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PRACTICE

RATIONAL TESTING

Raised inflammatory markers

What is the evidence for using C reactive protein, erythrocyte sedimentation rate, and plasma viscosity in diagnosis?

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 72 year old man consulted a general practitioner colleague of ours last week complaining of a non-specific feeling of malaise for about three weeks, with mild headache and pain in his left knee. He has generalised moderate osteoarthritis, mainly affecting his back and both knees. Our colleague had found nothing relevant on examination and had ordered several blood tests. A full blood count and liver and renal function were normal, but the erythrocyte sedimentation rate was moderately raised at 35 mm/h.

What is the role of inflammatory markers?

Measurement of inflammatory markers has two main functions: to detect acute inflammation that might indicate specific diseases, or to give a marker of treatment response (we will not consider this second indication here). Measurement of inflammatory markers can also be used as a general, but non-specific, test for serious underlying disease. Inflammatory markers are measured in about 4% of general practitioner consultations, for a range of indications, with 44-47% requested for specific diagnostic purposes, 27-33% for monitoring of disease, and 14-28% for non-specific diagnostic purposes.[1 2] There is considerable inter-practice variation in the measurement of inflammatory markers and in general practitioners' responses to abnormalities.[1 3 4] We found no health-economic analyses of these tests, but the total costs of testing must be considerable. For example, 63 000 primary care requests for inflammatory markers are tested annually at the University Hospitals Bristol NHS Foundation Trust, which serves a population of about 300 000 in 40 general practices (personal communication, W Woltersdorf, 2011).

Diseases with prominent activation of the inflammatory response fall into three main groups: infections, autoimmune diseases, and some haematological malignancies. Inflammatory markers include C reactive protein (CRP), erythrocyte sedimentation rate, plasma viscosity, fibrinogen, ferritin, and several other acute phase proteins, though only the first three are commonly referred to as inflammatory markers. CRP is considered to be particularly useful in detecting bacterial infection.[4] Plasma viscosity is now generally preferred to the erythrocyte sedimentation rate (ESR), as it is unaffected by anaemia or polycythaemia, or by delays between sampling and measurement, and has results independent of age or sex.[5] All these factors potentially affect the ESR. The change to use of viscosity is relatively recent, so most reports have studied the ESR or CRP. This article considers the evidence for and the rational use of CRP, ESR, and viscosity in diagnosis, both for specific diseases and non-specifically.

Diagnostic testing for specific diseases

The classic conditions for which testing may be useful are polymyalgia rheumatica or giant cell arteritis, recently reviewed in the *BMJ*.[6] Systemic features may predominate, with myalgia or headache minor or absent. A normal viscosity or ESR and normal CRP virtually rules out the condition. False negative results are rare—probably below 3%—though studies examining this required a positive result from a temporal artery biopsy, so the patients evaluated would have had more severe disease.[6] Another condition with characteristic raised inflammatory markers is myeloma.[7] If polymyalgia rheumatica, giant cell arteritis, or myeloma are suspected, measurement of inflammatory markers is a simple "rule out" test: normal inflammatory markers make the chance of any of these diseases being present so low as to allow the clinician to omit specific

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Learning points

- Normal levels of inflammatory markers are valuable in ruling out a few specific conditions, notably polymyalgia rheumatica, giant cell arteritis, myeloma, and infection of hip revisions
- Raised levels of inflammatory markers may be found in many other conditions, particularly infections, autoimmune conditions, and certain cancers. In these cases, they increase the probability of the condition being present, but additional information would be needed to be confident the disease is present or absent
- Inflammatory markers are too non-specific to be a useful tool for diagnosing serious underlying disease and should rarely be used in this situation
- In an incidental finding of raised levels of inflammatory markers, if history and examination yield no clues as to cause, it is reasonable to wait and see if symptoms develop. If levels are markedly raised (such as ESR >100 mm/h), the likelihood of disease is much higher, but history, examination, and focused investigations are usually sufficient to establish a diagnosis

testing with protein electrophoresis and urinary Bence Jones protein.[7]

CRP and ESR have been studied as an aid to differentiating between minor illness and more serious disease, either in primary care or emergency departments. Some subjects have been systematically reviewed (table 1⇓). Most of these reviews show a moderate relation between raised inflammatory markers and the target condition, but almost always the authors concluded that the sensitivities and specificities, on their own, were insufficient to rule in or rule out the condition safely. This was particularly so for primary care, where the prevalence of the target condition is usually lower. However, inflammatory markers may have some value as part of a clinical prediction rule incorporating other relevant clinical features, such as fever, although none seems to have entered mainstream clinical practice. One reason for this may be the inevitable delay in obtaining a result if the specimen requires analysis off site.

