VITICUSGROUP™
WVC ANNUAL CONFERENCE
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Holy CRP: when and how to use C-reactive protein in sick dogs.

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Financial Disclosure

I have a direct or indirect relationship with IDEXX. Because of the nature of the relationship, it **will not** influence my presentation.

Who knew?

- “C-reactive protein (CRP) is a powerful biomarker for inflammation, infection and sepsis, and is widely used in both human and veterinary medicine.”

- “Clinical serum canine CRP (c-CRP) measurement has been performed for over 30 years, and increased serum c-CRP concentrations are known to occur with several types of infection.”

- “CRP has become an integrated part of the routine blood panel analyzed at veterinary clinical pathology laboratories and inflammatory blood panels may be less optimal if measurements of CRP or other acute phase proteins are not included.”

What is C-reactive protein (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 effective treatment

- Opsonizes pathogens, clears apoptotic cells, promotes leukocyte chemotaxis, phagocytosis, and release of inflammatory cytokines

CRP tells you if your dog has **systemic** inflammation or not.

It does not tell you why or where.

Serial CRP will tell you if treatment is working (or if relapse).

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)?

Watch units!

- CRP in healthy dogs ≈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

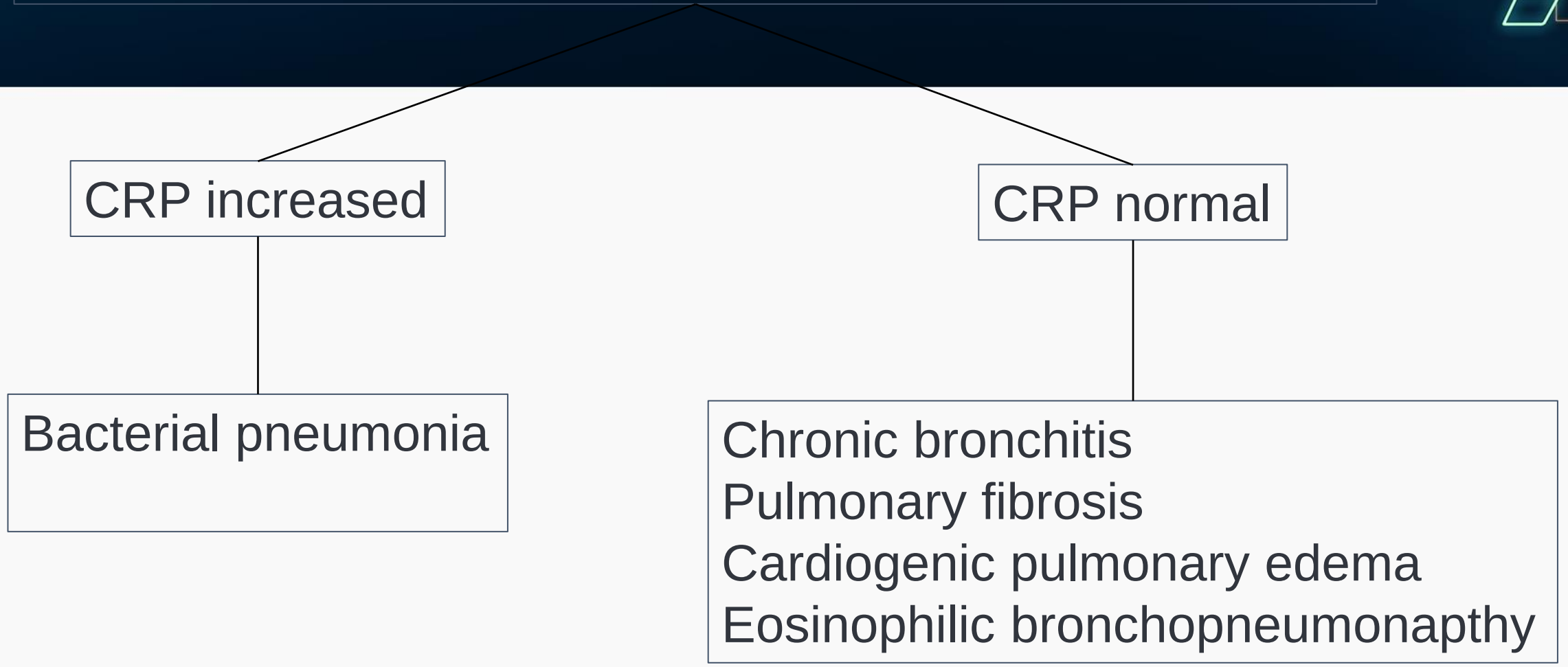
Hindenberg S, Bauer N, Moritz A. Extremely high canine C-reactive protein concentrations > 100 mg/l – prevalence, etiology and prognostic significance. BMC Veterinary Research (2020) 16:147 https://doi.org/10.1186/s12917-020-02367-7

CREATING CLARITY

I’m coughing.

