

Canine C-Reactive Protein - A Clinical Guide



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Introduction

This guide briefly describes the basic biochemistry and physiology of the C-reactive protein (CRP) and the regulation of the acute phase reaction. The main focus is on the clinical use of CRP. The aim is to illustrate clinical situations where CRP measurements can be useful.

This guide will explain:

- How CRP is linked to the canine inflammatory response.
- The advantages of using CRP for monitoring inflammation in dogs.
- The use of CRP to monitor the efficacy of antibiotic treatment.
- CRP behavior/change in some canine diseases.
- How CRP can be used to monitor treatment of inflammatory diseases e.g. bacterial infections.

CRP is an acute phase protein produced, mainly in the liver, in response to different inflammatory stimuli such as infection or tissue damage. CRP was first identified in 1930 in humans. Research on CRP in canine (dCRP or dog CRP) began as a model for studies of human inflammatory diseases and processes.

The main indication for measuring CRP is to detect and monitor systemic inflammatory activity and thus, help veterinary practitioners to monitor different types of inflammatory diseases. Measurement of CRP is also an effective tool for evaluating the efficacy of treatment. Repeating the CRP test during and after treatment will show if the selected treatment (i.e. antibiotics) is effective.

The Inflammatory Reaction

The clinical symptoms and signs of an inflammatory reaction are both local and general. The extent of these symptoms and signs depends on the severity and the amount of tissue involved in the inflammation.

The classical **local signs** of inflammation are:
heat, redness, pain, swelling and loss of function.

The **general symptoms** are:
fever, increased pulse-rate, hyperventilation, tiredness and loss of appetite.

The inflammatory reaction is caused by a multitude of different agents/processes: e.g. by infectious agents (bacteria, viruses, fungi and parasites), by non-infectious inflammatory stimuli (e.g., rheumatoid arthritis and tissue necrosis (e.g., cancer, anoxia, and burns), by toxins or irradiation). The inflammatory reaction, depending of the magnitude will affect a multitude of body-functions (Figure 1).