Recent studies have examined whether CRP testing influences the decision to prescribe antibiotics for respiratory infections in primary care. One study in Norway, Sweden, and Wales found that the CRP result was the strongest influence on the decision to prescribe antibiotics, outweighing physical signs such as crackles on auscultation.[18] A cluster randomised trial in the Netherlands examined the effect of two interventions: CRP testing or training in enhanced communication skills. Antibiotic prescribing was significantly reduced in both intervention groups—from 57% in control patients to 43% for those whose doctors were in an intervention group.[19] General practitioners responded positively to having point of care access to CRP, as it enhanced patients' and general practitioners' confidence in prescribing decisions and empowered the doctors to prescribe antibiotics less often.[20] In all these studies, negative tests seemed to give the doctors additional confidence in avoiding prescription of antibiotics: this is clinically supported by the negative likelihood ratio of 0.33,[11] meaning that bacterial infection is about a third less likely once a negative test has been reported. The health economic aspects of point of care access to CRP testing would need to be examined before its use was to be recommended.

Observational studies have shown that inflammatory markers may be raised in ovarian, renal, and colorectal cancers, especially in advanced disease.[21-23] However, has been shown to have no discriminatory value in diagnosing these conditions, even in secondary care, where there is a higher prevalence than in primary care.[24]

In summary, there are a few clinical situations in which testing of inflammatory markers is the optimum test, as either a "rule in" or a "rule out" test. These include suspected polymyalgia rheumatica or giant cell arteritis, myeloma (ESR or viscosity), and infection of hip revisions (ESR or CRP). In most conditions, however, there is only a moderate association between raised inflammatory markers and the disease of interest, so they can refine the probability of disease, particularly if the test result is used in conjunction with other factors, such as symptoms.

Non-specific testing for systemic disease

The previous paragraphs focus on the value of inflammatory markers when a specific disease is being considered. However, another use is as a general marker to differentiate between the presence and absence of disease. Several old, mostly small, studies have examined this use (table 2⇓).[25] Generally, when general practitioners test inflammatory markers for non-specific purposes the results are afterwards seen as being of little or no clinical value.[2] "Incidental" abnormalities in inflammatory markers are difficult to interpret and can lead to expensive and potentially harmful investigations. Although doctors may be reassured by negative testing when no disease is suspected,[26] diagnostic tests yielding normal results make hardly any difference to the level of reassurance of patients.[25]

What is the interpretation of an abnormal result?

Interpreting an abnormal result is relatively straightforward if there is a clear pretest hypothesis against which the test result can be evaluated—for example, if assessing the likelihood of serious infection in a child with a fever and abdominal pain. This was best shown in a Dutch study of patients in whom the raised ESR seemed to confirm an initial diagnosis as opposed to showing unexpected disease.[29] The difficulty lies in the interpretation of an "incidental" abnormality, when no specific disease is suspected, as in our hypothetical case. A systems inquiry, focusing on infection, autoimmune conditions, and malignancy, plus examination of the patient should generally point towards specific investigations. If history and examination yield no clues, it is reasonable to wait and see if symptoms develop rather than conduct an extensive search for occult disease. This investigation plan is supported by studies that have followed up patients with unexplained increases in levels of inflammatory markers. In one large (n=1462) study of asymptomatic Swedish women, 60% of these increases were transitory; none of the women with a raised ESR developed cancer; and in 46% of the women the cause of the increase remained undiagnosed over six years of observation.[30]

In cases with markedly raised levels of inflammatory markers (such as ESR >100 mm/h) the likelihood of disease is much higher. The diagnoses found in these conditions depend on study setting, but include infection (33-60%), inflammatory disease (14-30%), and malignancy (5-28%).[7 24 31-33] No diagnosis is found in fewer than 3% of patients with an ESR of >100 mm/h. In most patients, the diagnosis is likely to be clinically apparent; once again, history, examination, focused investigations, and careful follow-up should be sufficient to establish a clear diagnosis.

