The Value of High-sensitivity CRP in Clinical Use
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Introduction

The purpose of this booklet is to describe how Orion Diagnostica’s QuikRead go® hsCRP+Hb- test can be used in the diagnostics of various clinical conditions. QuikRead go hsCRP+Hb is a point-of-care test for measuring low C-reactive protein (CRP) and Hemoglobin (Hb) values in situations where an accurate and rapid treatment decision is needed. Regardless of the test measuring two analytes, this booklet focuses mainly on the use of CRP.

CRP is an extremely valuable hepatocytic marker, which is activated by a wide range of stimuli including inflammation, infection, tissue damage, and neoplasia. The major transcriptional upregulators of CRP are pro-inflammatory cytokines, especially IL-6. ¹

CRP is present in low concentrations in the blood of healthy individuals, but following an acute-phase stimulus the concentrations can increase thousand fold ¹–⁴. Elevated CRP concentrations can be detected within 6–12 hours after the stimulus ⁵,⁶. The half-life of CRP is constant 19 hours regardless of the cause of elevation, indicating that the concentration in blood is determined only by the synthesis rate ⁶.

Traditionally CRP assays have been used in evaluating inflammation, infection and tissue damage and thus providing valuable information to support diagnosis and treatment decisions. Later CRP has become valuable in distinguishing bacterial from viral infections, as CRP concentrations increase prominently in the former but more modestly in the latter case ², ³, ⁵, ⁷–¹¹. This information is critical for rapid diagnostics of infections and decisions on starting antibiotic treatment. Unnecessary use of antibiotics exposes patients to adverse drug effects and leads to emergence of resistant bacterial strains ¹²,¹³.

Recent development of highly sensitive CRP (hsCRP) assays has opened up the field for wider use of CRP in diagnostics. Modestly elevated CRP values as well as patient specific variations within the range of 0.5–5 mg/l, previously considered being within the reference interval of healthy adults ¹ or undetectable before 6–12 hours after symptoms ¹, ¹’, have shown to be clinically relevant in numerous patient groups and clinical applications.

QuikRead go hsCRP+Hb is a user-friendly test for fast and reliable measurement of low CRP values. The measuring range is wide (0.5–75 mg/l)
and suitable for various needs. The test is performed on a finger-prick blood sample and results are available in minutes during the patient consultation.

Baseline CRP values in general population

The median value of CRP in apparently healthy adults is 0.8 mg/l, with a distribution including 90% of the population below 3 mg/l and 99% below 10 mg/l 14. Normal baseline CRP values in healthy adults are therefore usually measurable only by hsCRP assays.

It is important to establish the true individual baseline CRP values before making assessments. Besides occasional spikes, CRP levels are stable on long term 1,15,16 and two separate measurements are considered adequate and take sufficiently into account the within-individual variability 15,17. The variation within the normal distribution in healthy adults is a consequence of different individual hereditable as well as environmental factors, presented below.

Determinants of baseline CRP level

CRP concentrations vary slightly between ethnic groups 18,19 and are somewhat higher in women compared to men 20,21. The difference between genders likely reflects effects of estrogen 22,23. CRP concentrations tend to increase marginally with age 1,20,21,24,25, assumedly due to more subclinical disease in older population 20,21. Baseline CRP levels are also affected by choice of lifestyle and several conditions presented on the next page 26,27.

Factors elevating baseline CRP

- Smoking
- Elevated BMI / Obesity
- Low HDL cholesterol
- High LDL cholesterol
- High triglyceride levels
- Elevated blood pressure
- Metabolic syndrome / Diabetes mellitus
- Chronic infections
- Chronic systemic inflammatory processes
- Estrogen/progesteron hormone use

Factors lowering baseline CRP

- Moderate alcohol consumption
- Increased activity
- Weight loss
- Smoking cessation
- Medication (e.g. statins)

Smoking

CRP concentrations are higher in active smokers 20,24,25,28–30, and rise with increasing amount of cigarette consumption 25,29. The elevation in CRP concentration is probably due to persistent low-grade inflammatory and tissue-damaging effects as well as increased susceptibility to respiratory infections 20.