IDEXX

Coughing, tachypnea, respiratory distress



CRP in pneumonia in dogs

- Diagnostic and monitoring biomarker in humans with pneumonia
- Increased in dogs with bacterial pneumonia (v noninfectious disorders)
- Guides duration of antibiotic therapy
  - Radiographic resolution lags clinical signs
  - Prolonged antibiotic use may not be necessary
  - CRP normalized before radiographs in dogs, shorter treatment may be effective[1]
  - Treating for 5-7 days after CRP normal effective without increased relapse[2]

CREATING CLARITY

I have a heart murmur and am tired.
Oh, and I have a soft cough.

Heart disease

CRP increased

Bacterial pneumonia concurrent
Infective endocarditis
Severe valvular disease

CRP normal

No infectious complication
Milder valvular disease

CRP with cardiac disease / murmur

- CRP may be increased (mild) with **severe** MMVD (stage D)
- CRP significantly higher with infective endocarditis than MMVD
- Increased CRP with chronic murmur
  - Mild increase = MMVD progressing?
  - Moderate/severe increase = concurrent bacterial pneumonia
- Increased CRP with new murmur → infective endocarditis?
- Consider CRP to
  - Determine if bacterial pneumonia is present in coughing dog with heart disease
  - Aid in diagnosis of IE
  - Differentiate MMVD from IE
  - Adjunct to determining severity of and monitoring treatment for MMVD

CREATING CLARITY

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

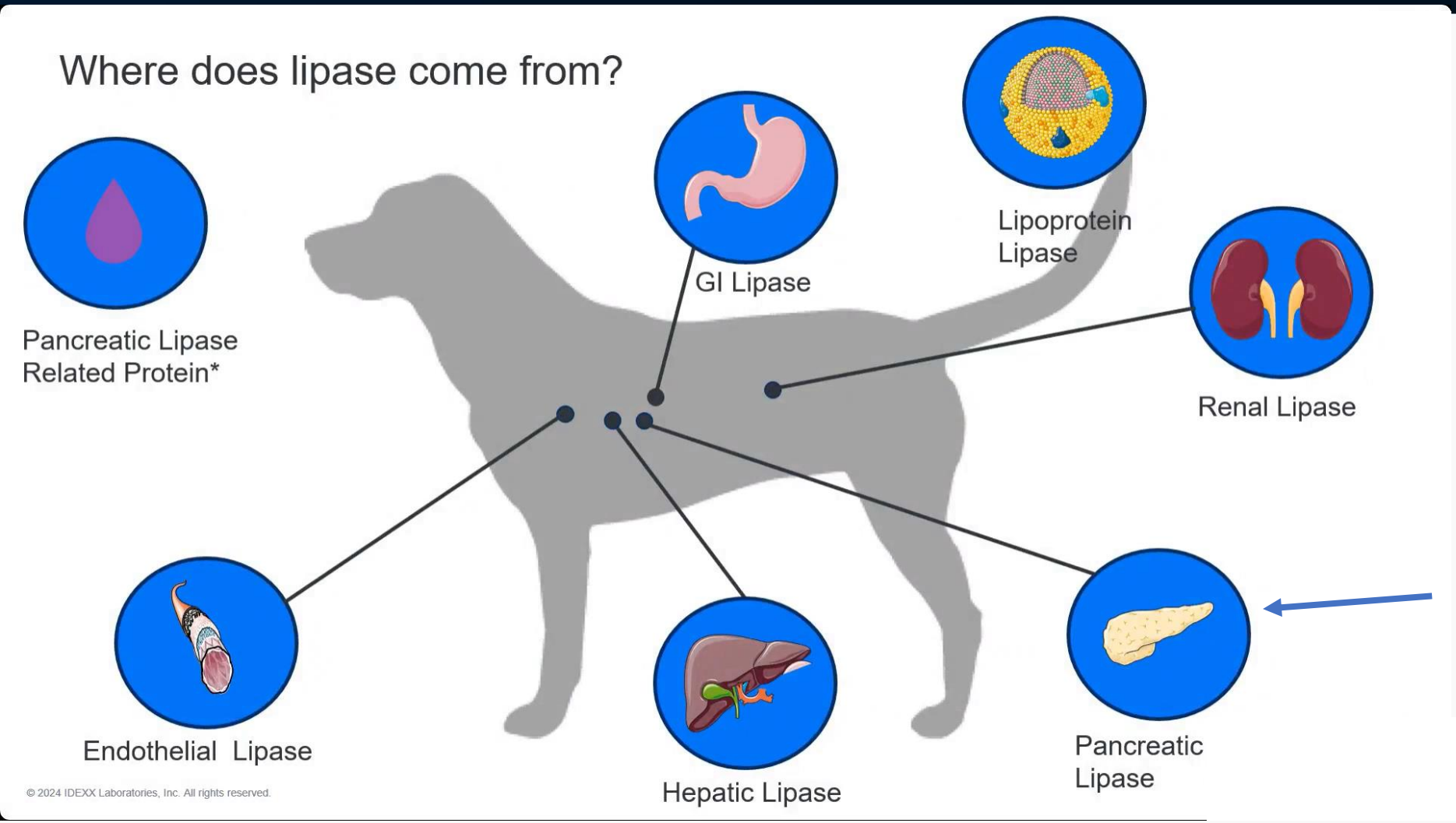
- Milder, localized acute or chronic disease

