



All systems go? Or all systems no? How and why to use C-reactive protein in dogs.

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IDEXX Medical Education Specialist

IDEXX

What is CRP?

- Positive acute phase protein
- Produce mainly in liver in response to proinflammatory cytokines
- Increased in serum within 4 hours of onset of systemic inflammation in dogs
- Peaks 24-48 hr (up to 1000x increase)
- T1/2 18 hr
- Decreases within 18-24 hr of appropriate treatment
- Opsonizes pathogens, clears apoptotic cells, promotes leukocyte chemotaxis, phagocytosis, and release of inflammatory cytokines

CRP IS a very SENSITIVE marker for systemic inflammation in dogs.

It is NOT specific as to cause.

CRP has been evaluated in dogs with:

- Bacterial pneumonia
- Acute pancreatitis
- Immune-mediated disease
- Kidney disease
- Neurologic disease
- Musculoskeletal disease
- Gastrointestinal disease
- Cardiac disease
- Infectious disease (tick-borne, parvovirus, leptospirosis...)
- Sepsis, SIRS
- Pyometra
- Neoplasia

What if CRP is extremely high (>100 mg/L)?

- CRP in healthy dogs \approx 1-2 **mg/dL**
 - CRP >100 **mg/L** indicate 'high grade' inflammation
 - Seen in 12% with disease in variety of systems
 - Did not discriminate among disease categories
 - E.g., infectious vs inflammatory, bacterial vs nonbacterial
 - Alone does not justify antibiotic use
 - 3-month survival 63%
 - Single value >10 mg/dL not *definitive* prognostic marker
 - Indication for early aggressive therapy, diagnostic evaluation, monitoring
 - Conclusion:
 - Severe disease with guarded prognosis
- } Watch units!

Hindenberg S, Bauer N, Moritz A. Extremely high canine C-reactive protein concentrations > 100 mg/l – prevalence, etiology and prognostic significance. BMC Veterinary Research (2020) 16:147 <https://doi.org/10.1186/s12917-020-02367-7>



My right rear limb hurts all of a sudden. I can barely put any weight on it.

IDEXX

Lameness, joint pain, joint swelling

CRP increased

Vector-borne disease
Immune-mediated polyarthritis
Suppurative arthritis

CRP normal

Osteoarthritis
Cranial cruciate rupture

CRP with lameness, joint swelling, joint pain

- CRP normal with osteoarthritis, cranial cruciate rupture
- CRP increased with:
 - **Immune-mediated polyarthropathy**
 - Serial CRP to guide therapy and monitor for relapse vs serial joint taps
 - **Suppurative arthritis**
 - Differentiates from osteoarthritis
 - **Vector-borne disease**
 - *Babesia, Ehrlichia, Leishmania, Hepatozoon*
 - Increase indicates active, acute, more severe disease (myelosuppressive *E. canis*)
 - Subsequent increase after recovery from acute phase indicates emergence of chronic form
 - Normalizes with effective treatment
 - Aids interpreting serology, i.e., titers may remain positive months to years



I'm coughing.

IDEXX

Coughing, tachypnea, respiratory distress

CRP increased

Bacterial pneumonia

CRP normal

Chronic bronchitis
Pulmonary fibrosis
Cardiogenic pulmonary edema
Eosinophilic bronchopneumonopathy

C-reactive protein in pneumonia in dogs

- Diagnostic and monitoring biomarker in humans with pneumonia
- Increased in dogs with bacterial pneumonia (v noninfectious disorders)
- Guide for duration of antibiotic therapy
 - Radiographic resolution lags
 - Prolonged antibiotic use may not be necessary
 - CRP normalized before radiographs in dogs, shorter treatment may be effective¹
 - Treating for 5-7 days after CRP normal effective without increased relapse²



My back hurts.

