1. Staging of CKD based on blood creatinine concentration

Staging is undertaken following diagnosis of chronic kidney disease (CKD) in order to facilitate appropriate treatment and monitoring of the patient.

Staging is based initially on fasting blood creatinine concentration, assessed on at least two occasions in the stable patient. The patient is then substaged based on proteinuria and blood pressure.

Separate but related algorithms for staging and substaging CKD in cats and dogs are available on pages 6 - 9 of this document.

Using these criteria, some empirical recommendations can be made about the type of treatment it would be logical to use for these cases. In addition, predictions based on clinical experience might be made about the likely response to treatment.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Blood creatinine µmol/l mg/dl</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dogs</strong></td>
<td><strong>Cats</strong></td>
<td></td>
</tr>
<tr>
<td>At risk</td>
<td>&lt;125 &lt;1.4</td>
<td>&lt;140 &lt;1.6</td>
</tr>
<tr>
<td>1</td>
<td>&lt;125 &lt;1.4</td>
<td>&lt;140 &lt;1.6</td>
</tr>
<tr>
<td>2</td>
<td>125 – 180 1.4 – 2.0</td>
<td>140 – 250 1.6 – 2.8</td>
</tr>
<tr>
<td>3</td>
<td>181 – 440 2.1 – 5.0</td>
<td>251 – 440 2.9 – 5.0</td>
</tr>
<tr>
<td>4</td>
<td>&gt;440 &gt;5.0</td>
<td>&gt;440 &gt;5.0</td>
</tr>
</tbody>
</table>

Note these blood creatinine concentrations apply to average size dogs – those of extreme size may vary.
Symmetric dimethylarginine (SDMA) and IRIS CKD guidelines

IRIS CKD staging is based currently on fasting blood creatinine concentrations, but there are indications that SDMA concentrations in blood plasma or serum may be a more sensitive biomarker of renal function. Accordingly, if blood SDMA concentrations are known, some modification to the guidelines might be considered, as follows:

A persistent increase in SDMA above 14 µg/dl suggests reduced renal function and may be a reason to consider a dog or cat with creatinine values <1.4 or <1.6 mg/dl, respectively, as IRIS CKD Stage 1.

In IRIS CKD Stage 2 patients with low body condition scores, SDMA ≥25 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 3 for this patient.

In IRIS CKD Stage 3 patients with low body condition scores, SDMA ≥45 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 4 for this patient.

These comments are preliminary and based on early data from the use of SDMA in veterinary patients. We expect them to be updated as the veterinary profession gains further experience using SDMA alongside creatinine, the long-established marker in diagnosis and monitoring of canine and feline CKD.
2a. Substaging by Proteinuria

The goal is to identify renal proteinuria having ruled out post-renal and pre-renal causes.

Standard urine dipsticks can give rise to false positives therefore practitioners should consider using a more specific screening test such as the sulphosalicylic acid turbidometric test.

The urine protein to creatinine ratio (UP/C) should be measured in all cases, provided there is no evidence of urinary tract inflammation or hemorrhage and the routine measurement of plasma proteins has ruled out dysproteinemias. Ideally staging should be done on the basis of at least two urine samples collected over a period of at least 2 weeks.

<table>
<thead>
<tr>
<th>UP/C value</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>0.2 to 0.5</td>
<td>0.2 to 0.4</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>&gt;0.4</td>
</tr>
</tbody>
</table>

Patients that are persistently borderline proteinuric should be re-evaluated within 2 months and re-classified as appropriate.

UP/Cs in the non-proteinuric or borderline proteinuric range may be categorized as ‘microalbuminuric’. The significance of microalbuminuria in predicting future renal health is not understood at present. IRIS’ recommendation is to continue to monitor this level of proteinuria.

Proteinuria may decline as renal dysfunction worsens and so may be less frequent in animals in Stages 3 and 4.