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

Diagnosing pancreatitis detour…

Many lipases in dogs and cats



We only care about

We need a lipase test that detects *only* pancreatic lipase

- Immunoassays most specific
  - Monoclonal antibodies detect only pancreatic lipase
  - No cross reaction with other lipases
  - SNAP cPL/fPL, Spec cPL/fPL, cPLI/fPLI

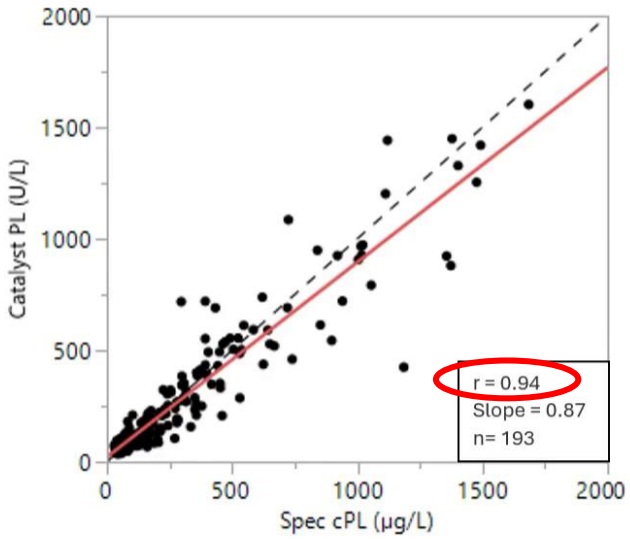
- Enzymatic assays
  - None inherently specific for pancreatic lipase
  - Detect lipases from any source
  - Amylase, lipase on standard biochemical profile

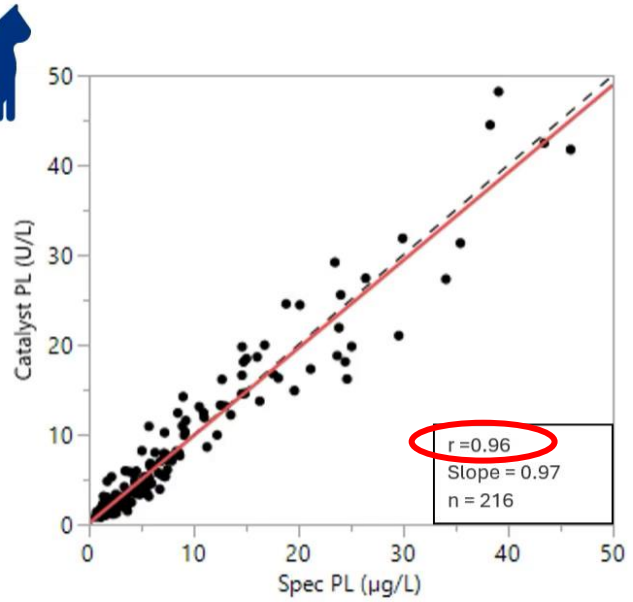
We need an **in-clinic quantitative lipase** test that is **specific** for pancreatic lipase…

