THE NORTHERN HOSPITAL

C-REACTIVE PROTEIN

"The Oracle of Delphi", oil on canvas, John Collier, 1891.

"The Lord Apollo whose oracle is at Delphi neither speaks nor conceals, but gives a sign…

Evil witnesses are eyes and ears for men, if they have souls that do not understand their language."

Heraclitus, 6th Century BC

"Heraclitus somewhere says that all things are in process and that nothing stays still, and likening existing things to the stream of a river he says you would not step twice into the same river"

Plato, 4th Century BC

Heraclitus was one of the very early great philosophers of the Classical Greek age of the 6th century BC. He was apparently revered by the great philosophers of later centuries, but tragically none of his works have survived to the modern age, apart from the barest few fragments. Perhaps they were lost with the enigmatic demise of the great library of Alexandria. Most of what we know of him comes to us second hand, albeit via some of the greatest of all including Plato and Aristotle.

One of Heraclitus's beliefs was that the evidence perceived by the human senses were imperfect and deceptive, and that they must always be used with caution. Indeed he wondered whether the human senses were in fact ever capable of fully understanding the world. A prescient sentiment echoing the great JBS Haldane, two and half millennia later, who famously wrote: "…Now my own suspicion is that the universe is not only queerer than we suppose, but queerer than we can suppose. I suspect that there are more things in heaven and Earth than are dreamed of, or can be dreamed of, in any philosophy".

Heraclitus likened his philosophy to the predictions and incantations of the great oracle of Delphi, great signs of the gods abounded all around, lightning, thunder Earthquakes, the stars of the firmament, but their precise meaning often remained tantalizingly obscure to the senses of mere mortals. When mortals consulted the gods themselves through the agency of the oracle, the answers they would get would still need to be interpreted with caution, the gods only spoke in a manner that mortals could not fully comprehend.

Heraclitus also believed that whatever we thought we may know about the natural world or the affairs of humanity, were merely transient notions. His famous aphorism "panta rhei", everything is in flux, prescient again, this time in respect of the great Roman poet Ovid's Metamorphoses 600 years later, says that "nothing ever stays the same", even our concepts of reality.

In the modern world of medical practice, the evidence of our own senses, as Heraclitus lamented two and a half millennia ago, are frequently sadly deficient. On occasions patients sometimes appear well when they are not, whilst on other occasions they may appear unwell, when they are in fact quite well. The evidence of our senses and perceptions cannot always assist us in our assessments. To this end we consult a host of

modern "oracles" to assist us, not the least of which includes the C-reactive protein. As Heraclitus cautioned however we must interpret the result with caution. The CRP can be a valuable sign, it does not conceal, yet it does not speak to us plainly either and so a precise diagnosis remains obscure. The clinical context must therefore play an important part in this interpretation. When we have a clear diagnosis the oracle need not be consulted. However when our senses are not helping us, the oracle can provide a valuable clue to the illness or otherwise of our patient.

Even as we obtain a vital clue or prediction from our modern oracle, it does not end there. Again we heed the wise words of the ancient philosophers, "nothing stays the same forever". This tells us that the clinical picture can sometimes change rapidly. This point is especially important when diagnoses are unclear. The "risk profile" each patient carries must be taken into careful consideration, all may be "in flux", and so a period of close observation and re-consultation with the oracle will be wise, especially for those whose risk profile is great.

The School of Athens. Raphael, Fresco 1510, Vatican City.

C-REACTIVE PROTEIN

Introduction

C-reactive protein (CRP) is a member of a range of proteins known collectively as "**acute phase reactants**", (**see Appendix 1 below**).

The levels of these proteins become raised in **infective** and **inflammatory** reactions occurring in the body.

C-reactive protein is most useful for:

1. The detection of infection or inflammation in the body, when this is clinically uncertain.

2. In some situations for the monitoring of disease activity.

3. Monitoring the response to treatment.

4. In many situations as a prognostic / severity indicator.

C-reactive protein is a much better indicator of inflammation than the traditional erythrocyte sedimentation rate (ESR).