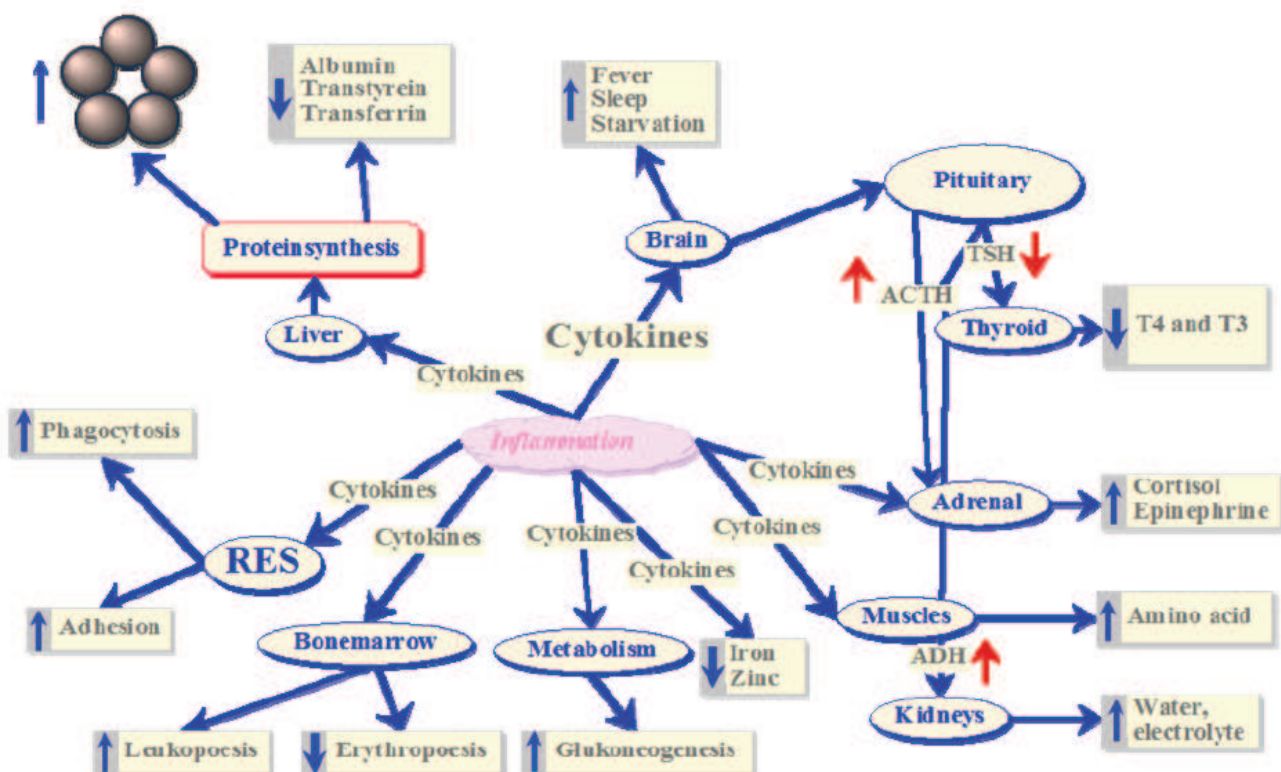


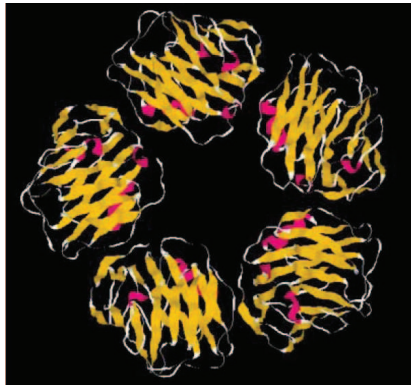
Figure 1. The inflammatory reaction, depending of the magnitude will affect a multitude of body-functions.
Source: Associate Professor Lars-Olof Hansson, Karolinska Hospital, Sweden.

CRP: A Marker of Inflammatory Activity

The CRP protein and the canine inflammatory response

(Ref. 1-2)

In 1985 the gene sequence was determined for human CRP and the protein structure determined by Shrive and colleagues in 1996 (Figure 2).



Human CRP is non-glycosylated and consists of 5 identical subunits with a total molecular mass of approximately 120 kDa. Canine CRP (dCRP) was isolated in 1970. The canine CRP protein is glycosylated, with a molecular mass of about 100-150 kDa.

Figure 2 – The structure of CRP, showing 5 identical subunits and two calcium atoms in each subunit. Source: Google.com, search CRP (<http://www.stefajir.cz/?q=crp>)

CRP protein is produced in the liver by the hepatocytes in response to inflammatory stimuli e.g. tissue damage and/or infections. The function of CRP is to bind many different molecules that are released or present during inflammation, such as different cell fragments, bacteria, chromatin and different polycations. When the inflammatory cells (e.g. macrophages or granulocytes) are activated by different inflammatory stimuli, the acute phase response is triggered and different cytokines are released from the inflammatory cells, e.g. interleukin 6 (IL-6), IL-8, IL-1 and TNF-alpha. These cytokines (especially IL-6) then induces an enhanced CRP-production in the liver within about 4-6 hours. If the inflammation ceases, the CRP concentrations in the blood peak within 48 hours and then return to normal level within 1-2 weeks (Figure 3).