SNAP cPL/fPL used to rule OUT pancreatitis. SnOUT

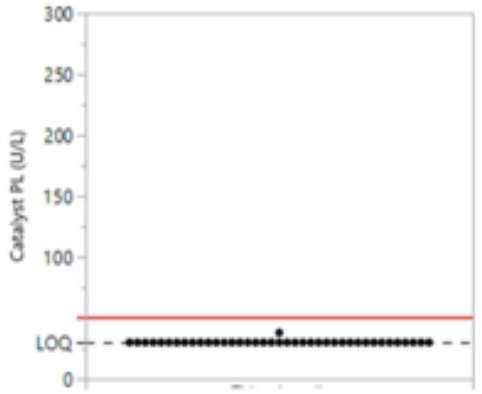
Catalyst qPL for dogs and cats. Quantitative. Specific.

- DGGR assay
  - Ref Lab lipase and ‘regular’ Catalyst lipase also DGGR
- Not all DGGR assays are created equal
  - Catalyst qPL slide engineered to make it specific for pancreatic lipase
- Excellent correlation with Spec cPL/fPL (internal and external validation)
- Excellent precision (5.2%) and reproducibility (6.6% dog, 6.1% cat)
- **Quantitative** result within minutes
- Minimal to no interference from lipemia, icterus
  - Marked hemolysis may lower result


Catalyst PL (U/L)
Spec cPL (µg/L)
0
500
1000
1500
2000
r = 0.94
Slope = 0.87
n= 193

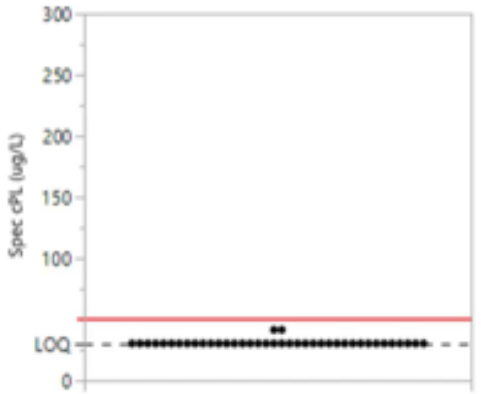

Catalyst PL (U/L)
Spec PL (µg/L)
0
10
20
30
40
50
r =0.96
Slope = 0.97
n = 216

Dogs with EPI prove specificity of qPL for pancreatic lipase…



Catalyst PL

3 samples > 30 U/L
0 samples > 50 U/L



Spec cPL

5 samples > 30 ug/L
0 samples > 50 ug/L

Back to CRP with pancreatitis…

Initial CRP prognostic in dogs with acute pancreatitis

- 503 dogs with PLI >600 µg/L
  - CRP <10 mg/L (normal) – 4% died
  - CRP >10 mg/L ≈5.5x more likely to be hospitalized or die
  - CRP > 30 mg/L (severe inflammation) – 23% died
  - OR 7.1 for death w CRP >30 mg/L vs <10 mg/L