Metabolic syndrome

A low-level systemic inflammation has been identified as the driving force for metabolic syndrome 21,31. CRP levels rise in metabolic syndrome and many metabolic factors, especially BMI, blood pressure and lipid levels, are significantly associated with CRP 21,32. The association between CRP and metabolic risk exists across all age groups and in both genders 21.

Obesity

Obesity raises CRP levels, possibly due to greater amount of adipose tissue and increased cytokine production 24,33,34. Elevated CRP levels are associated with both central abdominal obesity 32 and elevated BMI 24,25,34,35. Even young persons with BMI ≥25 kg/m² are likely to have elevated CRP levels, which suggests the presence of a low-grade systemic inflammation in all overweight and obese persons 34.
Main indications for QuikRead go hsCRP+Hb

Mild elevations in CRP concentrations are associated with various disorders and clinical conditions. The most prominent therapeutic areas, where measuring low CRP concentrations is of value are presented in the following chapters. The main areas of use with clinical importance are:

- **Recurrent coronary events** 36-42
  
  Use: Prediction of recurrent coronary events and course of disease, selection of individuals for treatment and intensified patient monitoring

- **Neonatal sepsis** 43-46
  
  Use: Diagnosis and exclusion of bacterial infection, guidance in antibiotic treatment, management of infection, monitoring response to treatment

- **Chronic obstructive pulmonary disease (COPD)** 47-54
  
  Use: Prediction of prognosis and complications, assessment of disease activity, monitoring response to treatment, CVD risk assessment

- **Rheumatoid arthritis (RA)** 55-60
  
  Use: Prediction of outcome and complications, assessment of disease activity, monitoring response to treatment, CVD risk assessment

- **Other conditions that include systemic inflammation**
  
  Asthma, Systemic Lupus Erythematosus, Osteoarthritis, Osteoporosis, Diabetes Mellitus.

HsCRP in diagnosis of recurrent coronary events

Atherosclerosis is the major cause of premature death in Europe 41. The chronic disease includes thickening of arterial walls due to accumulation of lipids and formation of plaques, and a chronic inflammatory process 1,62,63. All stages in development of atherosclerotic plaques are considered inflammatory responses to injury 36. Morphological changes in blood vessel walls, erosion and rupture of atherosclerotic plaques, thrombosis, narrowing of blood vessels and restricted blood flow to the heart form the basic pathophysiological mechanisms in most cardiac events 63,64.

Recurrent coronary events, some of which are listed below, are serious cardiac complications in patients that have already experienced a previous coronary event.

- **Stable angina** is an often exertion-induced chest pain appearing in a typical pattern when the heart is working harder. Symptoms ease during rest or with medication. 65

- **Unstable angina** is a cardiac-induced unexpected chest pain. The condition is critical and might lead to myocardial infarction or revert. It is also considered to be intermediate in severity between stable angina and myocardial infarction. 66

- **Myocardial infarction (MI)** is a coronary event that involves damage or death of heart muscle cells caused by limited blood supply to the heart. Depending on the extent of damage the condition can be fatal. 67,68

Elevated plasma hsCRP levels are associated with increased likelihood of recurrent coronary events in patients with stable angina 37, unstable angina 36-40 and MI 36,41,42. The acute-phase response may reflect the intrinsic inflammation and tissue damage within arterial lesions 37. The elevation is associated with poor outcome at the time of event 36-39, and on long term from 6 months up to 4 years 41,42,69-73.
Elevated hsCRP after angina

Plasma hsCRP levels remain elevated (>3 mg/l) in about half of patients with unstable angina. Elevated levels at discharge are associated with recurrent episodes, including phases of instability and myocardial infarction, within 1 year. Phases of instability might be associated with persistent inflammation and seem to occur more often the higher the hsCRP concentration is. Measuring hsCRP at discharge might be useful in identifying patients who need to be treated and monitored more closely.

