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REVIEW

Inflammation markers in point-of-care testing (POCT)

Albrecht Pfäfflin · Erwin Schleicher

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Abstract Inflammation is a central issue in medicine. Inflammatory processes may be local or systemic, acute or chronic, and they may be benign or fatal. In bacterial or viral infections fast and reliable diagnosis is essential for appropriate treatment, e.g. antimicrobial therapy. The time to diagnosis is critical because uncontrolled infections may lead to sepsis with a mortality rate close to 50%. Beside clinical signs, laboratory markers are important in detecting, differentiating, and monitoring inflammation, particularly acute infections. Currently several inflammation markers including leukocyte count and leukocyte differentiation, C-reactive protein (CRP), procalcitonin (PCT), and interleukins (IL) 6 and 8, is available, and potential future serum markers are under development. In this article the clinical use of these markers in routine laboratory and in point-of-care testing is described and the diagnostic value of the four groups of laboratory marker is compared. Current data show that leukocyte count or, better, neutrophil count, CRP, and PCT are well suited to support of rapid diagnosis of inflammation and infections in children and adults whereas measurement of IL-6 and 8 are preferable for detection of sepsis in neonates.

Keywords Point-of-care testing · Inflammation · Infection · Sepsis · CRP · Procalcitonin · Leukocyte · Granulocyte · Interleukin cost-efficiency · Clinical outcome

A. Pfäfflin · E. Schleicher (✉)
Department of Internal Medicine IV, Clinical Chemistry Unit,
University Hospital of Tübingen,
Hoppe-Seyler-Str. 3,
72076 Tübingen, Germany
e-mail: Erwin.Schleicher@med.uni-tuebingen.de

Introduction

Inflammation is a reactive state of the organism against disturbances of homeostasis with the goal of healing and repair of the injured tissue [1]. These disturbances include infections by viruses, bacteria, fungi, and parasites, tumours or other harmful artificial or natural agents, and traumatic damage. Consequently a variety of defence mechanisms against these numerous and very variable disturbances have developed. According to different criteria, inflammatory responses can be classified by time e.g. acute or chronic, the main inflammatory manifestation, the degree of tissue damage, the characteristic picture, and underlying immunopathological mechanisms. In *acute* inflammation the body responds to harmful stimuli by increased movement of plasma and leukocytes from the blood to the effected tissues. Subsequently a cascade of events propagates the inflammatory response which involves the local vascular system but also causes systemic reactions (see below). The responses are mediated by a variety of factors and involve the immune, the complement, the coagulation, and the fibrinolytic systems. *Chronic* inflammation is characterised by a failure to terminate the inflammatory response because of prolonged "frustrated" repair. The inflamed tissue shows infiltration of immune cells which may lead to tissue destruction by, e.g., scarring, with impaired or total loss of tissue function. Examples are asthma, rheumatoid arthritis, autoimmune disease, and inflammatory bowel diseases but also "non-immune" diseases, for example cancer and atherosclerosis.

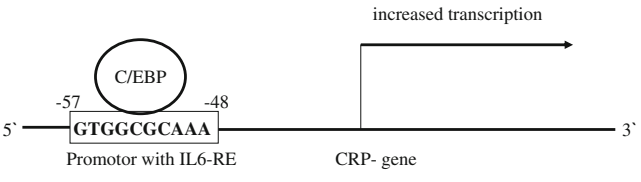
Inflammation is a time-dependent process, usually starting locally, and is recognized centrally later via blood-borne mediators. If infectious agents, e.g. bacteria, enter the skin, neutrophil granulocytes recognize bacterial structures and endotoxins, are activated, and liberate numerous substances