Outcome

The patient was asked to reattend surgery. His headache had settled, though he still felt non-specifically unwell. Nothing untoward was found on history or examination. He gradually improved over the next two weeks without treatment or further investigation. Measurement of ESR was not repeated.

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Tables

Table 1| Reviews of inflammatory markers for diagnosis of specific conditions

Target condition (test)	Setting	Study type	Outcome
Chorioamnionitis in premature delivery (CRP)	Secondary care	Systematic review (6 reports; 466 patients)[8]	Summary sensitivity 73%, specificity 76%
Serious infections in febrile children (CRP, ESR)	Secondary care	Systematic reviews (5/6 reports on CRP/ESR; 1379 patients having CRP)9 [10]	Likelihood ratio of raised CRP 3.2 (95% CI 2.7 to 3.7); negative likelihood ratio 0.33 (0.23 to 0.49).[10] Similar results in second review[9]
Bacterial chest infection in children (CRP)	Secondary care	Systematic review (8 reports; 1230 patients)[11]	Pooled odds ratio for raised CRP and bacterial infection 2.6 (1.2 to 5.6)
Bacterial chest infection in adults (CRP)	Primary care; accident and emergency departments	Systematic review (8 reports, with 2194 patients)[12]	Likelihood ratio of raised CRP 2.1 (95% CI 1.8 to 2.4); negative likelihood ratio 0.33 (0.25 to 0.43). Similar results in an earlier review[13] and a subsequent study in primary care[14]
Appendicitis in children with abdominal pain (CRP, ESR)	Secondary care (mainly emergency departments)	Systematic review of all features of appendicitis, including 5 studies of CRP, 1 of ESR; 730 and 162 children repsectivley[15]	Likelihood ratio of raised CRP increases as CRP increases: 5.2 (1.7 to 16) for CRP >25 mg/L. For normal CRP, 0.44 to 0.47. For ESR >20 mm/h, 3.8 (1.8 to 8.1)
Osteomyelitis of the leg in diabetes (ESR)	Secondary care (inpatients and outpatients)	Systematic review of all features of osteomyelitis, including 3 studies of ESR; 92 patients[16]	Summary likelihood ratio of ESR >70 mm/h 11 (1.6 to 79).
Infection in revision hip arthroplasties (CRP, ESR)	Secondary care	Cohort study of 178 patients; 202 arthroplasties [17]	ESR >30 mm/h: sensitivity 0.82 (0.65 to 0.93), specificity 0.85 (0.78 to 0.91); CRP >100 mg/L 0.96 (0.78 to 1.0), 0.92 (0.85 to 0.96). No patient with an infected arthroplasty had negative result on both tests

CRP=C reactive protein; ESR= erythrocyte sedimentation rate. 95% CI= 95% confidence interval.

Table 2| Community and primary care studies investigating the diagnostic role of inflammatory markers as diagnostic or screening tools for non-specific disease

Setting (test)	Study type	Participants	Outcome
Israeli airmen (ESR)	Prospective study, 15 year follow-up[27]	1000 healthy men aged 18-33 years: yearly ESR measurement	44 had persistently raised ESR; of these, 10 subsequently developed disease (4 myocardial infarctions, 3 ankylosing spondylitis, and one each of inflammatory bowel disease, psoriasis, benign monoclonal gammopathy)
Community study of ageing in the US (ESR)	Prospective study, 12 month follow-up[28]	100 healthy men and women aged over 70 years	9 subjects had an ESR >30 mm/h for ≥6 months; a previously undiagnosed illness was identified in 4 of these (2 polymyalgia, 1 pancytopaenia, 1 anaemia)
Primary care in the Netherlands (ESR)	Prospective study, 3 month follow-up[29]	362 patients presenting with a new complaint for which the general practitioner considered ESR to be indicated	ESR values were on average higher in those with malignancy or inflammatory diseases. Almost all diagnoses "revealed" by the raised ESR had been suspected at the initial consultation before the ESR result was known

ESR=erythrocyte sedimentation rate.