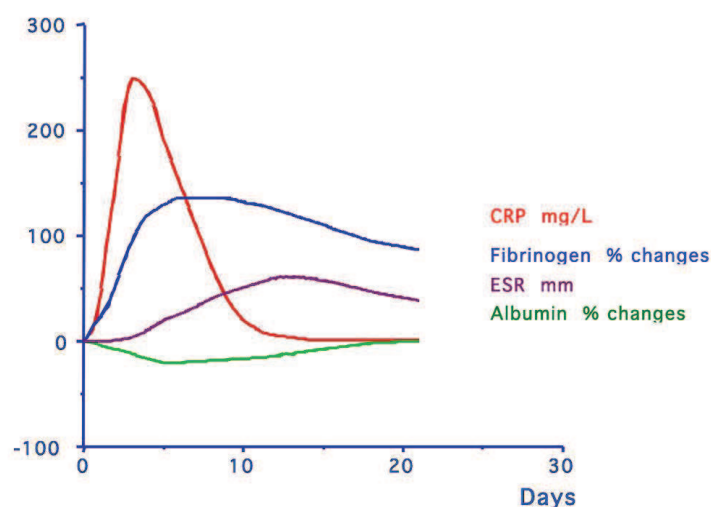


Figure 3 – Changes in CRP are the most rapid in response to inflammation when compared to fibrinogen, erythrocyte sedimentation rate (ESR) and albumin. Source: Associate Professor Lars-Olof Hansson, Karolinska Hospital, Sweden

This rapid response makes CRP an almost real-time marker of inflammatory activity and response to treatment. In the postoperative situation CRP is a very useful marker for excluding a postoperative complication. Postoperatively, CRP normally reaches peak level on the second or third post-op day and if CRP then starts to normalize the chance for a successful and complication-free post-op course is very high and no antibiotic treatment will be needed.

Advantage of using CRP to monitor canine inflammation

(Ref. 3-12)

- Storage of samples

CRP is stable during storage both in whole blood for a short period and in serum or plasma for longer time. Blood samples containing CRP can be stored overnight at 4°C, serum or plasma samples can be stored more than 2 months at -20°C and several years at -80°C.

- Dynamics of the CRP response

Any change in CRP indicates a change in the inflammatory burden in the subject. CRP is present in the blood at very low concentrations in healthy individuals, often below 5 mg/L, but rises to very high concentrations during ongoing inflammation, even above 600 mg/L, depending on the severity of the inflammatory process, e.g. bacterial infections. Pregnant dogs also have increased serum concentration of CRP up to about 80 mg/L four to five weeks after ovulation. CRP then returns back to normal level within another five weeks.

- Diagnostic Specificity

CRP is almost exclusively elevated if inflammatory stimuli is present. The increase in CRP is an effect of the increased release of cytokines, e.g. IL-6 from the activated inflammatory cells. False-positive results are not induced by excessive stress, as seen, for example, with some leukocyte markers of inflammation and rectal temperature.

- Treatment-independent marker

dCRP as an inflammatory marker is not influenced by standard therapy; inflammation can be measured/monitored using CRP in dogs undergoing steroid therapy, or being given medication and/or antibiotics. Steroid therapy, either in short-term or long-term doses, did not influence CRP concentrations in healthy dogs. Treatment with the non-steroidal anti-inflammatory drugs (NSAIDs) carprofen, etodolac and meloxicam, and the opiod butorphanol, had no affect on CRP concentrations.

- *CRP vs White blood cell count (WBC)*

CRP provides specificity and enables quantification of inflammatory activity. CRP accurately reflected inflammation in all dogs following gastric surgery, while changes in leukocyte counts were either small or not detected. A correlation between CRP concentration and white blood cell count was evaluated in a study examining 914 dogs with different diseases and canine babesiosis. It was concluded that the dCRP measurement provided additional diagnostic information in comparison to the leukocyte count. While CRP concentrations drop, WBC can remain high even after sutures are removed following surgery.