to attack the bacteria and mediators to attract other cells, e.g. monocytes. The complex interplay between different cytokines and chemokines is reviewed elsewhere [2]. The activated monocytes/macrophages in turn produce and secrete interleukins particularly IL-6 and other cytokines into the circulation (Fig. 1). These mediators cause an unspecific inflammatory response by inducing the production of acute phase proteins, for example C-reactive protein (CRP), serum amyloid A, fibrinogen, ferritin, α_1-antitrypsin, ceruloplasmin, and complement and coagulation factors in the liver. The unspecific response is generated within hours, therefore detection of such a response is well suited to recognizing diseases in their very initial phase. For illustration, and as an example, the molecular mechanism of IL-6-induced CRP biosynthesis is shown schematically in Fig. 2. After IL-6 has bound to its hepatic receptor the corresponding signalling cascade is activated and, in turn, several transcription factors are activated/translocated into the nucleus (for clarity, only C/EBP is shown). Subsequent to the binding of the transcription factor C/EBP to an IL-6-responsive element CRP expression is markedly increased [3]. The sequence of events is depicted in Fig. 3. The generation of a specific response (cellular or humoral) implies molecular recognition of epitopes, e.g. via antibodies, takes much longer, and is, therefore, not suited to diagnosis of acute states of diseases. The danger caused from infections depends, among other things, on the presence of positive feedback loops which may eventually lead to treatment inefficiency and, finally, to systemic inflammatory response syndrome (SIRS) with a high rate of fatal outcome.

Clinical importance

In all medical disciplines, inflammation is an important and common process. It ranges from local abscesses which may lead to tissue destruction to sepsis which may lead to shock and may end lethally. Sepsis is one of the leading causes of death after coronary heart disease and cancer. Sepsis is a clinical syndrome which is characterized by systemic inflammation caused by infection. Over 750,000 cases of sepsis occur in the US each year, resulting in 200,000 fatalities [4]. In a multi-centre study, 28-day mortality of up to 60% in patients with severe sepsis is reported [5]. There are many inflammatory diseases with high fatality rate or which lead to irreversible damage, for example bacterial pneumonia, meningitis, abscesses, ascending urinary tract infections, infectious endocarditis, osteomyelitis, and others. For example, for community-acquired bacterial meningitis a mortality rate of 27% is reported [6]. For community-acquired pneumonia the mortality rate ranged from 5.1% for combined ambulatory and hospitalized patients to 13.6% in hospitalized patients and to 36.5% in patients admitted to the intensive-care unit [7].

From several studies there is circumstantial evidence that the beginning of antibiotic therapy is extremely time-critical. In a retrospective cohort study performed between 1989 and 2004 14 intensive care units and 10 hospitals in Canada and the US were evaluated [8]. Among the 2,154



IL6-RE=IL-6 response element, C/EBP=CCAAT/Enhancer Binding Protein

Fig. 2 Production of IL-6 leads to increased CRP-transcription. Binding of the transcription factor C/EBP at positions 57 to 48 to the promoter of CRP relative to the transcription start site leads to increased transcription. C/BEBP is one of several sites transducing the effects of IL-6 on CRP expression

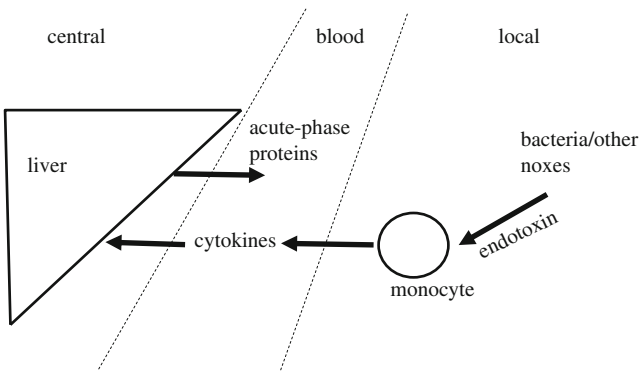


Fig. 1 Schematic depiction of how local inflammation induces the liver to produce acute-phase proteins including CRP, serum amyloid A, fibrinogen, ferritin, ceruloplasmin etc. The respective compartments are separated by *dashed lines*