- ↑↑ CRP at diagnosis = more aggressive treatment / monitoring

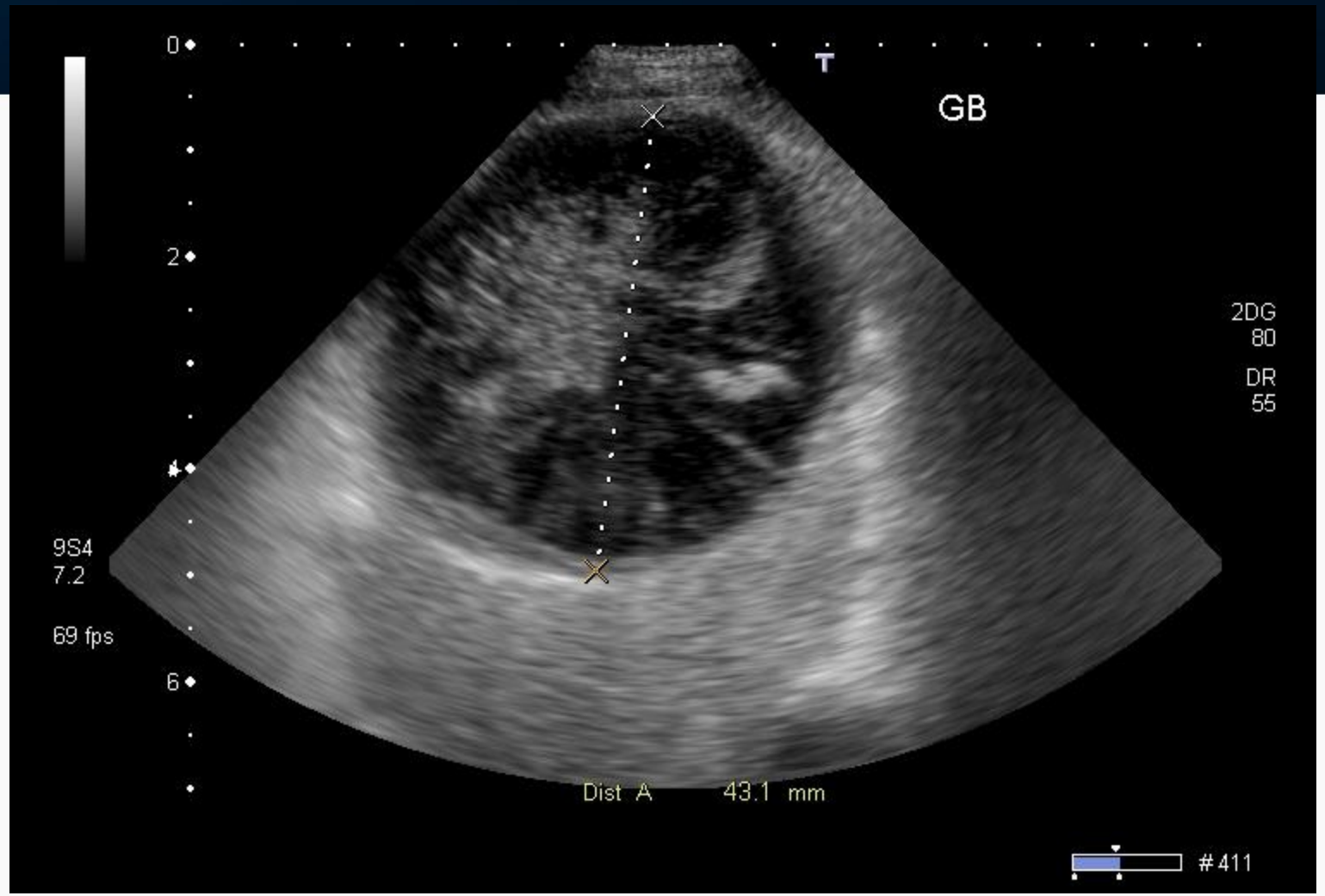
Cook et al. JAVMA 2024.