IDEXX

Back pain, neck pain

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graph TD; A[Back pain, neck pain] --> B[CRP increased]; A --> C[CRP normal]; B --> D["Discospondylitis<br/>Steroid-responsive meningoencephalitis"]; C --> E[Intervertebral disc disease];
```

CRP increased

Discospondylitis
Steroid-responsive meningoencephalitis

CRP normal

Intervertebral disc disease

CRP with neck pain.

Is it steroid-responsive meningitis-arteritis?

- Young <2 yr medium to large breed dogs, no sex predilection
 - Resistance to relapse (16-60%) develops around 2 yr
- Beagles, Bernese Mountain dogs, Boxers, and others predisposed
- Waxing waning neck pain, fever, lethargy
- Prednis(ol)one monotherapy effective in most
- CRP significantly increased at presentation
- Near normal at remission of clinical signs (≈ 14 d)
- Normal at resolution (=4 wk after stopping therapy without recurrence of signs)

CRP with immune-mediated disease in general

- CRP increases in immune-mediated conditions regardless of type
 - **IMHA, ITP, IMPA, steroid-responsive meningoencephalitis**
 - No significant difference in CRP level among them
- No correlation between initial CRP and survival in IMHA
 - CRP 142 ug/mL (+/- 89 ug/mL) on admission in most
- Should normalize with effective treatment
- Subsequent increase in CRP as prednis(ol)one tapered indicates relapse

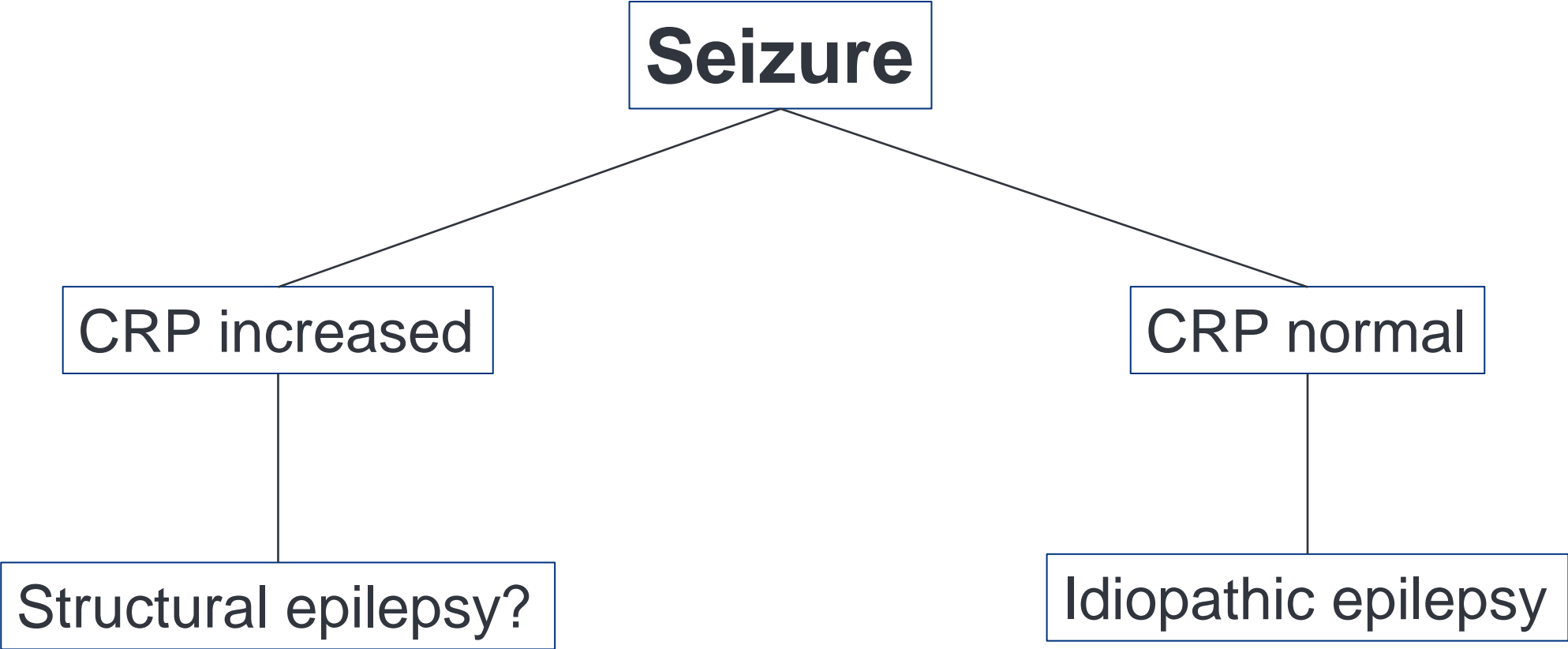
1 microgram/mL = 1 milligram/L

Malin, K.; Witkowska-Piłaszewicz, O. C-Reactive Protein as a Diagnostic Marker in Dogs: A Review. *Animals* 2022, 12, 2888. <https://doi.org/10.3390/ani12202888>



I just had a seizure and am a little dizzy.

IDEXX



CRP with epilepsy: idiopathic or structural?

- Epilepsy = 2 or more seizures at least 24 hours apart
- Idiopathic epilepsy diagnosis of exclusion
 - 6 mo – 6 yr of age, normal labs, normal interictal neurologic exam typical
- Structural epilepsy caused by intracranial pathology
 - Neoplasia, vascular, anomalous, degenerative, inflammatory
 - Advanced diagnostics (MRI, CSF tap) under anesthesia to diagnose
- Overlap in signalment and neurologic examination findings between IE and SE
- CRP higher with SE (8.9 mg/L, median) than IE (2.2 mg/L, median)
- Increased CRP with seizures increases likelihood of SE and need for referral...



I have a heart murmur and am tired.
Also, I've been coughing more.

IDEXX

Heart disease

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graph TD; A[Heart disease] --> B[CRP increased]; A --> C[CRP normal]; B --> D["Bacterial pneumonia concurrent<br/>Infective endocarditis<br/>Severe valvular disease"]; C --> E["No infectious complication<br/>Milder valvular disease"];
```