HsCRP in patients with Myocardial Infarction (MI)

MI involves myocardial cell damage, an acute inflammation, as well as CRP and activated complement in the infarcted myocardium. CRP levels reflect the degree of tissue injury and myocardial necrosis, and a massive peak in CRP concentration, associated with the acute-phase response, is seen approximately 50 hours after onset of pain. The peak CRP concentration may be 50–350 mg/l. Aside from this major CRP response, slightly elevated CRP levels at admission and on long-term after MI are associated with increased likelihood of recurrent coronary events.

Elevated hsCRP at admission

Elevated hsCRP (>3.6 mg/l) at admission (>3.6 mg/l) is associated with increased likelihood of subsequent MI or sudden coronary death in patients with stable or unstable angina. When comparing to unstable angina patients with normal hsCRP levels, unstable angina patients with elevated hsCRP (>3.0 mg/l) levels also experience longer hospital stay, more ischemic episodes and recurrent angina during the hospital stay, as well as poorer clinical short-term outcome including MI and death.

The relative risk of coronary events is 2 times greater for patients with unstable and stable angina with hsCRP concentration >3.6 mg/l at admission compared to patients with lower hsCRP values.

HsCRP in patients with stable and unstable angina

Elevated hsCRP (>2–3.6 mg/l) concentration is seen in most patients with stable and unstable angina. The elevation of hsCRP level and subsequent coronary event rate seems to be slightly milder in stable angina compared to unstable angina.

Elevated hsCRP level at admission

Elevated hsCRP level at admission (>3.6 mg/l) is associated with increased likelihood of subsequent MI or sudden coronary death in patients with stable and unstable angina. When comparing to patients with normal hsCRP levels, unstable angina patients with elevated hsCRP (>3.0 mg/l) levels also experience longer hospital stay, more ischemic episodes and recurrent angina during the hospital stay, as well as poorer clinical short-term outcome including MI and death.
up hsCRP levels immediately after coronary events such as angina pectoris and MI, in order to recognize recurrent complications and provide treatment early. 41

**Elevated hsCRP after MI**
Permanently high or rising CRP levels after non-fatal MI might indicate poor short-term outcome 76–79, whereas levels normalize or at least decrease close to normal in patients who experience a better recovery 76. Permanently slightly elevated hsCRP levels (>4.24–6.6 mg/l) among MI-survivors on long term, from half a year to many years after the infarction, are evidence of persistent inflammation and correlate with increased likelihood of subsequent recurrent MI or coronary death 41,42. Follow-up of hsCRP levels in MI-survivors is thus also emphasized, as patients who need to be monitored more closely can be identified.

*CRP concentrations >6.6 mg/l measured 9 months after MI are associated with a 1,8 relative risk of recurrence, when comparing to MI-patients with CRP concentration ≤6.6 mg/l. hsCRP tests might thus provide a mechanism of dividing post infarction patients into groups with high and low likelihood of recurrent events. 41*

**Cut-off values for increased likelihood of recurrent coronary events**
Diagnosis and treatment strategies for recurrent coronary events need to address both the acute phase and longer term management.

*The hsCRP concentration of approximately 3 mg/l (>90th centile of normal distribution 14) is widely used as a cut-off value for increased likelihood of recurrent coronary events 36–38.*

Measuring CRP during the event:
- During and immediately after acute ischemia, levels of CRP can rise substantially 36,76,77 and baseline CRP level might thus be hard to interpret. Measures of ventricular function and infarct size might have greater predictive value immediately after an infarct 82.
- If CRP levels are measured during and after coronary events, serial measurements are recommended.
- Declining CRP levels are reassuring while increasing levels might indicate recurrence.