- *CRP vs Erythrocyte sedimentation rate (ESR)*

ESR is a crude test based on increased sedimentation of the erythrocytes (red blood cells). The increase of the ESR depends on an increase in above all the fibrinogen concentration in the blood as e.g. in different inflammatory diseases. However, this increase in ESR normally is delayed 2-4 days compared to the increase in CRP. ESR is not an accurate measure of inflammation if the disease involves altered or reduced red blood cells. In these cases, CRP can be used to monitor inflammation. A study of canine babesiosis showed that CRP concentrations were a more optimal test than ESR when monitoring inflammation associated with this hemolytic illness.

- *CRP vs other acute phase proteins.*

Information regarding treatment effectiveness using CRP verses other acute phase proteins, such as serum amyloid A (SAA), haptoglobin (Hp) or fibrinogen has been presented in a limited manner. Following treatment of dogs for infections, CRP concentrations dropped within one day following treatment, while a decrease in SAA was for delayed at least 2 days. Similarly, Hp and fibrinogen concentrations continued to rise or remained unchanged, thus, not reflecting treatment efficacy.

CRP concentrations in dogs without disease*(Ref 13-18)****- Healthy dogs***

CRP concentrations measured in healthy dogs have been low (most often below 5 mg/L), compared to those found in dogs with systemic inflammation. Reports in the literature vary due to differences in the method or assay used to detect CRP. When making clinical decisions, it is important to refer to the normal CRP intervals specific for the method or analysis being used. For the LifeAssays[®] Canine CRP kit, a normal dCRP concentration is below 35 mg/L.

- Age

Age does not affect the concentration of CRP in the blood. However, CRP is not recommended as a sensitive marker for inflammation in dogs less than 3 months old.

- Gender and Pregnancy

CRP concentrations are the same in male and female dogs. One exception is pregnant dogs in days 21-55 following ovulation, when CRP is elevated (up to about 80 mg/L).

- Obesity and Exercise

CRP remained normal in dogs with experimental short-term obesity. However, very obese dogs seem to have a lower CRP level than non-obese dogs (this is opposite to the situation in humans where obese individuals have in general a higher CRP level than people with normal BMI). Extremely active dogs, however, may have elevated CRP concentrations due to exercise-induced inflammation.



CRP In Clinical Settings

Using CRP in the clinic

(Ref. 19-21)

When a dog gets an inflammatory disease, for example, a bacterial infection or an exacerbation of an inflammatory bowel disease (IBD), the CRP synthesis in the liver will increase and within about four to six hours the level or concentration of CRP in the blood will increase. The increase will depend on two factors: 1. the severity of the inflammatory disease and 2. the duration of the inflammatory process. Commonly, when a sick animal is brought to a veterinary clinic, the CRP serum concentration has already increased in response to the disease or trauma. In healthy dogs, the level of CRP can differ slightly between individual dogs, but most commonly the level is far below 35 mg/L. This marked difference with inflammation makes dCRP one of the few parameters where pre-establishment of an individual baseline is not necessary.

When monitoring CRP, a reduction of the dCRP serum concentration in a diseased dog with a previously measured increased dCRP can indicate that:

- the intensity of the inflammatory disease is decreasing naturally,
- an infection is responding to antibiotic therapy,
- an inflammatory disease is responding to steroid therapy,
- the post-operative condition period is free from complicating infections.

Non-inflammatory disease

(Ref 22-23)

Some diseases in dogs do not cause inflammation or increases in CRP (Table 1). However, if a dog with a non-inflammatory disease gets an infection or undergoes surgery, the CRP measurements can be used to detect and monitor the infection or the post-operative recovery (see below).

