and its influence on the clinical presentation, therapeutic options, and outcome of AKI. Subgrading on the requirement for RRT is established on the need to correct life-threatening iatrogenic or clinical consequences of AKI including severe azotemia, hyperkalemia, acid-base disorders, overhydration, oliguria or anuria, or the need to eliminate nephrotoxins. The requirement for RRT could occur at any AKI grade. Subgrading based on the requirement for RRT has similar clinical, therapeutic, and prognostic implications as for urine production to categorize the severity of the renal injury as well as its influence on outcome.

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Table 1: IRIS AKI Grading Criteria

AKI Grade	Blood Creatinine	Clinical Description
Grade I	<1.6 mg/dl (<140 µmol/l)	Nonazotemic AKI: a. Documented AKI: (historical, clinical, laboratory, or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness‡) and/or b. Progressive nonazotemic increase in blood creatinine: ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within 48 h c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	Mild AKI: a. Documented AKI and static or progressive azotemia b. Progressive azotemic: increase in blood creatinine; ≥ 0.3 mg/dl ≥ 26.4 µmol/l) within 48 h),or volume responsiveness‡ c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade III	2.6 – 5.0 mg/dl (221 – 439µmol/l)	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	
Grade V	>10.0 mg/dl (>880 µmol/l)	

(‡Volume responsive is an increase in urine production to >1 ml/kg/h over 6 h; and/or decrease in serum creatinine to baseline over 48 h)

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Table 2: IRIS AKI Subgrading

AKI Grade	Blood Creatinine	Subgrade
Grade I	<1.6 mg/dl (<140 µmol/l)	Each grade of AKI is further subgraded as:
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	1. Non oliguric (NO) or oligo-anuric (O) 2. Requiring renal replacement therapy (RRT)
Grade III	2.6 – 5.0 mg/dl (221 – 439µmol/l)	
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	
Grade V	>10.0 mg/dl (>880 µmol/l)	

Just as IRIS staging for CKD has facilitated consistency of recognition and categorization of the management and outcome predictions for CKD, IRIS grading for AKI provides an instrument for the earlier recognition, therapeutic stratification, and outcomes assessment of AKI in dogs and cats. Animals recognized and managed with IRIS AKI Grades I and II may regain adequate renal function within 2 to 5 days, forestalling life-threatening azotemia and electrolyte disorders and usually needing only short-term support. Those with higher IRIS AKI grades at presentation, or whose grade progresses during hospitalization, may require weeks of supportive care before the onset of renal repair. Animals with severe kidney failure, IRIS AKI Grade IV or V, may die within 5 to 10 days despite appropriate conventional management unless supported with RRT for an indefinite time. This disparity between the window of survival with conventional supportive therapy and the extended time required to repair severe AKI underlies, in part, the poor prognosis and outcomes associated with severe stages of AKI.

Table 3: Illustration of IRIS AKI Grading During Hospitalization*

	Day 1	Day 2	Day 3	Day 4	Day 5
Patient 1	0.9	1.5	1.5	1.5	1.7
Patient 2	2.3 CKD	2.5 CKD	2.7	3.5	2.4
Patient 3	5.3	5.2	3.6	2.4	1.6
Patient 4	4.8	5.8	6.9	10.8	RRT
Patient 5	18.2	RRT	RRT	RRT	RRT

● Non AKI ● AKI Grade I ● AKI Grade II ● AKI Grade III ● AKI Grade IV ● AKI Grade V

*Blood creatinine in mg/dl, RRT: renal replacement therapy

Table 3, above, illustrates the use and concept of IRIS AKI grading in 5 hypothetical patients at presentation and during 5 subsequent dadays of hospitalization.

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Patient 1 illustrates a animal admitted to the hospital for an acute history of anorexia and vomiting. On Day 1 (the first day of presentation) the patient has no evidence of renal dysfunction. However, on Day 2, the blood creatinine concentration has increased even though it remains within the reference range, and it is clear the patient has an AKI and a diagnosis of IRIS AKI Grade I is established, prompting heightened therapeutic attention and monitoring. The patient remains at IRIS AKI Grade I for the next 2 days, but on Day 5 the classification is revised to IRIS AKI Grade II, indicating worsening of the renal injury.

Patient 2 is an 8 year old cat with a history of renal pelvic and ureteral stones and an earlier diagnosis of IRIS CKD Stage 2. Now the cat presents with an acute illness characterized by depression, lethargy, and anorexia. At presentation the azotemia is at historical levels but is noted to be increased by 0.2 mg/dl on Day 2. On Day 3, however, the creatinine has increased by 0.4 mg/dl from the baseline (within 48 hours) and now prompts a diagnosis of IRIS AKI Grade III on pre-existing CKD. Despite therapy, on Day 4, the AKI has worsened although the cat remains within Grade III. Sequential updating of the AKI grade documents the clinical course and severity of the kidney injury in a systematic manner that can be universally interpreted by attending colleagues or consultants. On Day 5 the AKI grading is updated to IRIS AKI Grade II predicting the therapy has started to work and the kidney injury is improving.