Measuring after CRP concentrations have stabilized:
- Elevated hsCRP levels in patients after coronary events and at readmission predict poor outcome and recurrence 36–42,76.
- If a baseline CRP level is sought, two measurements optimally two weeks apart should be done 26. CRP levels are stable on long term 1,15,16 and two separate measurements are considered adequate and take sufficiently into account the within-individual variability 15,17.
- If the initial result is below 1 mg/l a single measurement is considered sufficient 1.
- The assay should be performed in metabolically stable persons without signs of inflammatory or infectious conditions. CRP levels over 10 mg/l might indicate other inflammatory diseases. The result should be discarded and the test repeated after two weeks or later, when a possible acute inflammation has passed. 26

Using hsCRP measurement alone as an alternative to ECG (electrocardiogram) and major risk factors in assessment of likelihood of recurrent CVD is discouraged 1,26. Due to the nonspecific character of the CRP response it is of high importance to evaluate the overall situation, full history and physical examination of the patient 1,61. Other factors and determinants of CRP level should also be taken into consideration before making decisions based on hsCRP measurements 1,61.
HsCRP in diagnosis of neonatal sepsis

Neonatal sepsis is usually defined as bacterial blood stream infection within approximately the first 28 days of life. It is a major cause of neonatal mortality and morbidity despite advances in perinatal and neonatal care.

Sepsis presenting within the first 3 days of life is classified as early-onset sepsis (EOS) and associated with organisms acquired in utero or during delivery. Later cases are classified as late-onset sepsis (LOS) and usually associated with bacteria acquired after delivery from nosocomial or community sources. The occurrence of EOS is 1–8/1000 live births, and mortality rates range from 1.5% in term neonates to almost 40% in neonates with low birth weight.

Diagnostic measures for neonatal sepsis include blood culture, urine culture, CRP measurement and complete blood count. CRP measurement has proven to be superior to many other markers in diagnosis of neonatal sepsis. It is one of the most widely available, studied and used test for this purpose and considered very reliable. Besides aiding in the diagnosis, serial CRP measurements can aid in monitoring response to and determining duration of antibiotic treatment in septic neonates.

The natural CRP level and the CRP response are however lower in neonates than in adults, and more sensitive tests than traditional CRP assays are needed to diagnose neonatal sepsis fast enough. Considering the doubling time of CRP and lower CRP concentration in cord blood, even up to 8 hours or more might elapse before a neonate who becomes bacteraemic at birth presents CRP levels detectable by traditional CRP assays (>5mg/l). QuikRead go hsCRP+Hb makes serial measuring of low CRP concentrations and thus earlier detection and closer monitoring of neonatal sepsis fast and easy. The test is reliable and has a wide measuring range covering CRP values of both healthy and septic neonates. QuikRead go hsCRP+Hb also helps when making urgent decisions on starting, withholding and especially...

Markers for recurrent coronary events

Presentation of established CVD risk factors, whereof some are listed below, increases the likelihood of recurrent CVD events.

- Hypertension
- Hyperlipidemia
- Low HDL cholesterol
- High LDL cholesterol
- High BMI
- Diabetes
- Cigarette smoking
- Physical inactivity
- Age
- Low diastolic blood pressure
- Previous history of CVD

Also biomarkers like e.g. troponins, creatine kinase MB, creatinine, N-terminal prohormone brain natriuretic peptide (NT-proBNP), albuminuria, circulating tissue plasminogen activator antigen (tPA) and soluble vascular cell adhesion molecule (VCAM) might be useful in assessing likelihood of recurrent coronary events.

Guideline on use of hsCRP when assessing likelihood of recurrent CVD

The American Heart Association (AHA)/Centers for Disease Control and Prevention (CDC) statement on use of markers of inflammation and cardiovascular disease state that hsCRP may be useful as an independent marker of prognosis for recurrent events, including death, MI and restenosis after percutaneous coronary intervention in patients with stable coronary disease or acute coronary syndromes. The benefits of therapy based on this strategy do however remain uncertain.
CRP reference intervals for healthy neonates

Healthy newborns experience a natural physiological increase in CRP concentration after birth, reaching a peak during the first days after birth and then decreasing slowly \(^43,44,46,109\). Different CRP reference intervals are needed for healthy term and preterm neonates due to the strong positive effect of gestational age and birth weight on the elevation (fig. 1) \(^43,112\).