It is more sensitive than ESR and responds more quickly to changes in the clinical situation.

False negative and false positive results are more common when measuring the erythrocyte sedimentation rate.

Note also that CRP values are dynamic and so should not just be considered as one off isolated results.

Serial measurements are also invaluable in assessing patients especially where uncertainly exists.

History

CRP was discovered by Tillett and Francis in 1930.

It was first discovered in the serum of patients with pneumococcal pneumonia.

It was initially thought that it might be a pathogenic secretion since it was elevated in a variety of illnesses, including cancer.

The later discovery of its hepatic synthesis however demonstrated that it is a native protein.

Physiology

C-reactive protein is an annular shaped, pentameric plasma protein produced by the liver, in response to inflammation, primarily to interleukin-6, but other cytokines are also involved.

It plays a key role in the host's defense against infection.

It was so named because it reacts with the C-polysaccharide of *Streptococcus pneumoniae*.

C-reactive protein specifically binds to polysaccharides such as phosphocholine moieties present on the cell surface of many pathogenic microbes.

The C-reactive protein binding then activates the classical complement pathway and opsonises (prepares) ligands for phagocytosis by macrophages.

Normal Values

The median normal concentration of C-reactive protein is 0.8 mg/L.

90% of apparently healthy individuals have a value less than 3 mg/L.

99% of apparently healthy individuals have a value less than 12 mg/L.

The normal value for CRP is generally taken < 8mg/L, (but quoted values may vary according to individual laboratories).

The utility of CRP in comparison with the ESR

Traditionally the erythrocyte sedimentation rate (ESR) was a test that was used for the above indications, however CRP has a number of advantages, including:

1. The levels will *rise and fall more quickly* in response to infection and inflammation than will the ESR.

2. The CRP is more *specific* for infection and inflammation than is the ESR

3. In practical terms a CRP can be measured more quickly than an ESR level, (which takes one hour at the *very* minimum).

ESR measurements however remain helpful in a limited number of certain specific clinical situations. These include:

1. Detecting low-grade bone infection

2. Monitoring some patients with systemic lupus erythematosus.

3. The detection of paraproteinaemias, *which often do not elicit an acute phase response.*

Time Courses for CRP Responses

These include:

- **CRP levels begin to rise within 6 hours of an acute inflammatory response in the body.**
- **It has a doubling time and a decay time of around six hours.**
- **Maximal concentrations are reached in less than two days.**
- **After the inflammation has resolved, concentrations fall rapidly.**

Indications for Testing

C-reactive protein is indicated for:

1. The detection of infective or inflammatory disease, particularly when this is **clinically uncertain**.
2. In some situations for the monitoring of **disease activity**.
3. The **response to treatment**.
4. As a prognostic / severity indicator.

   Examples include:

   For CAP (i.e Community Acquired Pneumonia): [2]

   - A CRP < 100 mg/L on admission is associated with reduced 30-day mortality, need for mechanical ventilation and/or inotropic support, and complicated pneumonia.
   - Failure of C-reactive protein to fall by 50% or more at day 4 is associated with increased risk of 30-day mortality, need for mechanical ventilation and/or inotropic support, and complicated pneumonia.

   For ACS:

   - Higher levels correlate with worsening prognosis

   For pancreatitis:

   - Levels above 150 mg/L at 24 or 48 hours predicts severe pancreatitis.

For Cellulitis:

- Elevated levels predict the need for a more prolonged hospital admission (i.e. > 24 hours), and so can assist in disposition planning (e.g. SSU admission versus ward admission). [5]

For Ulcerative colitis:

- CRP is a good indicator of the severity of UC - it can assist in the stratification of disease severity into mild, moderate and severe.

  A CRP level > 30 mg/L is one of the standard **Truelove** and **Witts Criteria** that define **acute severe ulcerative colitis.**

- CRP is also used to assess the response to treatment (or otherwise) for UC.