Serial CRP in acute pancreatitis prognostic

- Persistent increase poor prognosis

- CRP ≥ 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


0
2
4
6
T
GB
2DG
80
DR
55
9S4
7.2
69 fps
Dist A 43.1 mm
#411

Gallbladder mucocele

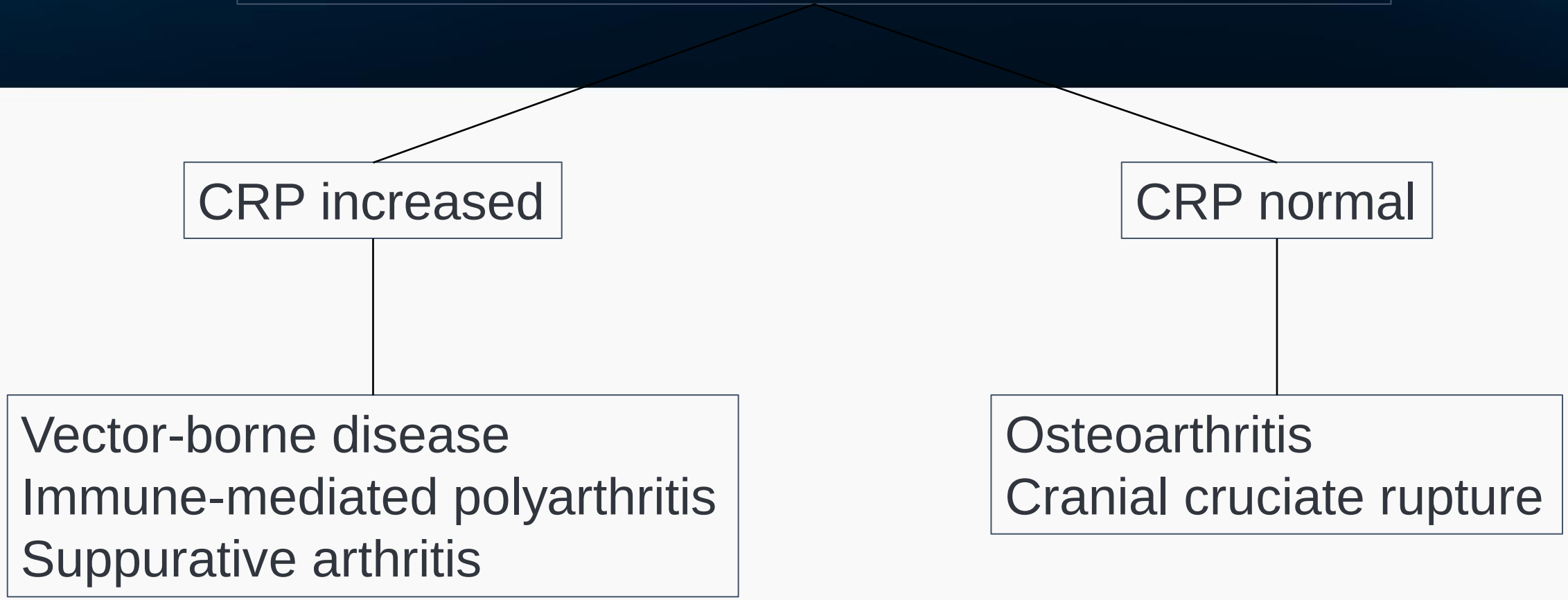
- GB dysmotility, altered bile acid composition, bile stasis, mucin defects
- Shetland Sheepdogs, Cocker Spaniels, Miniature Schnauzers predisposed
- Cushing's syndrome increases odds of mucocele 29x
- Gallbladder rupture in 20-61% with mucocele
- CRP >6.3 mg/dL 100% sensitive, 67% specific for gallbladder 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

CREATING CLARITY

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

IDEXX

Lameness, joint pain, joint swelling



CRP with lameness, joint swelling, joint pain

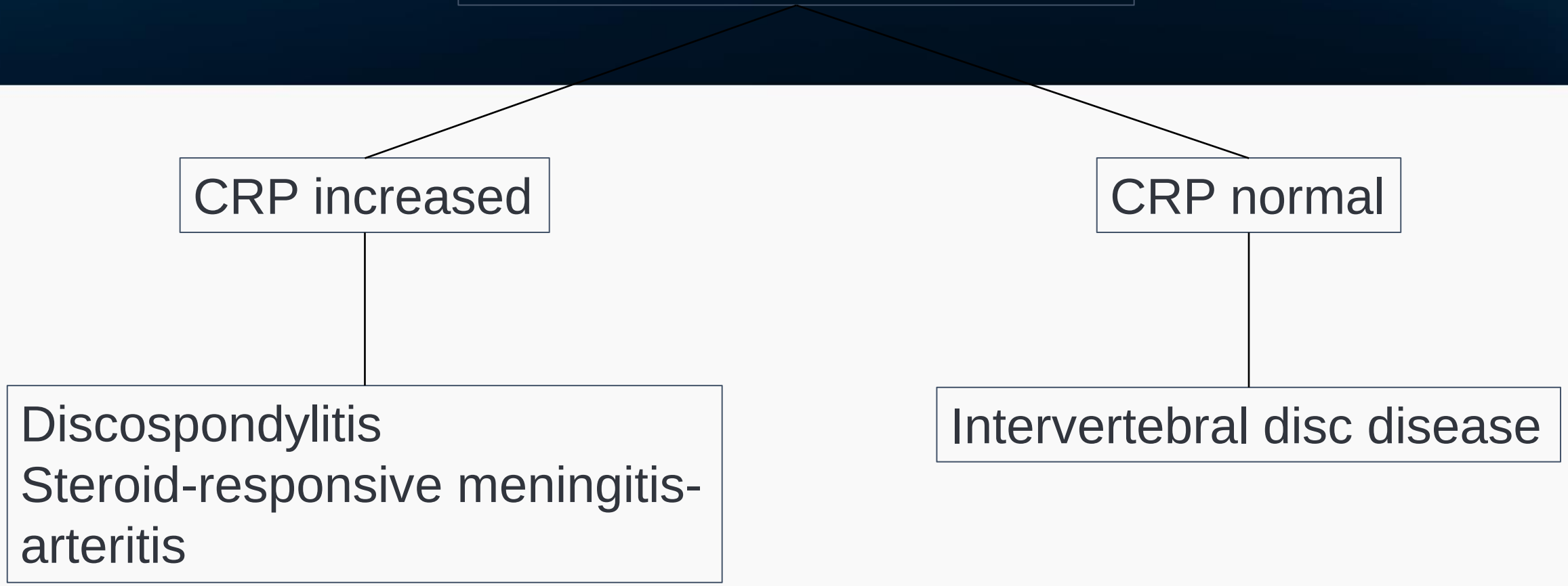
- CRP normal with osteoarthritis, cranial cruciate rupture
- CRP increased with:
  - **Immune-mediated polyarthropathy**
    - Serial CRP to guide therapy and monitor for relapse vs serial joint taps
  - **Suppurative arthritis**
    - Differentiates from osteoarthritis
  - **Vector-borne disease**
    - *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 *E. canis*
    - Normalizes with effective treatment
      - Aids interpreting serology, i.e., titers may remain positive months to years