Generally the nonspecific elevation seen in neonates during the first days of life is considered to reflect stress during the birth process \(^109,112\). Duration of active labor, prenatal steroid exposure, PROM, intrapartum antimicrobial prophylaxis, mode of delivery and intrapartum fetal distress \(^43\) as well as maternal infections or resuscitation \(^44\) have an effect on CRP concentration of neonates. Neonates born by vaginal delivery have higher CRP concentrations than those born by cesarean section \(^43,99\). Mean CRP levels at birth can increase 0.4–40% due to these various factors, most by prenatal steroid exposure and intrapartum antimicrobial prophylaxis \(^43\).

CRP concentrations in early-onset sepsis (EOS)

Neonates suffering from sepsis present, besides other nonspecific signs of sepsis, an acute-phase reaction and rising CRP concentrations. CRP secretion starts 4–6 hours after stimulation and peaks at 24–48 hours \(^99\). The rise is separate from the natural physiological increase seen after birth and more modest than the rise seen in septic adults. Most adults with severe bacterial infection present CRP concentrations over 100 mg/l \(^3,7,8\).
Neonatal infections progress rapidly and any delay in treatment can be critical. Starting antibiotic therapy in all neonates showing symptoms exposes them to adverse drug effects and nosocomial complications and can lead to emergence of resistant bacterial strains. Infants who receive antibiotics for more than 3 days have an increased risk of abnormal bacterial colonization and in extremely low birth weight infants prolonged antibiotic therapy increases the risk of necrotizing enterocolitis and death.

If only bacterial culture is used, time to results can be 24–48 hours, and antibiotic treatment might therefore be started before the infection is clinically proven and the antibacterial sensitivity testing has been completed. Obtaining adequate samples for blood cultures from preterm neonates is challenging due to small blood volumes, and since implementation of guidelines on maternal intrapartum antibiotic prophylaxis blood culture results can also often be unreliable. Sepsis diagnostics cannot thus rely only on bacterial culture.

Besides aiding in the diagnosis of sepsis, CRP measurements are valuable when making antibiotic treatment decisions. Sensitivity is more important than specificity in diagnosis of early onset sepsis, as unnecessary treatment has fewer consequences than leaving the neonate untreated. The sensitivity of CRP is lowest during early stages of infection and increases with serial determinations. As the negative predictive value of CRP measurement is high (approx. 99%), serial measurements of CRP are especially useful for ruling out bacterial infections, monitoring the patient and guiding in decisions on when to start or end antibiotic treatment.

Neonates need to be protected both from the consequences of sepsis and adverse effects of unnecessary antibiotics. Current recommendations support initiation of antibiotic therapy in all neonates showing infection-like symptoms. Detecting subtle and various non-specific clinical features is however difficult and can lead to unnecessary antibiotic therapy, based solely on clinical grounds.

Practical advice on using CRP in diagnosis of neonatal sepsis

Measuring CRP is the preferred index in most neonatal intensive care units but current literature does not support use of only CRP when deciding on antibiotic treatment. Nor is a single CRP determination enough to diagnose...
Elevated hsCRP levels are associated with increased risk of incident COPD, and hsCRP levels are higher in COPD patients compared to healthy individuals 47–54. The median hsCRP concentration in COPD patients is 1.92–5 mg/l 50, 51, 53, 54 depending on severity of disease.

COPD patients are classified in different disease or GOLD (Global Initiative for Chronic obstructive Lung Disease) stages according to degree of airflow limitation. CRP correlates with disease stage and thus severity of disease 51, 53, and rise in COPD patients during exacerbations 127.