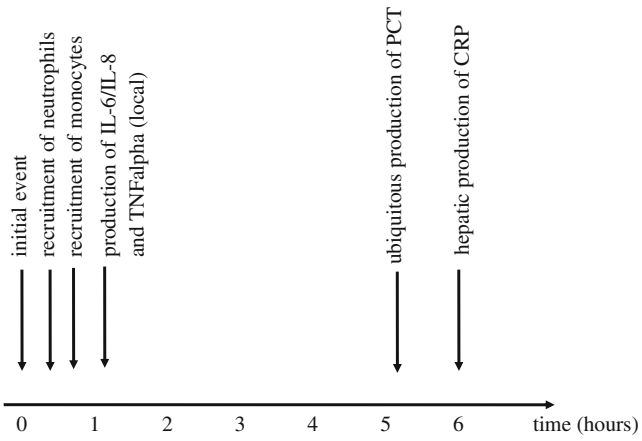


Fig. 3 Sequential events during inflammation. The amount of mediators locally or in blood may vary, depending on severity of inflammation, blood flow, tissue damage, and other factors. The time indicated must, therefore, be regarded an approximation

septic shock patients a strong relationship between delay in effective antimicrobial initiation and in-hospital mortality was found. Administration of an antimicrobial effective for the isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 80% ("golden hour"). Each hour delay in antimicrobial therapy over the ensuing six hours was associated with an average decrease in survival of 7.6%. Multivariate analysis of the data showed that the time to effective antimicrobial treatment was the single strongest predictor of outcome. Together these examples emphasise that early recognition and characterisation of the causative injury and subsequent appropriate treatment is an important aspect of beneficial outcome for the patient [9].

Assessments about the aetiology of inflammation with inflammation laboratory data, at least until now, are somehow limited without further specific information (e.g. history, results of blood cultures, etc.). Of course, in combination with results (e.g. bacterial/viral antigens) revealing, eventually, the aetiology of the inflammatory process, the value of information from such tests would be quite high. Until now, inflammation biomarkers only in combination with clinical and radiological results allow valuable assessments in clinical practice. They are especially important in monitoring of diseases, e.g. to assess the success of an antibiotic or anti-inflammatory treatment.

Diagnosis of inflammation

Since the ancient Greek and Roman eras, inflammatory signs have been detected clinically. The five typical signs are redness (rubor), swelling (tumor), pain (dolor), impaired function (functio laesa), and, eventually, fever (calor). However, these signs are rather subjective and may be weak or even absent. Determination of biomarkers in blood samples is, therefore, extremely valuable in the early detection, characterisation, and treatment of inflammation. About fifty years ago, only leukocyte count and the erythrocyte sedimentation rate were available for laboratory detection of inflammation. The underlying principle of the latter test is that acute-phase proteins interfere with negative surface charge on erythrocytes leading to increased erythrocyte sedimentation in cases of inflammation. However, because of slow reaction time and lack of specificity, the erythrocyte sedimentation rate has lost significance since then. Leukocyte count, although not very specific, is still used for the detection of inflammation (see below). For nearly twenty years there has been widespread availability of serum markers in clinical practice. Here these markers will be introduced and evaluated for their clinical utility in detecting and monitoring inflammatory diseases, particularly in the context of point-of-care testing.

Laboratory markers

Leukocytes: well established markers of inflammation

Mostly, but not always, during inflammation the amount of leukocytes in the circulation increases. However, leukocytes might be spent in the inflammation process and leukocyte number in blood may therefore be normal or even reduced, thus a normal or reduced leukocyte count does not rule out even severe inflammation. On the other hand, leukocytes may also be increased in "non-immune" events, for example myocardial infarction. Furthermore, some therapies e.g. immunosuppressive therapies, may diminish the number of leukocytes; in these cases the number of leukocytes is of no value for detection or monitoring of an inflammatory status. There are also therapies which increase the number of leukocytes. Therefore, the number of leukocytes has to be interpreted in the clinical context. Although the leukocyte count is clinically accepted and widely used, it should be noted that it is neither specific nor very sensitive. For rapid differential diagnosis a rough differentiation of leukocytes may be helpful. The consensus definition of systemic inflammatory response syndrome in paediatrics recommends the leukocyte count and the differentiation of neutrophils (<10% immature) [10].