Table 1 – Examples of diseases that do no affect CRP concentrations in dogs.	
Allergic bronchitis	Hypothyroidism
Atlantoaxial subluxation	Intervertebral disk protrusion
Brain tumor	Leiomyosarcoma
Bronchitis	Urolithiasis
Diabetes mellitus	Megaesophagus
Epilepsy	Mitral valve insufficiency
Hydrocephalus	Necrotizing meningoencephalitis
Hyperadrenocorticism	Protosystemic shunt
Hypoadrenocorticism	Rhinitis
	Tracheal collapse

Source: Ref 32

Infectious disease***(Ref. 24-31)******- Detecting infections***

The CRP serum concentration rises in response to inflammation that may be caused by infection. It has been demonstrated that elevated CRP concentrations are found in dogs infected with bacteria and parasites, but sometimes also in viral infections (Table 2). However, if an infection is mild or localized, or in a state that does not cause inflammation, CRP may not be severely elevated. In these situations antibiotic treatment of the infection is commonly not indicated, but a second CRP test within 12-24 hours might be of diagnostic value. One shall always remember that CRP indicates an inflammatory process and its increase can be caused by an e.g. bacterial infection. It is the combination of symptoms and change in CRP level that helps the veterinarian to properly diagnose the infection. The type of infection is then clarified by proper microbiological tests.

Table 2 – Examples of infections producing elevated CRP concentrations in dogs.

Bacterial - Bordatella bronchiseptica - Escherichia coli - Erlichia canis - Leptospira interrogans - Staphylococcus aureus - Pyometra	Parasitic - Leishmaniasis - Babesia canis Viral - Parvovirus
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- Monitoring infection treatment and efficacy of antibiotics

CRP can be used to monitor the efficacy of the antibiotic treatment given for a bacterial infection. Repetitive CRP measurements, during and after treatment, will show if the selected treated (i.e. antibiotics) is effective. If the symptoms and signs have been present only for a limited period (< 4-8 h) a second sample, within 12-24 h, is recommended to monitor the development of the disease. In the parasitic infection canine babesiosis, CRP concentrations dropped the day following treatment, and continued to decline to normal concentrations within 1-2 weeks after start of treatment. Postoperative infections can be suspected if CRP does not decrease after surgery as expected within 3-5 days.

Inflammatory disease

(Ref 32-41)

- Detecting inflammation

Typically, inflammatory diseases generate an increase in the concentration of CRP in the blood. Thus, CRP can be used to monitor and to assess the severity of inflammatory diseases.

(Table 3). For example, CRP concentrations were elevated in dogs with arthritis, but not in those with several neurological conditions causing lameness. This suggests that CRP can be of value in differentiating if an ongoing problem is related to inflammation or a neurological disease.

Table 3 – Examples of inflammatory diseases that can be monitored using CRP in dogs.

Arthritis
Canine inflammatory bowel disease
Immune-mediated hemolytic anemia (IMHA)
Pancreatitis – acute, necrotizing
Periodontitis
Pyogranuloma
Steroid-responsive meningitis arteritis (SRMA)
Type II immune-mediated polyarthritis (IMPA)

- Monitoring treatment of inflammatory diseases

CRP can be measured in different inflammatory diseases as an objective indicator of the efficacy of treatment. The response to an anti-inflammatory treatment is normally very rapid (CRP decreases with about 50% within 2-3 days). As an example, in a study following a dog with type II immune-mediate polyarthritis (IMPA), CRP decreased in clear response to steroid treatment, but increased during relapse, reflecting an ineffective anti-inflammatory therapy.

- Predicting mortality from inflammation

In general, if the CRP level remains high or increases during treatment in a dog with severe inflammatory disease, it is recommended to re-evaluate the chosen therapeutic strategy, e.g. the antibiotic therapy, in order to save the dog. Thus, monitoring CRP can at an early time point help detect treatment failure that may lead to a poor outcome. In a study of dogs with immune-mediated hemolytic anemia (IMHA), the dogs survived if the CRP concentrations dropped more than 3 fold in 3 days following treatment. However, dogs showing a less than 2 fold decrease did not survive.