CRP increased

Bacterial pneumonia concurrent
Infective endocarditis
Severe valvular disease

CRP normal

No infectious complication
Milder valvular disease

CRP with cardiac disease

- Cardiovascular disease affects at least 11% canine population
 - Mitral valve disease most common heart disease and 3rd most common cause of death in dogs
- Acquired MVD
 - Myxomatous mitral valve degeneration
 - Infective endocarditis
- CRP significantly higher with IE than MMVD
- CRP correlated with MMVD Stage, significantly higher in Stage D
- Consider CRP to
 - Aid in diagnosis of IE
 - Differentiate MMVD from IE
 - Adjunct to determining severity of and monitoring treatment for MMVD
 - Determine if bacterial pneumonia is present in coughing dog with heart disease



My stomach hurts.

IDEXX

GI Disease

CRP increased

Acute pancreatitis
Parvoviral enteritis
Acute abdomen
Gallbladder mucocele leakage
Chronic inflammatory enteropathy
Protein-losing enteropathy

CRP normal

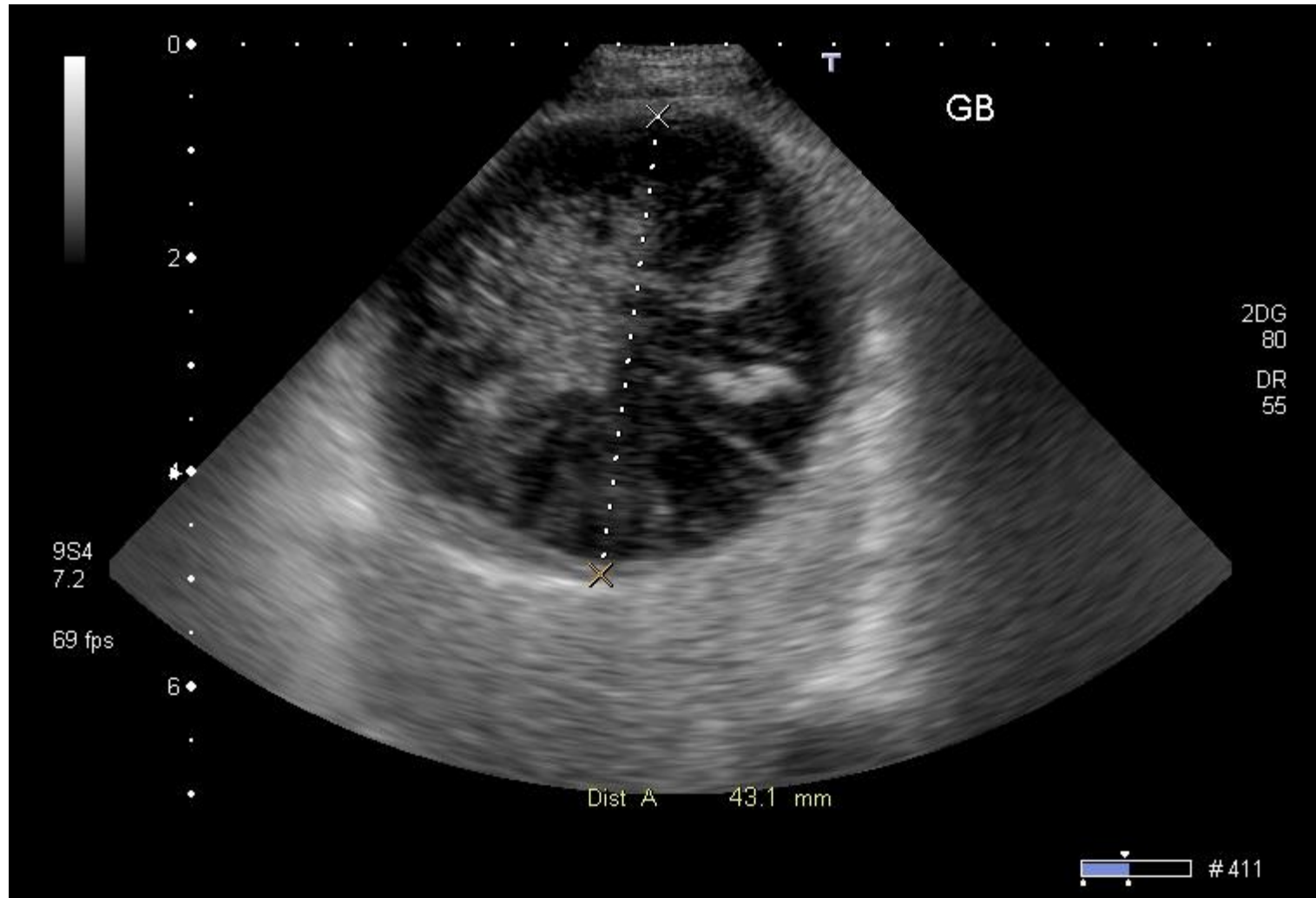
Milder, localized acute
or chronic disease