Table 1. Effects of pulmonary function, airflow limitation, predicted severity of airflow limitation, mean CRP levels, and age-adjusted percentages of subjects with CRP over 3.0 or 10.0 mg/l, in a study made as part of the Third National Health and Nutrition Examination Survey (NHANES III) 51. The fixed FEV1/FVC ratio of <0.70, defines airflow limitation and confirms the presence of COPD, whereas FEV1 is used for classification of severity of airflow limitation 129. FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity.

<table>
<thead>
<tr>
<th>Lung function</th>
<th>Airflow limitation (FEV1/FVC)</th>
<th>Severity of airflow limitation (FEV1)</th>
<th>Mean CRP (mg/l)</th>
<th>CRP ≥ 3.0 mg/l (%)</th>
<th>CRP ≥ 10.0 mg/l (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe COPD</td>
<td>&lt;0.70</td>
<td>&lt;50%</td>
<td>4.7</td>
<td>52</td>
<td>23</td>
</tr>
<tr>
<td>Moderate COPD</td>
<td>&lt;0.70</td>
<td>≥50 to &lt;80%</td>
<td>3.6</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>Mild COPD</td>
<td>&lt;0.70</td>
<td>≥80%</td>
<td>2.9</td>
<td>27</td>
<td>6</td>
</tr>
</tbody>
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HsCRP in diagnosis of Chronic obstructive pulmonary disease (COPD)

COPD is a complex inflammatory disease and an increasing cause of morbidity and mortality worldwide 57, 123, 124. It is often progressive and untreatable, includes airflow limitation through airway obstruction, lung inflammation and low grade systemic inflammation 47–52, 123, 124. The regulation of inflammation in the pulmonary and systemic compartments as well as the relationship between the compartments are still unclear 13, 125.

Sepsis. The prognostic value of CRP in neonatal sepsis improves when doing serial determinations or using many markers in parallel.

- An hsCRP assay is recommended when measuring neonatal CRP values 44.
- Serial hsCRP measurements are valuable in determining neonatal baseline CRP level, recognizing significant rises in hsCRP and ruling out infection when suspecting sepsis 44, 94, 96, 109.
- Serial hsCRP measurements can be used to guide duration of antibiotic treatment in septic neonates 58, 109–111, thus restricting unnecessary use of antibiotics.
- If at least two hsCRP measurements are normal at 48 hours and the infant is stable, discontinuing antibiotics can be considered 98, 99.
- Due to the nonspecific character of the CRP response and confounding factors it is of high importance to evaluate the overall situation, history as well as physical and clinical course of the mother and neonate 98. The natural physiological rise of CRP in the neonate after birth should also be taken into consideration.
- Best diagnostic accuracy is reached when measurement of CRP is combined with other confirmative methods such as bacterial culture or white blood cell differential count 98, or another infection marker like procalcitonin, IL-6 or IL-8 43, 46, 96, 108, 120, 122. Combining CRP measurement with early sensitive markers increases the sensitivity to 90–100% 46.

COPD treatment is intended to slow down disease progression and to prevent exacerbations. COPD is commonly treated with inhaled corticosteroids 49, 50, 130, bronchodilators 111, antibiotics 112–114 or some combination of the aforementioned. Inhaled corticosteroids decrease CRP concentrations significantly 49, 50 and withdrawal of inhaled corticosteroid treatment can result in a drastic increase in baseline CRP 49.
CVD in COPD patients

Over half of COPD patients die from cardiovascular causes. COPD and poor lung function are known risk factors for atherosclerosis, ischemic heart disease and other cardiac complications, elevating the risk of CVD to 2–3 fold.

Airflow obstruction alone is associated with increased occurrence of ischemic changes and cardiac injury, but in the presence of elevated hsCRP the risk increases additionally almost 2-fold. This indicates an additive effect of COPD and higher hsCRP levels on risk of cardiac injury. The persistent systemic inflammation in COPD may contribute to the pathogenesis and explain the high risk of cardiovascular mortality in patients with COPD.