CREATING CLARITY

My back hurts.

IDEXX

Back pain, neck pain



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

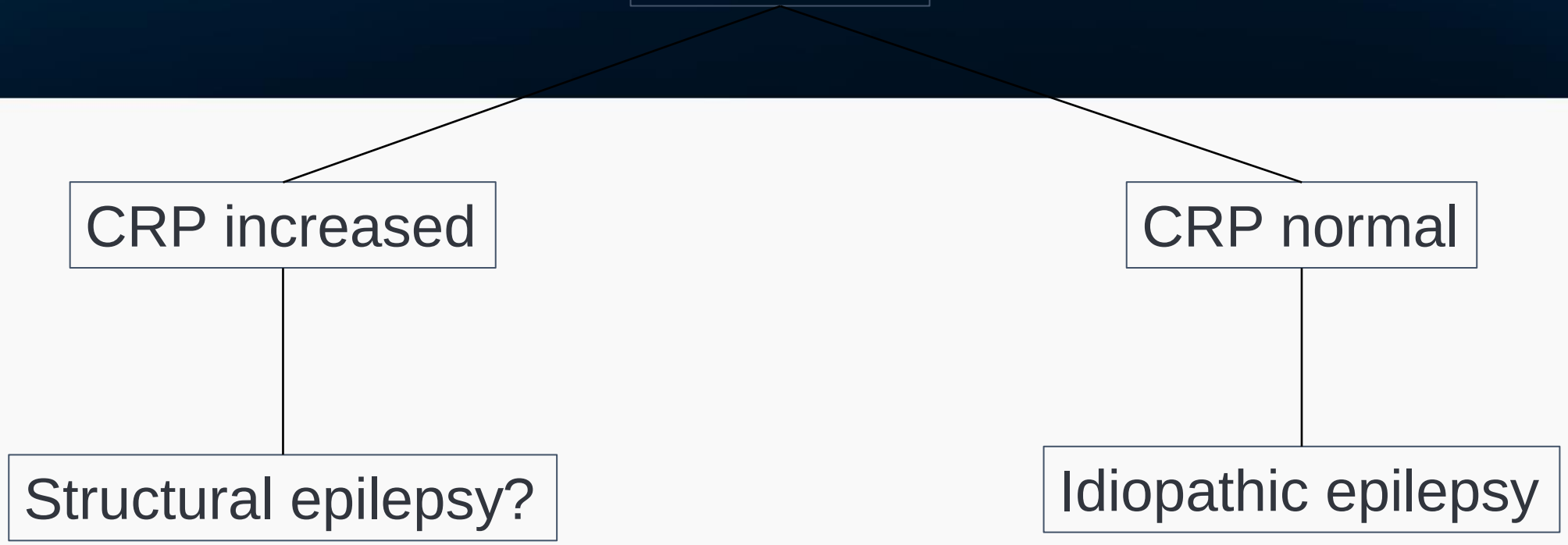
- CRP increases in immune-mediated conditions regardless of type
  - **IMHA, ITP, IMPA, steroid-responsive meningitis-arteritis**
  - No significant difference in CRP level among them
- No correlation between initial CRP and survival in IMHA
  - CRP 142 mg/L (+/- 89 mg/L) on admission in most
- Should normalize with effective treatment
- Serial CRP as taper meds
  - Remains normal → excellent
  - Increased → out of remission

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

CREATING CLARITY

I just had a seizure and am a little dizzy.