CRP in acute pancreatitis

- Not always increased (mild, subclinical)
- If increased at admission = more severe disease
- Higher in nonsurvivors than survivors in most studies
- Serial assessment important for monitoring if initial value increased
- Should see significant decrease within 5 days
- Persistent increase day 3-4 negative prognostic sign

Serial CRP in acute pancreatitis prognostic

- Persistent increase poor prognosis
- CRP \geq 6.5 mg/dL on days 3 or 4 zero survivors
- Poor prognosis also with
 - Thrombocytopenia
 - >10% band neutrophils
 - Hypo- or hyperglycemia
 - Azotemia
 - Hypoalbuminemia
 - Decreased iCa
 - Hyperbilirubinemia
 - Spec cPL >1000 ug/L



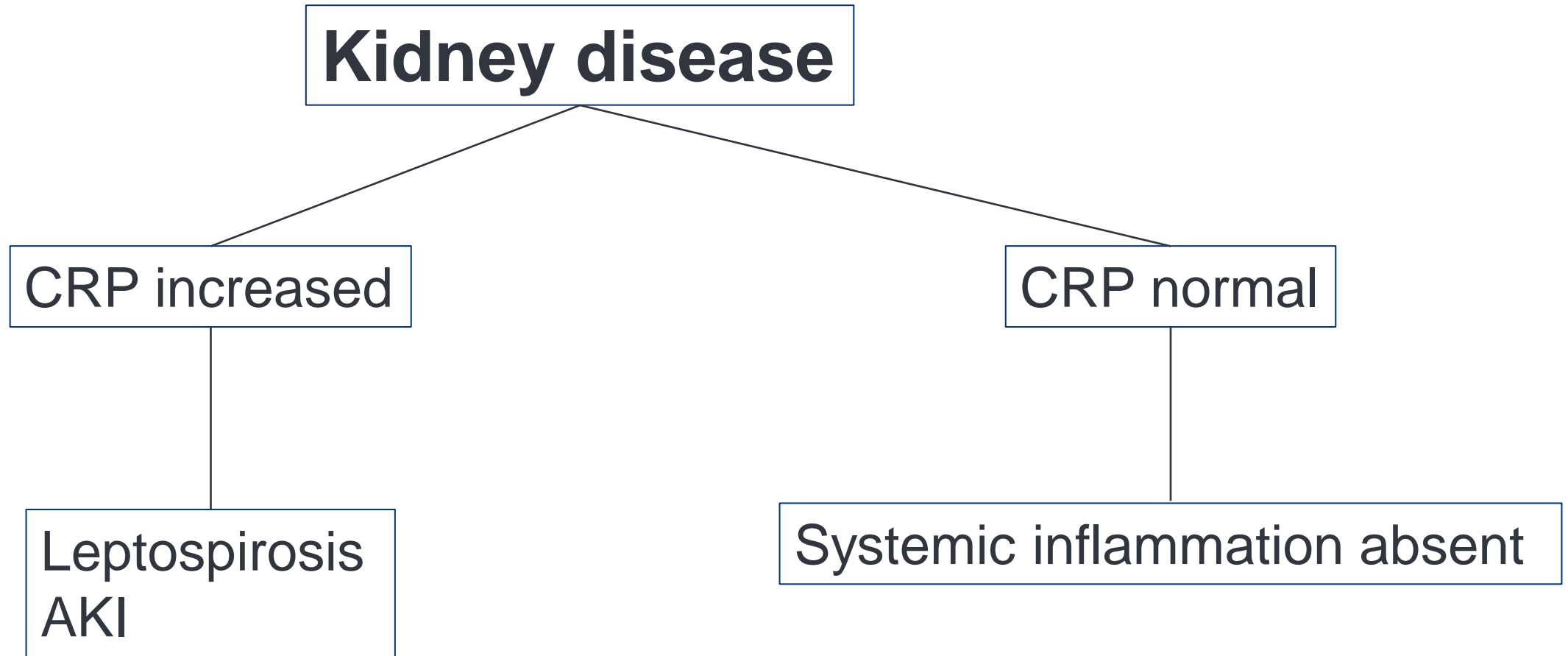
Gallbladder mucocele

- GB dysmotility, altered bile acid composition, bile stasis, mucin defects
- Shetland Sheepdogs, Cocker Spaniels, Miniature Schnauzers predisposed
- Cushing's syndrome increases odds of mucocele 29x
- Gallbladder rupture in 20-61% with mucocele
- CRP >6.3 mg/dL 100% sensitive, 67% specific for gallbladder rupture
 - Comparable to abdominal ultrasound
- Combined CRP and abdominal ultrasound 100% sensitive, 93% specific
- Serial CPR may be useful in monitoring medical management in stable patients



I played in the river a few days ago
and now I'm sick. Plus, I might have
eaten a few grapes...