Response to any treatment given to reduce glomerular hypertension, filtration pressure, and proteinuria, should be monitored at intervals using UP/C.
2b. Substaging by Arterial Blood Pressure

Patients should be acclimatized to the measurement conditions and multiple measurements taken. The final classification should rely upon multiple systolic blood pressure determinations, preferably done during repeated patient visits to the clinic on separate days, but acceptable if during the same visit with at least 2 hours separating determinations. Patients are substaged by systolic blood pressure according to the degree of risk of target organ damage, and whether there is evidence of target organ damage or complications.

For most dogs, the IRIS blood pressure substages are as follows:

<table>
<thead>
<tr>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Blood Pressure Substage</th>
<th>Risk of Future Target Organ Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normotensive</td>
<td>Minimal</td>
</tr>
<tr>
<td>150 – 159</td>
<td>Borderline hypertensive</td>
<td>Low</td>
</tr>
<tr>
<td>160 – 179</td>
<td>Hypertensive</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥ 180</td>
<td>Severely hypertensive</td>
<td>High</td>
</tr>
</tbody>
</table>

However, some breeds, particularly sight hounds, tend to have higher blood pressure than other breeds. It is preferable to use breed-specific reference ranges if available. The classification of risk of future target organ damage in “high-pressure breeds” might be adjusted as follows:

- **Minimal risk** – systolic pressure <10 mm Hg above the breed-specific reference range
- **Low risk** – systolic pressure 10-20 mm Hg above the breed-specific reference range
- **Moderate risk** – systolic pressure 20-40 mm Hg above the breed-specific reference range
- **High risk** – systolic pressure >40 mm Hg above the breed-specific reference range.

As with proteinuria, in the absence of evidence of existing target organ damage, demonstration of persistence of blood pressure readings within a particular category is important. ‘Persistence’ of increase here should be judged on multiple measurements made over the following timescales in these blood pressure substages:

- **Hypertensive** – systolic blood pressure 160 to 179 mm Hg measured over 1 to 2 months
- **Severely hypertensive** – systolic blood pressure ≥180 mm Hg measured over 1 to 2 weeks.
3. Revision of staging and substaging after treatment

The stage and substages assigned to the patient should be revised appropriately as changes occur. For example, a substantial increase in blood creatinine concentration might warrant reassignment to a higher stage to reflect the new situation.

Similarly, if antihypertensive (or antiproteinuric) treatment has been instituted, the patient’s classification on re-evaluation should be adjusted if necessary to reflect the new blood pressure (or UP/C) rather than the original status, with the addition of an indication that the current classification is affected by treatment.

The following two examples illustrate the process of revision, where ‘treating’ is used as an indicator of ongoing treatment.

**Example 1**

Cat before treatment

Creatinine 200 µmol/l (2.3 mg/dl)

UP/C 0.3

Systolic blood pressure 200 mm Hg

Classification – *IRIS CKD Stage 2, borderline proteinuric, severely hypertensive.*

Same cat after antihypertensive treatment

Creatinine 300 µmol/l (3.4 mg/dl)

UP/C 0.3

Systolic blood pressure 155 mm Hg

New classification – *IRIS CKD Stage 3, borderline proteinuric, borderline hypertensive (treating).*

**Example 2**

Dog before treatment

Creatinine 160 µmol/l (1.8 mg/dl)

UP/C 0.8

Systolic blood pressure 155 mm Hg

Classification – *IRIS CKD Stage 2, proteinuric, borderline hypertensive.*

Same dog after antiproteinuric treatment

Creatinine 170 µmol/l (1.9 mg/dl)

UP/C 0.4

Systolic blood pressure 155 mm Hg

New classification – *IRIS CKD Stage 2, borderline proteinuric (treating), borderline hypertensive.*
History and/or physical examination suggest chronic kidney disease (CKD)

Measure blood creatinine

- Creatinine <125 µmol/l <1.4 mg/dl
  - Firm evidence of CKD present
  - Radiographs and ultrasound, UP/C, BP and urine culture
  - Institute management plan for Stage 1 patients
  - Re-evaluate in 2-3 months, then every 3 months if creatinine rising; every 3-6 months if creatinine stable

- Creatinine 125 – 180 µmol/l 1.4 – 2.0 mg/dl
  - Measure urine specific gravity
  - Clinical evaluation
  - If underlying systemic abnormalities, correct and re-evaluate within 6 months