Patient 3 is a 9 year old cat with no previous history of illness, but presented to the hospital with an acute onset of depression, lethargy, anorexia, fever, and large painful kidneys on abdominal palpation. Based on the clinical and laboratory findings (azotemia, bacteriuria) and results of abdominal ultrasonography that revealed mild pelvic dilation, a diagnosis of IRIS AKI Grade IV secondary to pyelonephritis is made, and the cat is started on antimicrobial therapy and fluids. Daily re-grading of this patient revealed a progressive lowering of the AKI grade on Days 3 through 5, categorizing the progressive improvement in the kidney injury.

Patient 4 is a 4 year old Cocker Spaniel who presented to the emergency service for a 3 day history of acute depression, anorexia, and vomiting. The history reveals he has been treated for 16 days with daily subcutaneous injections of amikacin for the management of an antibiotic resistant pyoderma. Based on clinical findings and laboratory evaluation, a diagnosis of IRIS AKI Grade III (O) is established and the dog is started on conventional medical therapy. Despite the therapy, the azotemia progressed during hospitalization. On Days 2 and 3, the condition is updated to IRIS AKI Grade IV suggesting progressive and worsening kidney injury and lack of responsiveness to conventional therapy. On Days 4 and 5 the grading is adjusted further, and on Day 5 to IRIS AKI Grade V (O, RRT) indicating the decision to institute hemodialysis.

Patient 5 is a 3 year old Domestic Short Haired cat who presented with a 4 day history of anorexia, depression, vomiting, and no notable urine production. The owners of the cat celebrated an anniversary 5 days previously with the introduction of several bouquets of flowers (including lilies) to which they insist the cat could not have had access. On the basis of this information and laboratory

and imaging (abdominal radiographs and ultrasound) findings, a diagnosis of AKI was established. The condition was graded as IRIS AKI Grade V (O). On Day 2 the cat was started on hemodialysis and the classification was updated to IRIS AKI Grade V (O, RRT) for the following 4 hospital days based on pre-dialysis creatinine concentration and urine production. After the initial 5 days of hospitalization shown, the cat remained dialysis-dependent at IRIS AKI Grade V for 3 weeks before the kidney injury repaired, and he was subsequently discharged with an uneventful recovery at IRIS CKD Stage 1.

Figure 2 illustrates the use of progressive IRIS AKI grading in a canine patient treated with gentamicin for approximately 15 days. IRIS AKI Grade I (NO) was defined for the first 15 days based on the history of gentamicin administration and progressively decreasing urine specific gravity. The subsequent updated assessments were based on the serial changes in blood creatinine measurements and portray the progressive worsening and recovery of the kidney injury
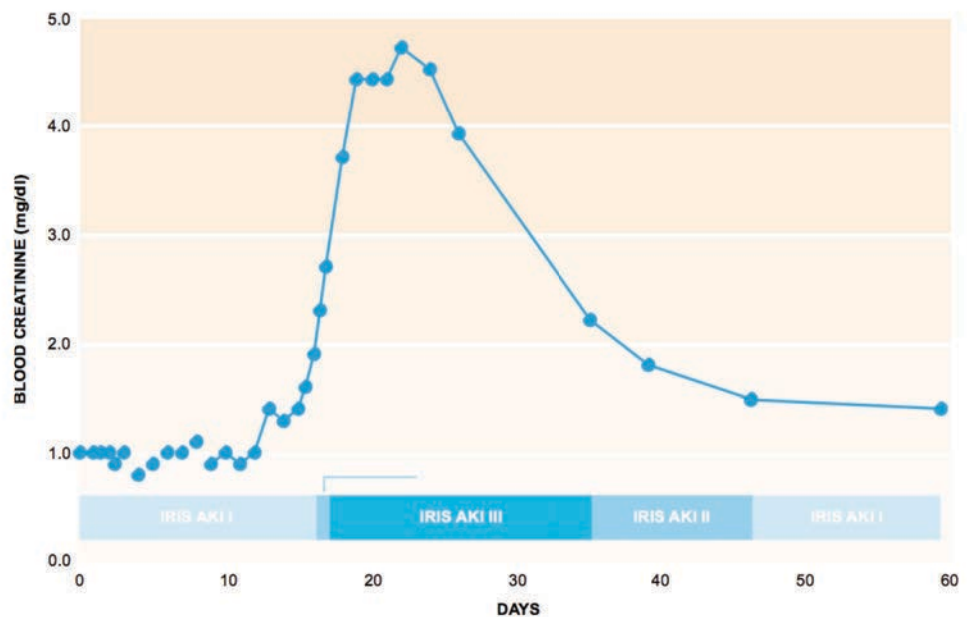
Figure 2. Serial changes in blood creatinine concentration and IRIS AKI grading in a dog with gentamicin-induced AKI. The IRIS AKI grading effectively categorized the sequential course of the AKI from inapparent to failure and subsequent recovery. Shaded area reflects the reference range for blood creatinine. (Patient information courtesy of Dr. Carrie Palm, UC Davis)

As has been demonstrated in human nephrology, AKI classification has the potential to better discriminate the pathophysiologic and therapeutic spectrum of AKI. It, very importantly, has the potential to sensitize clinical evaluation of patients to promote earlier recognition of AKI. Like IRIS staging of CKD, grading of AKI should enhance comparative assessment of clinical status and therapeutic strategies. Finally, AKI grading (in conjunction with scoring strategies for AKI) hopefully will promote more realistic prediction of outcomes in affected patients. In the longer term, it may facilitate accumulation and analysis of prognosis and treatment outcomes for AKI in dogs and cats.

Selected Reading

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