CRP: well established marker of inflammation

In clinical practice, C-reactive protein (CRP), a pentamer of 120 kDa has revealed as the most important marker of inflammation for diagnostic purposes. It was recognized several decades ago as serum protein capable of agglutinating a carbohydrate substance in pneumococci [11]. CRP is an evolutionarily ancient molecule, even lower organisms express CRP-like molecules for their defence. Apart from newborns, particularly preterm infants, no states are known where an inflammatory CRP response is missing, nor are there situations where (even when theoretically imaginable) CRP completely disappears during severe inflammation. CRP-levels may rise within six hours of a noxious event, and may rise up to 1000-fold compared with basal plasma/serum levels. The biological half-life time is 19 hours. The reference range is below 5 mg L^{-1}. CRP has inflammatory properties, it recognizes organic structures (e.g. phosphorylcholine) which are exposed at the cell surface during inflammation and cell death. Binding of CRP to ligands leads to conformational changes, subsequently leading to activation of the complement system [12]. Further, CRP binds to the Fc-part of IgG to favour opsonisation via macrophages [13]. CRP also exerts anti-inflammatory properties [14]. Interestingly, for CRP no mutations are described affecting immunological detection methods. These proper-

ties have led to the establishment of CRP as the clinically most important acute-phase protein. The role of CRP in arteriosclerosis, not only as an indicator, but also as an active participant, is still a matter of debate [15]. However, this is feasible only with high-sensitivity methods with low imprecision [16].

CRP is the most widely used and preferred marker for inflammation [11] and is considered traditionally for monitoring infection and autoimmune disorders [16]. In comparison with traditional markers CRP is much more sensitive than sedimentation rate and leukocyte count [11]. Furthermore higher CRP values indicate bacterial infections. CRP is not elevated in cases of localized inflammation; in cases of immuno-suppression of the patient and in neonates less pronounced increases of CRP are possible. It might, therefore, be speculated that high-sensitivity determination of CRP is preferable in neonates; no clinical evidence is yet available, however.

Cytokines: interleukin-6 (IL-6), Interleukin-8 (IL-8): less established markers of inflammation

The term interleukin was introduced because these molecules were recognised first as messenger molecules between leukocytes. The cytokines IL-6 and IL-8 have a molecular weight of approximately 20 and 11 kDa respectively. They are mainly produced by monocytes, but also by other cells, especially under certain conditions e.g. hypoxia may lead to production of these interleukins. The half-life is short so they may disappear rapidly. Reference ranges are <10 ng L^{-1} for IL-6 and <10 ng L^{-1} for IL-8. IL-6 and IL-8 are especially suitable for monitoring newborns with suspected infections during stationary stays. In a prospective study Mathers and Pohlandt found that CRP had no value in the early diagnosis of neonatal infection [17]. In another study Lam et al. reported that in the diagnosis of neonatal sepsis IL-6 and IL-8 have been demonstrated to have good diagnostic utility as early-phase markers whereas CRP and PCT have superior diagnostic properties during the later phases [18].

Procalcitonin (PCT): less well established marker of inflammation which has recently attracted more attention

Calcitonin and its precursor PCT, a 13 kDa protein, was initially used as serum marker for detection and monitoring of therapy of neuroendocrine tumours. Subsequently it was found that PCT is also increased in the plasma/serum of patients with severe systemic inflammation, for example trauma, burn injury, systemic bacterial infection, and sepsis [19]. Under these conditions the main sources of PCT are non-neuroendocrine parenchymal cells of all major organs [20]. In healthy subjects, plasma/serum levels are test-dependant, but mostly reported as below 0.05 μg L^{-1} [21]. PCT is markedly elevated in severe forms of systemic inflammation or in bacterial infections within 2–4 hours, reaching up to 5,000-fold values in very severe cases and persisting until recovery. PCT is used for guidance of antibiotic therapy [22]. The biological half-life is 22–26 hours. Several studies in experimental animals suggest that PCT has toxic functions in severely sick animals, because artificially increasing PCT enhanced the severity of the disease whereas immuno-neutralization ameliorated the symptoms of the disease. Interestingly no apparent effect was found when PCT was injected into healthy animals.