CRP in diagnosis of Rheumatoid arthritis (RA)

RA is a chronic and progressive systemic inflammatory disease that leads to joint damage and functional disability. Disease progression occurs at any stage but apparently faster early on in the disease. Frequent assessment of disease activity allows timely adaptation of therapy, which is essential in preventing disease progression. The ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function and decrease pain.

RA can be diagnosed by many indices, that usually include e.g. joint symptoms, serological markers such as Rheumatoid factor (RF) and/or Anti-citrullinated protein antibody (ACPA), symptom duration (>6 weeks), and acute-phase reactants (CRP and/or Erythrocyte sedimentation rate [ESR]). Acute-phase reactants are well known markers of RA disease progression and predictors of disease outcome, and included both in e.g. the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines for diagnosis and assessment of RA. Despite being well known and commonly used as an aid in the evalua-
tion of RA disease activity, acute-phase reactants are not used as independent guides for therapy.149

Elevated CRP levels reflect RA disease activity56–58 and CRP concentrations may rise already prior to RA being clinically evident150. CRP can help in predicting outcome in patients with early undifferentiated inflammatory arthritis58 as well as progression to joint replacement in patients that already have established disease57. It may also aid in identifying patients likely to progress rapidly and who require intensive therapy55.

CRP concentrations in RA patients vary depending on disease activity and degree of control from median values of approx. 5.0 mg/l56,59 to values well into clinical range, e.g. 15 mg/l or more53,60,151. HsCRP assays can be used to identify mild disease activity that is associated with inflammation but not detectable by traditional CRP tests56. The need of tests that measure both low CRP values (<5 mg/l) and higher concentrations within the clinical range of CRP is thus evident.

QuikRead go hsCRP+Hb can be used as an aid in predicting outcome as well as assessing disease activity in patients with RA. It can also aid in deciding whether therapy is needed and in evaluating possible increased risk of CVD in patients with RA. The wide measuring range of 0.5 – 75 mg/l enables the use of QuikRead go hsCRP+Hb in various settings, regardless of whether the RA patient’s CRP levels are below or within the clinical range.

CVD in patients with RA

There is excess cardiovascular mortality and morbidity linked to systemic inflammations in RA patients152–156 and this is the predominant cause to reduced life expectancy in patients with the disease157–160. CRP is an independent predictor for preclinical CVD, cardiovascular events and cardiovascular mortality in RA patients160–165 and especially informative when serial measurements are performed and clinical course evaluated. Increased incidence of CV events does not seem to be connected to traditional cardiac risk factors156.

The majority of RA patients have CRP levels associated with increased risk of cardiovascular events (>3 mg/l)19 and having a CRP level over 5 mg/l is associated with a 3.3 relative risk of cardiovascular death in patients with RA162.

HsCRP measuring is also of use in distinguishing between asthma exacerbations with moderate hsCRP elevation (e.g. 9 mg/l) and antibiotic treatment requiring respiratory illnesses177.

Other indications

HsCRP measurement is valuable in patient-specific assessment of disease activity and response to treatment in conditions that include systemic inflammation. Elevated or increasing hsCRP levels can encourage starting treatment while low and decreasing levels can be reassuring. Some indications where hsCRP seems to have a role are described below.

In some of the conditions CRP values rise into the clinical range. As QuikRead go hsCRP+Hb has a wide measuring range (0.5 – 75 mg/l), it is suitable for these purposes as well.

Asthma

Asthma is a chronic inflammatory disease of the airways. HsCRP levels are increased in asthmatics169–172, especially in uncontrolled172–174 and severe cases175 as well as during attacks169,173. HsCRP levels in asthmatics correlate with severity of disease173,175 and may also be related to the state of asthma exacerbation and possibly allergic inflammation169,171.

Serial hsCRP measurements can be used for assessment of grade of asthma severity and control when monitoring patients and response to treatment. Publications show an hsCRP range of 1.33 – 3.15 mg/l in asthmatics172,174,175. HsCRP measuring is also of use in distinguishing between asthma exacerbations with moderate hsCRP elevation (e.g. 9 mg/l) and antibiotic treatment requiring respiratory illnesses177.
Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease. Impaired clearance of apoptotic cells is important in the pathogenesis of SLE, and CRP dysregulation may play a part in this process.