IDEXX

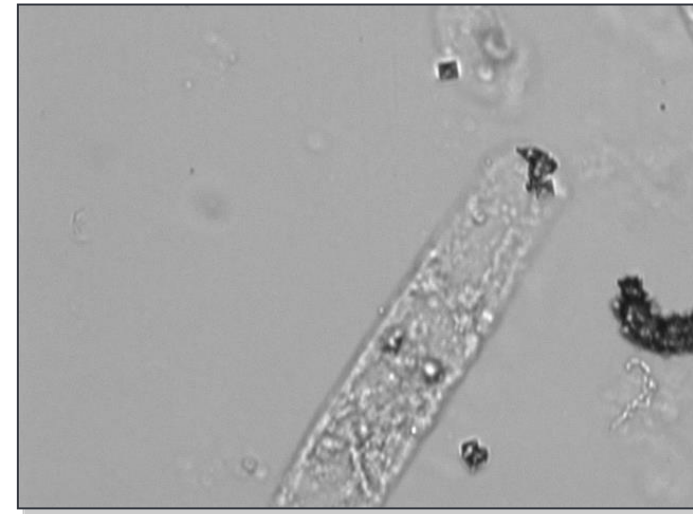


CRP with acute kidney injury

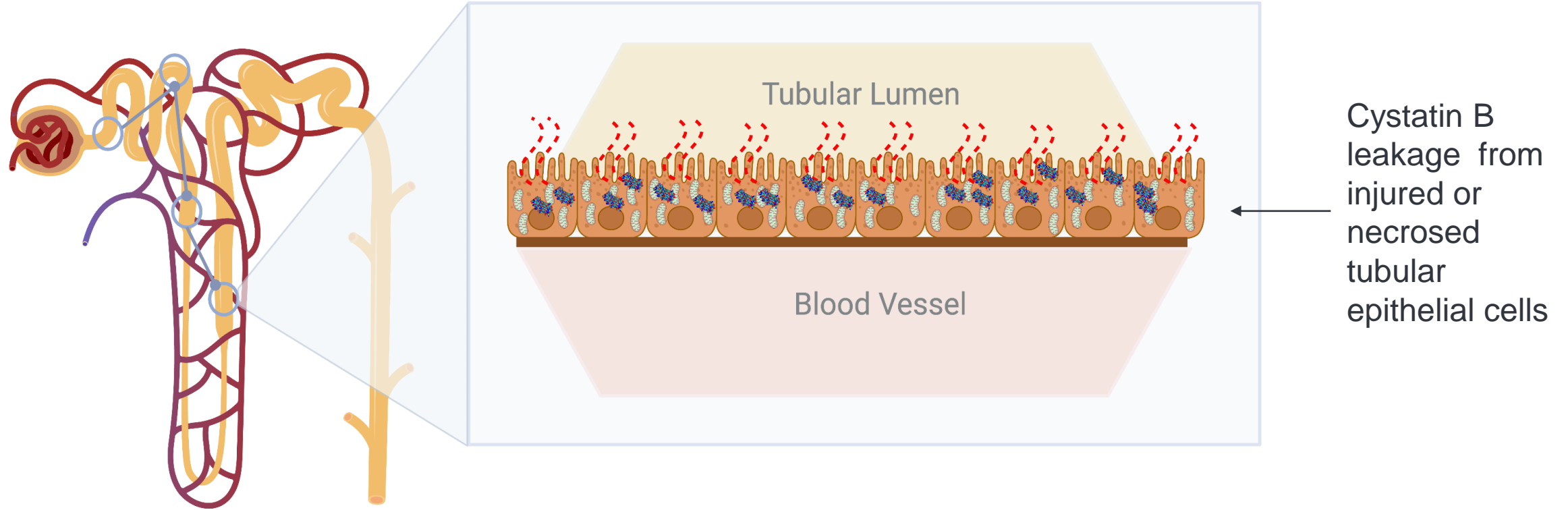
- Hospital acquired AKI in 12-16% of dogs in ICU
 - Sepsis, post-operative, critical illness in general
- Mortality up to 45% in dogs with AKI
- IRIS criteria for AKI
 - Increase of ≥ 0.3 mg/dL (≥ 26.4 $\mu\text{mol/L}$) in 48 hr +/- urine output < 1 ml/kg/hr over 6 hr
- Inflammation linked to development and progression of kidney disease
- CRP indicator and possible mediator of AKI
- Consider serial CRP with AKI (with urine cystatin B)
 - Leptospirosis prognosis associated with changes in CRP from presentation to day 2

AKI: tubules hit first. Evidence is in URINE.

- Proteinuria
- Hematuria
- Pyuria
- Bacteriuria
- Renal epithelial cells
- Glucosuria (+ALT increase = ?)
- + Urine culture
- Granular casts $\approx 16\%$
- Decreased urine production
- Decreased USG



Urine Cystatin B detects *active* kidney tubular damage (ALT of the kidney)



Consider Cystatin B with:

- AKI
 - Confirm active injury following toxin exposure
 - Monitor treatment and recovery from acute injury event
 - Monitor high risk patient on NSAIDs
 - Monitor kidneys during shock, heat stroke, pancreatitis, envenomation...
- CKD
 - Predict progression of Stage 1 CKD in dogs
 - Identify early CKD (?)
- Others...??

Post-op patient

CRP increased

CRP normal

Incision site infection
Implant infection
Dehiscence
Other complication

Systemic inflammation absent

CRP in post-operative period

- Obtain baseline before surgery
- CRP increases within 24 hr due to surgery alone
- Serially assess in post-op critical patients
 - Early detection of complications regardless of type, length, or site of surgery
 - Persistent or further increase suggests complication (dehiscence, sepsis...)
 - Longer hospitalization
- Should be normal at suture removal
- If elevated at suture removal consider incision or implant infection
- Aid in interpreting WBC count
 - WBC increased, CRP normal – inflammation unlikely cause of WBC increase
 - WBC increased, normal or decreased, CRP increased – systemic inflammation present

Do I still need a CBC?

- Please get a CBC with complete differential including band neutrophils but:
- CRP may increase before changes in WBC count (more sensitive indicator)
- CRP independent of neutrophil dynamics and bone marrow response
 - Normal total WBC or neutrophil count in 50% dogs with infection/inflammation
 - Neutrophils low with acute overwhelming infection
 - Neutrophils high (rebound) post-op (e.g., pyometra), i.e., when no infection
- Increased WBC not always infection/inflammation – stress, excitement, drugs
- CRP not affected by corticosteroids, epinephrine, (or NSAIDs)

Thank you!