In clinical settings elevated PCT plasma/serum concentrations have been reported in non-infectious systemic inflammation such as pancreatitis, heat stroke, inhalational injuries etc., severe bacterial local (pneumonia, pyelonephritis, or arthritis), and systemic bacterial infections and sepsis. It is worthy of note that in one study PCT plasma/serum concentrations were undetectable or very low in nearly all patients with viral infections [23] indicating that PCT may be useful for discrimination of infections of bacterial and viral origin; this has also been shown for meningitis. The predictive value of PCT has been tested in several studies [24, 25], and in a recent prospective multicentre study [26]. PCT is useful not only for monitoring bacterial infections but also for differential diagnosis of systemic inflammatory response syndrome, which is a serious medical condition. Apart from better specificity, PCT also offers a time advantage when compared with CRP. In a study with 150 patients in an intensive care unit, Castelli et al. observed that PCT serum concentration correlated more closely with the sequential organ failure assessment (SOFA) score than with CRP [27]. Furthermore, the authors observed that PCT serum concentrations reacted more rapidly than CRP.

Potential future candidates: lactoferrin, TNF, myeloperoxidase, neopterin, prostaglandins

Lipopolysaccharide-binding protein, sialic acid, HLA-DR expression in monocytes, and others [28–35] have been evaluated only in a very restricted number of studies and patients, and none has yet gained wide acceptance (Table 1). Use of such markers for POCT purposes cannot, therefore, yet be recommended.

Recommended sample

Markers of inflammation are usually measured in serum or plasma. However, the inflammation might be locally confined e.g. in abscesses. Therefore, the testing might also be performed with, e.g., ascites or pleural fluid or even abscess material. In these fluids, counting of leukocytes is

Table 1 Potential future candidates for POCT and examples of their evaluation

Candidate	Suitable for
Lactoferrin	In stool; not suited for differentiating diarrhoea [28]
TNF	Rheumatoid arthritis [29]
Myeloperoxidase	Mortality after infarction [30]
Neopterin	Infection marker in patients with neutropenia [31]
Prostaglandin	Kidney rejection [32]
Lipopolysaccharide binding protein	Marker for bacteremia in some patients [33]
Sialic acid	Diagnostic marker in colorectal cancer [34]
HLA-DR expression	Renal transplantation [35]

well established, but not, e.g., determination of CRP or other cytokines.

Comparison of the utility of the laboratory markers

As pointed out above and illustrated in Figs. 1, 2, and 3, the inflammation-induced production of interleukin 6 and 8 and CRP and other acute phase proteins is not independent. In contrast, PCT production is also induced in numerous non-hepatic tissues upon not yet well-defined stimuli during inflammatory events. Therefore several studies have compared the diagnostic value of these serum/plasma markers. One study evaluated the diagnostic value of signs, symptoms, and laboratory results in lower respiratory tract infection in 243 patients [36]. They found a low overall sensitivity and specificity of signs and symptoms for bacterial lower respiratory tract infection requiring antibiotic therapy. The sensitivity of infiltrates, CRP (>50 mg L^{-1}) and PCT (>0.1 ng L^{-1}) were 96.9, and 93.8% respectively. The highest specificity was found for PCT (>0.25 ng L^{-1}). A similar study was performed in children with lower respiratory tract infection [37]. The sensitivities and specificities for distinguishing pneumococcal from other aetiologies were 90.3 and 74.1%, respectively, for PCT and 90.3 and 60% for CRP. Together they found that high CRP and procalcitonin values show a significant correlation with the bacterial aetiology of lower respiratory tract infection and that PCT showed higher specificity than CRP. In acute sepsis, PCT or CRP levels per se poorly predicted outcome, but decreasing levels were associated with higher probability of survival. PCT was found to be an earlier marker [38] similar to findings of Castelli et al. [27]. In a more general study the clinical utility of six serum markers to diagnose infections was performed in a prospective study [39]. In addition to the established biomarkers CRP, procalcitonin, and neutrophil count, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor and soluble triggering receptor expressed on myeloid cell-1 was studied in 151 patients. Of these 96 had proven bacterial infections. The data revealed that the established biomarkers PCT, neutrophil count, and CRP either separately but particularly, in combination were useful in the diagnosis of infections whereas determination of the other three markers was of limited value. One problem with such evaluation studies is that the gold-standard, e.g. definition of infection, is quite hard to obtain. If definition of the infection depends on the cultivation of microorganisms, false-negative results have to be considered.