- Creatinine >180 µmol/l >2.0 mg/dl
  - Measure urine specific gravity
  - Pre- or post-renal azotaemia

Stage 1
Substage by UP/C & BP

Radiographs and ultrasound, UP/C, BP and urine culture

Stage 3 or 4
Substage by UP/C & BP

Institute treatment

Correct underlying abnormalities and re-evaluate immediately

Stage 2
Substage by UP/C & BP

Normal: re-evaluate within 2 months
Abnormal: Clinical evaluation

Institute treatment
Algorithm for Staging of Chronic Kidney Disease in Cats

History and/or physical examination suggest chronic kidney disease (CKD)

Measure blood creatinine

- **Creatinine**
  - <140 µmol/l <1.6 mg/dl
  - 140 – 250 µmol/l 1.6 - 2.8 mg/dl
  - >250 µmol/l >2.8 mg/dl

- **Firm evidence of CKD present**
- **Firm evidence of CKD absent**

**Stage 1**

Substage by UP/C & BP

Radiographs and ultrasound, UP/C, BP and urine culture

Institute management plan for Stage 1 patients

Re-evaluate in 2-3 months, then every 3 months if creatinine rising, every 3-6 months if creatinine stable

Measure urine specific gravity

- <1.035
- ≥1.035

- Pre- or post-renal azotaemia
- Renal azotaemia

**Stage 3 or 4**

Substage by UP/C & BP

Institute treatment

Clinical evaluation

- Normal: re-evaluate within 2 months
- Abnormal: **Stage 2** Substage by UP/C & BP

If underlying systemic abnormalities, correct and re-evaluate within 6 months

Correct underlying abnormalities and re-evaluate immediately

If underlying systemic abnormalities, correct and re-evaluate within 6 months

© Eli Lilly and Company, its subsidiaries or affiliates. Elanco® and the diagonal bar are trademarks owned and licensed by Eli Lilly and Company, its subsidiaries or affiliates.
Algorithm for Substaging by Proteinuria

CKD diagnosed & staged 1-4
Urine dipstick examination

+ Questionable proteinuria;
  Urinalysis with sediment examination

- Non-proteinuric

Sediment abnormal/‘active’

Conduct further work-up (eg rule out lower urinary tract disease)

Sediment ‘inactive’/ unremarkable/ hyaline casts

Determine UP/C

Cat

UP/C <0.2
Non-proteinuric

UP/C 0.2 – 0.4*
Borderline proteinuric
Re-evaluate within 2 months

UP/C >0.4*
Proteinuric

UP/C >0.5*
Proteinuric

Dog

UP/C <0.2
Non-proteinuric

UP/C 0.2 – 0.5*
Borderline proteinuric
Re-evaluate within 2 months

* demonstrate persistence by re-evaluating:
  if Borderline Proteinuric, in 2 weeks to 2 months
  if Proteinuric, in 2 to 4 weeks
  If UP/C>2, no need to demonstrate persistence prior to initiating therapy (severe proteinuria)
Algorithm for Substaging by Blood Pressure
(risk of target organ damage from hypertension)

CKD diagnosed & staged 1-4
Measure blood pressure (BP)

- Systolic BP < 150 mm Hg
  (or <10 mm Hg above reference range for breed)
  - Minimal Risk
    of target organ damage

- Systolic BP 150-179 mm Hg
  (or 10-40 mm Hg above reference range for breed)
  - Clinical evaluation

- Systolic BP ≥ 180 mm Hg
  (or >40 mm Hg above reference range for breed)
  - Clinical evaluation

  - No extra-renal evidence of hypertension
    - Low to Moderate Risk
      of target organ damage
      Re-evaluate within 2 months
  
  - Extra-renal evidence of hypertension
    (retinopathy and/or left ventricular hypertrophy)
    - Low to Moderate Risk
      of target organ damage with complications

  - No extra-renal evidence of hypertension
    - High Risk
      of target organ damage
      Re-evaluate within 1-2 weeks

  - Extra-renal evidence of hypertension
    (retinopathy and/or left ventricular hypertrophy)
    - High Risk
      of target organ damage with complications