Seizure


CRP increased
CRP normal
Structural epilepsy?
Idiopathic epilepsy

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)*
- CRP >normal in ≈60% with SE
- Increased CRP with seizures increases likelihood of SE and need for referral…

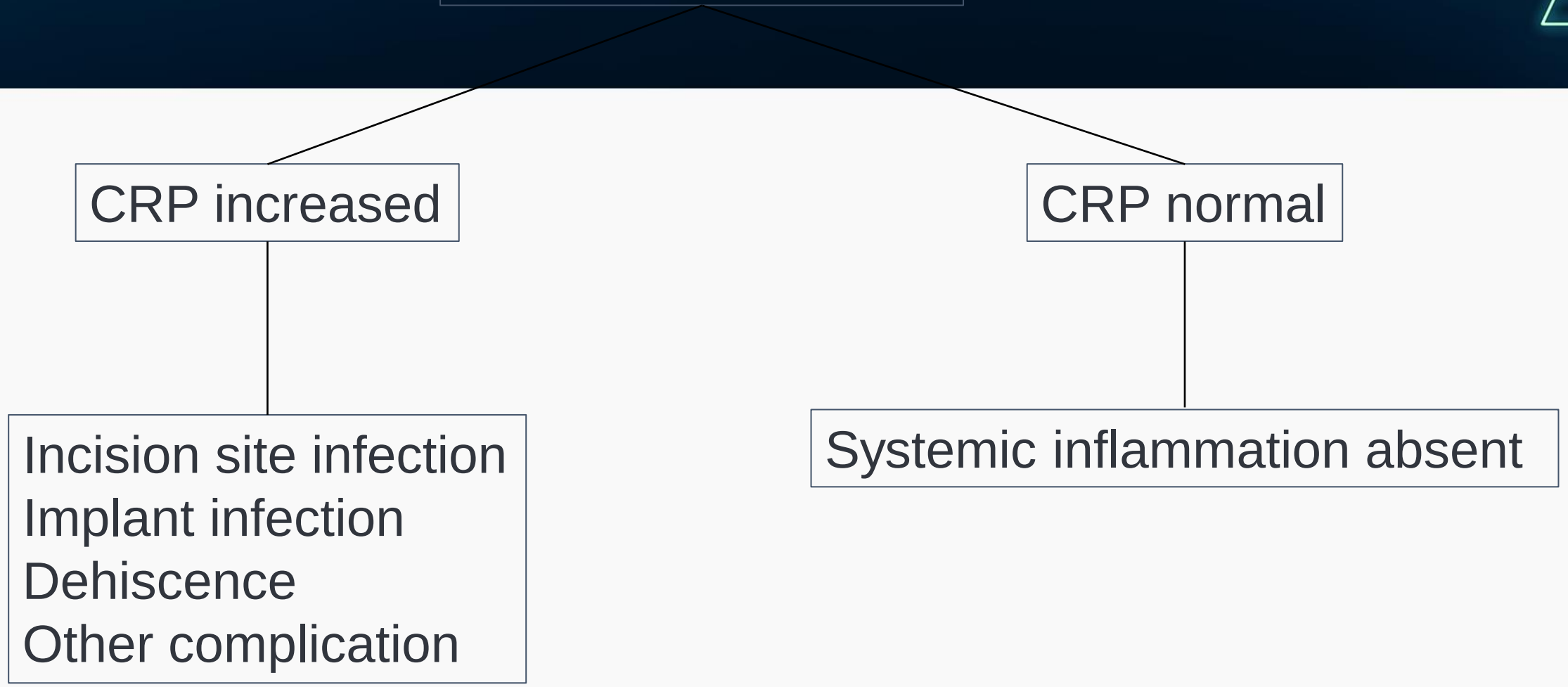
*Mahon et al. Vet Record. 2023

CREATING CLARITY

I’m about to have a complicated surgery.

IDEXX

Post-op patient



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
  - CRP is truth regarding presence of absence of systemic inflammation
  - WBC can be high from other causes (stress, neoplasia)
  - WBC can be normal (or low) with infection

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)
- 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!