Surgery and postoperative care

(Ref 42-43)

- Post-operative course

In dogs, as in humans, surgery induces tissue damage and thus, an inflammatory reaction, which severity (measured by the peak height of the CRP increase) depends on the extent of the surgical procedure. However, if no post-operative complication occurs the increased CRP concentration starts to decrease on the third to fifth post-operative day and is back to normal level within one to two weeks. Following orthopedic surgery, the CRP concentrations increased dramatically and were significantly higher than following surgery for superficial tumors or after contraceptive surgery. In minor surgical procedures, like after a tooth excision, the inflammatory process may stay local and the CRP concentration remains normal or unchanged.

- Post-operative complications

If the post-operative recovery is complicated by infections, CRP concentrations will not start to decrease as expected within three to five days. If an effective antibiotic treatment is started, the CRP concentration should then begin to normalize as the post-operative infection subsides. In dogs having an ovariohysterectomy, CRP concentrations in uncomplicated cases decreased 3 days after surgery while CRP in dogs with postoperative infections remained high (Figure 4). CRP decreased in dogs with complicating infections after start of an effective antibiotic treatment.

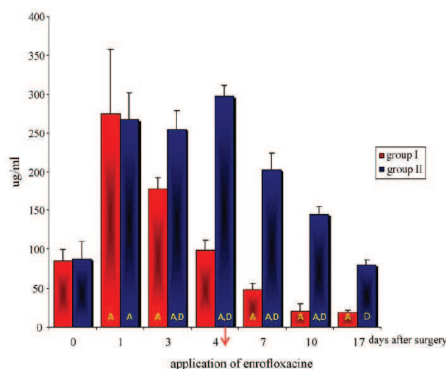


Figure 4 - Serum CRP concentrations in bitches with normal (group I) and complicated (group II) postoperative period following postovariohysterectomy. Adapted from Dabrowski R., K. Kostro et al. 2009. *Usefulness of C-reactive protein, serum amyloid A component, and haptoglobin determinations in bitches with pyometra for monitoring early post-ovariohysterectomy complications.* Theriogenology 72:471-6.

Tumors and cancer

(Ref 44-45)

Some neoplasia induces inflammation due to tissue invasion and destruction or release of pro-inflammatory mediators. Increased CRP concentrations were observed in neoplastic diseases including several types of cancer affecting systemic organs, particularly leukemia, lymphoma and hemangiosarcoma. Dogs with localized tumors, such as brain tumors or leiomyosarcoma did not show increased CRP. In dogs with neoplastic disease, which are immune-compromized during cytostatic therapy, CRP is especially of great value to detect early complicating bacterial infections, although a suppressed response can be expected due to the immunosuppression.

CRP in Point-of-Care Testing For Dogs

(Ref 46-48)

CRP is gaining an important position in veterinary point-of-care settings to more effectively take care of diseased dogs with suspected inflammatory diseases especially suspected infectious diseases. Another aim with using dCRP as a diagnostic marker is to monitor the efficacy of antibiotic treatment. For an efficient work-flow within emergency settings, the test result must have a short turn around time, optimally less than at least 15 minutes. Additionally, the test-format has to be easy-to-use so that non-laboratory personnel are able to perform the test.

LifeAssays® Canine CRP test kit provides a point-of-care quantitative measurement of canine CRP in serum or plasma, in 11 minutes. This two-site immunoassay requires only a small sample volume (5µl), and uses two polyclonal antibodies, one magnetically labeled, directed against canine CRP. The LifeAssays® Canine CRP test kit helps veterinary professionals to easily integrate CRP measurements as a point-of-care tool. Routine measurements of CRP provide safer diagnosis, better estimation of prognosis and correct treatment of dogs with suspected inflammatory diseases. The use of the point-of-care CRP test also helps monitor the efficacy of antibiotic treatment. Repeating the CRP test during and after treatment (i.e. antibiotics) indicates if the selected treatment is effective.

Table 4 – Suggested Clinical Decision Limits for LifeAssays® Canine CRP Test (mg/L).	
No Significant Evidence of Systemic Inflammation	<35
Presence of Systemic Inflammation	≥35



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