5. TIA/Stroke:

   - Current National Stroke Foundation Guidelines recommend CRP (or ESR) as part of the **routine** workup for TIA/ Stroke patients, (*TIA in National Stroke Foundation Guidelines, Website, accessed November 2017*).

Causes of an Elevated CRP

1. Infection:

   - Bacterial or viral

2. Inflammatory conditions

3. Malignancy.

4. Necrosis:

   - Myocardial infarction

   - Acute pancreatitis

5. Trauma:

   - Burns

   - Fractures

6. Clozapine induced myocarditis:

- In patients taking clozapine an unexplained rise of CRP of more than 50 mg/L may herald the onset of myocarditis. [4]

Causes of a Falsely Elevated Value:

Minor elevations may be seen in:

1. Renal dysfunction

2. Obesity

Causes of a Falsely Low Value:

These include:

1. Severe hepatic failure.

2. Caution in neonates, as levels may not significantly rise, even with serious bacterial infection.

3. Some specific inflammatory conditions do not show significant elevations in CRP, and so a CRP level may be less reliable in these conditions, (see appendix 2 below).

4. Caution in the *early* time frame of a disease process.

Interpretation of CRP Results

The CRP is an indicator of infection and inflammation occurring in the body.

It is sensitive but not specific.

An elevated CRP level should be interpreted in the light of the overall clinical assessment of a patient, including the history, the examination and the results of other investigations.

The particular risk profile a patient has for any given pathology is also an important overall consideration.

In general terms the higher the level of the CRP, the more likely it is that serious bacterial infection exists, (although this correlation in less reliable in neonates)

Correlation of CRP levels with likelihood of infection:

In general terms:

1. A normal C-reactive protein is unlikely in the presence of significant bacterial infection.

2. Intermediate C-reactive protein concentrations (10–50 mg/L) may be seen in both bacterial and viral conditions.

3. A very high C-reactive protein (**greater than 100 mg/L**) is more likely to occur in **bacterial** rather than viral infection.

4. **Note also that CRP values are *dynamic* and so should not just be considered as one off isolated results.**

   Serial measurements are also invaluable in assessing patients especially where uncertainly exists.

Clinical Utility of the CRP in the Emergency Department:

In the Emergency Department it is most useful for raising or lowering the index of suspicion for disease when the presence of significant disease is uncertain.

It hence may assist in guiding important clinical decisions regarding:

- **Initiation of empirical treatments.**
- **The need for further investigation.**
- **Disposition, (the need for admission for treatment and/ or close monitoring).**

Additionally it should be noted that a *normal* CRP result does *not* exclude the possibility of serious bacterial infection, especially in *early* presentations or neonates and hence clinical context again will be important when interpreting a *negative* result.

Appendix 1

Acute Phase Proteins [1]

Acute-phase proteins

	Increased concentrations	Decreased concentrations
Protease inhibitors	$alpha_1$-antitrypsin antichymotrypsin	
Coagulation proteins	fibrinogen prothrombin factor VIII plasminogen	
Complement proteins	C1s, C2, C3, C4, C5 factor B C1 esterase inhibitor plasminogen	
Transport and storage proteins	haptoglobin haemopexin caeruloplasmin ferritin	transferrin
Miscellaneous	C-reactive protein procalcitonin serum amyloid protein fibronectin $alpha_1$-acid glycoprotein	albumin pre-albumin

Minor or no elevations

Inflammatory disease	systemic lupus erythematosus systemic sclerosis dermatomyositis ulcerative colitis Sjogren's syndrome

References

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3. M. Harrison, Erythrocyte sedimentation rate and C-reactive protein. Aust Presc 2015; 38:93 - 4

4. Clozapine-induced Myocarditis - Monitoring Protocol Policy Directive: NWS Health PD2012_005 Issue date: January 2012.

5. Jeremy W Abetz, Nicholas G Adams Harvey Newnham, De Villiers Smit and Biswadev Mitra. Transfer of care and overstay in the management of cellulitis in the emergency short stay unit: A retrospective cohort study. Emergency Medicine Australasia (2017) 29, 143 -148.

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