Established systems for inflammation markers in POCT testing

Although several commercially available, small, hand-held systems are available for POCT of the described markers, small multi-marker devices are not yet available. Most devices offer rapid (<10 min) and single CRP testing semi-quantitatively with dip sticks or agglutination test (e.g. actim CRP test or RapiTex CRP) or quantitative with good correlation with established procedures, for example the i-Chroma hs-CRP assay [40], the ABX-CRP assay [41], or the Nycocard assay [42], whereas other POCT assays, for example the Quikread, are reported to perform less satisfactorily [42]. Only recently small, hand-held POCT devices for leukocyte count are offered [43]; a device from Hemocue is under evaluation. For PCT, a semi-quantitative test is commercially available and suited to point-of-care testing. For first decisions this test seems to be sufficient; for monitoring a patient, however, quantitative measurements should be preferred because, as mentioned above, monitoring the success of a specific treatment is of importance [44]. Such tests were also developed for cytokines, e.g. an immunoaffinity electrophoretic device for testing cerebrospinal fluid [45]. Applications are also reviewed elsewhere [46]. Some of the commercially available devices with some technical specifications are shown in Table 2. Although it is beyond the scope of this article to review the performance of individual devices, in this context it is important to notice that clinical improvements usually result from changing the whole process, not from changing a single device. Inflammation markers have not yet been widely applied in a POCT setting. Reasons are high costs (immunological assays), reliability of available test systems, workload, reimbursement policy, and habits. However, a potential for widespread application and distribution for POCT of inflammatory markers is highly probable.

Table 2 Examples of different POCT-devices for inflammation

Test	Company	Analyte	LOD	Linearity	Principle of determination	Low-level for <10% imprecision	Range	Volume needed	Specimen	source
i-Chroma hs-CRP assay	BodiTech Med, Korea	CRP (high-sensitivity)	n.a.	n.a.	Fluorescence immunoassay	0.5 mg L^{-1}	0.5–300 mg L^{-1}	15 µL blood or 10 µL serum	Blood	[40]
Sysmex Smart 546	Sysmex, Japan	CRP, high-sensitivity (hs)-CRP	n.a.	2–170 mg L^{-1}	Immuno-turbidimetry	5 mg L^{-1}	2–200 mg L^{-1} for CRP; 0.5–120 mg L^{-1} for hs-CRP	5 µL	Blood/serum	Homepage Sysmex; www.sysmex.de (accessed 29.10.2008)
ABX-CRP	Axonlab, Germany	CRP and blood count	0.1 mg L^{-1}	0.3–60 mg L^{-1} at 20% error limit	Immuno-turbidimetry	0.7 mg L^{-1}	0.3–387 mg L^{-1}	18 µL (blood count included)	Serum, EDTA, Li-heparin blood	[41]
RapiTex	Siemens, Germany	CRP	n.a.	n.a.	Agglutination	n.a.	>6 mg L^{-1} qualitative	40 µL	Serum	Package insertion
PCT-Q	Brahms, Germany	Procalcitonin	n.a.	n.a.	Lateral-flow immuno-chromatography	n.a.	>0.5 ng mL^{-1}; semiquantitative	200 µL	Serum/plasma	http://www.procalcitonin.com/ (accessed 29.10.2008)
IL-6	Milenia Biotec, Germany	IL-6	n.a.	n.a.	Lateral-flow immuno-chromatography	n.a.	>100 pg mL^{-1}; semiquantitative	50 µL	Blood	http://www.milenia-biotec.com/ (accessed 29.10.2008)

n.a.: not available

Published evaluation of diagnostic laboratory tests has been described as "mediocre at the best". It is noteworthy that systematic evaluation of the performance of commonly used laboratory markers for the diagnosis of severe infections has not yet been performed, e.g. leukocyte count (absolute or differentiation), determination of granulocyte immaturity, pool studies in different settings (CRP) [47]. However, on the basis of the literature discussed above one may suggest determination of the following four groups of markers:

- leukocyte count (neutrophil count, percentage of immature neutrophils)—not specific, may give false negative results, widely accepted;
- CRP—very sensitive, low specificity;
- PCT—sensitive, more specific for bacterial infections, faster than CRP
- IL-6/IL-8—particularly valuable in neonatalogy

Rationale for on-site testing of inflammatory markers

Despite infrequent application of inflammation markers in a POCT setting, the speed of identification of inflammatory diseases is of special importance, because these diseases often show acute onset, might be life-threatening, eventually necessitating fast treatment. Further, positive feed-back loops during inflammation are also described on the molecular level [48] which may lead to even fatal outcome (e.g. septic shock) if not treated within an appropriate time frame. For example, paediatricians or general practitioners have to decide rapidly whether or not they should administer antibiotics. The speed of availability of results may reduce the number of laboratory and other investigations. The cost effectiveness of testing inflammatory markers seems to be evident; here, especially, CRP alone, in combination with PCT, or in combination with leukocytes seems important [49].

Interestingly, even for nowadays very well established analytes such as glucose, reports of the modest performance of glucose meters are still being published [50], indicating there is a long way to go before introduction of a laboratory marker for POCT with satisfactory performance. A recent study from Scandinavia indicates that point-of-care testing has a limited effect on time to clinical decision in primary health care [51]. The clinical outcome is a summary of several steps, so changing only one step in the whole process should not lead to the expectation that the outcome for patients will improve substantially. The whole organisation, e.g. the availability of radiological diagnosis, availability of the deciding physician, etc., is also important, so the effects are difficult to prove, and will depend on circumstances in the particular institution.

Economic aspects

The economic impact of POCT is not readily obvious. Although it is true for most POCT devices that the costs for POCT reagents are much higher than those used in large central laboratories, because these laboratories use large quantities of reagents, and therefore get better prices, and because "wet" reagents are usually cheaper. The contribution of the cost of the measurement device cannot be generally estimated, because it depends not only on the marker but, particularly, on the number of determinations performed per year. Therefore the cost relationships have to be calculated on the basis of the individual situation. However this view (price/analysis) is far too narrow-sighted, because further indirect costs are not taken into account. These include time of the medical staff/nursing personal needed to perform the test, quality control, documentation, and maintenance, and, on the other hand, savings because no sample preparation or transport is necessary for POCT. Furthermore, there are no solid data on time savings when POCT is used and how these time savings reduce overall costs. It is worthy of note that the general organization of daily work in the clinic needs to be adapted to POCT to increase savings if POCT is used. One study has shown that determination of CRP by the general practitioner helps to reduce unnecessary antibiotic therapies in cases of lower respiratory tract diseases [52]. Therefore, costs of supplementary POCT devices cannot be calculated from reagent costs, and often seem impossible to determine.

Perspective

Inflammation and, particularly, infections are a central issue in all medical disciplines. Especially for infections in neonates, children, and adults, early diagnosis is essential for fast and adequate treatment to reduce mortality. At present, four groups of markers that can be determined routinely in clinical laboratories have evolved to support the diagnosis in inflammatory/infectious diseases. However, currently no POCT device is commercially available for fast quantitative determination at the patient's site for the three of the above discussed markers (leukocyte (and differentiation), CRP and PCT) useful for children and adults and, additionally, IL-6 and 8 for neonates. Even if such devices were available at moderate cost, they should, nevertheless, be used critically. It may be more because of marketing than for technical reasons that, until now, POCT for inflammation markers is rarely applied. Nevertheless, these relevant biomarkers differ greatly in nature and concentration ranges and new technical developments will be necessary to provide fast, accurate, reliable, and quantitative POCT determinations in one device. Further-

more, innovative and powerful proteomic or metabonomic screening methods may help to discover new, more sensitive, and specific markers for diagnosis of inflammatory diseases.

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