Median CRP levels in SLE range from 4 mg/l in inactive SLE, to 14 mg/l in active SLE, with concentration increasing by severity of disease. Plasma CRP levels over 9 mg/l are associated with increased risk of cardiovascular events in patients with SLE (Odds ratio 2.6).

Osteoarthritis (OA)

OA or degenerative joint disease is a common and disabling musculoskeletal disorder, involving destruction of cartilage and bony remodeling. Modest but significant increases in hsCRP can be seen in osteoarthritis. Elevated hsCRP is considered a predictor of progressive disease and a marker of clinical severity of OA.

The hsCRP elevation in OA is more modest than in RA, according to publications. Mean hsCRP concentration is elevated in women with early knee OA and in patients whose disease progress. Elevated hsCRP values predict patients whose disease will progress over 4 years and could benefit from more aggressive treatment.

Osteoporosis

In osteoporosis bone resorption exceeds bone formation. Elevated hsCRP levels are associated with lower bone mineral density in healthy women and men. Odds ratio for osteoporosis and osteopenia are 1.35 when hsCRP is >1.2 mg/l in pre-menopausal women, and odds ratio for osteoporosis is 1.54 when hsCRP is >1.8 mg/l in postmenopausal women. Some indications also exist for an association between elevated hsCRP levels and risk of bone fractures.

Diabetes mellitus type 2 (DM2)

A low-level systemic inflammation plays a key role in pathogenesis of insulin resistance and DM2, and in closely linked conditions such as obesity and the metabolic syndrome. Insulin resistance correlates with the risk of CVD, thus explaining some of the excess mortality in patients with DM2. HsCRP is a clinically valid biomarker to predict and monitor development of insulin resistance and DM2, as well as to assess and monitor cardiovascular risk in diabetic individuals.

CRP levels are chronically elevated in patients with clinical DM2 and according to publications slightly elevated CRP levels even within the conventional healthy reference range predict development of DM2. E.g. apparently healthy elderly people with hsCRP>2.86 mg/l are approximately two times more likely to have DM2 on 3–4 years’ follow-up than persons with hsCRP <0.82 mg/l.

Diabetes mellitus type 2 subtype HNF1A-MODY

Maturity-onset diabetes of the young (MODY) subtypes are characterized by autosomal dominant inheritance and onset before the age of 25. HsCRP is a clinically valid biomarker for identifying the most common subtype, HNF1A-MODY. Hepatocyte nuclear factor 1-a (HNF1A) is expressed in the liver and involved in the regulation of several liver specific genes, but in the MODY subtype the gene is mutated and its dysfunction causes diabetes.

The HNF1A-MODY subtype requires different treatment, but because of high costs and restricted availability of molecular testing many patients are left with undiagnosed or incorrectly diagnosed diabetes.

HNF1A is required for CRP expression and CRP levels do not rise in the HNF1A-MODY subtype. Median hsCRP levels in HNF1A-MODY patients are 0.03–0.25 mg/l, i.e. significantly lower than in healthy adults. As hsCRP assays are affordable and widely available, they could translate rapidly into clinical practice and improve diagnosis rates in monogenic diabetes considerably.
QuikRead go® hsCRP+Hb

Flexibility and speed for various situations

- Versatile use
- Fast results
- Reliable with high quality

QuikRead go®

Your support in treatment decisions

Orion Diagnostica’s next generation point-of-care test system is designed to support the diagnosis and treatment management in healthcare settings by providing valuable information for decision making. The system is easy to use as well as connectable, and requires minimal hands-on time. Presently the following tests are available for the system:

- CRP
- CRP+Hb
- hsCRP+Hb
- Strep A
- New! iFOBT

Please also visit www.quikread.com


