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Sepsis Biomarkers in Early Diagnosis and Treatment Planning: An Economic Appraisal

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The approach of using biomarkers for diagnosing and assessing illness severity and treatment response has become a new hype in modern intensive care medicine. Procal-citonin, and to a lesser extent, C-reactive protein, may have, beside the considerable cost and other non-economic implications as well, substantial value with regard to the earlier mentioned goals in case of rational usage in well-selected severely ill patients admitted to the intensive care unit.

Diagnostic and Treatment Planning Potential of Serum Biomarkers in Septic Severely Ill Patients

Sepsis is a major problem in severely ill patients (Martin et al. 2003). It is responsible for high morbidity and mortality and poses a substantial economic burden at the individual, institutional, and national levels (Angus et al. 2001; Vandijck et al. 2007b). Accurate risk stratification, appropriate and institution-specific triage to interventional or medical strategies, and optimal anti-infective therapy constitute major goals in the management of septic patients. In addition, delays in diagnosis and/or treatment often result in rapid progression to haemodynamic collapse, multiple organ failure, and eventually death. Hence, timely detection will limit morbidity, reduce costs, and decrease unwelcome patients' outcome (Kumar et al. 2006; Warren 1997).

In an attempt to improve current sepsis definitions, biomarkers were put forward as additional diagnostic tools to optimise and expedite the clinical diagnosis (Levy et al. 2003). Aside from conventional risk factors, physicians have taken a substantial interest in the use of novel biomarkers to identify which of their patients are at increased risk for or are actually developing sepsis, and who could thus benefit from life saving therapies. As such, the search for specific sepsis biomarkers has been intensified, and to date, ca. 80 markers of sepsis have passed the revue (Vincent and Abraham 2006). The markers provide information about one or more of the following: diagnosis, prognosis, and response to therapy. Obviously, any severe systemic infection is far too complex to be reduced to a single cut-off of any surrogate marker. Different aetiology of invading germs might induce a distinct host response resulting in a variable repertoire of circulating biomarkers and infectious mediators (Muller et al. 2007). Among the almost non-exhaustive list of biomarkers that have been proposed, two, respectively C-reactive protein (CRP) and procalcitonin (PCT), have received particular attention (Christ-Crain and Muller 2005; Vandijck et al. 2006).

C-Reactive Protein

Determinations of CRP serum concentration, an acute phase protein, are widely used as a relatively non-specific marker of inflammation, and salient studies have found increased serum concentrations in patients with sepsis; however, some could not demonstrate such a relationship (Povoa et al. 1998; Smith et al. 1995; Yentis et al. 1995; Vandijck et al. 2007c). Likewise, CRP has been found valuable to monitor response to treatment (Povoa et al. 2005). Also, the kinetics of a prospective biomarker should be considered along with its sensitivity and specificity. CRP secretion begins within 4 to 6 hours after stimulation, and peaking after 36 hours (Enguix et al. 2001). The assay for determining CRP concentrations is easy to perform, frequently automated, and less expensive (ca. €5) (Simon et al. 2004). This low associated cost is a commonly raised argument for the low threshold among physicians to order the latter test.

Procalcitonin

Determinations of PCT serum concentration, a propeptide of calcitonin, is one of the most upcoming biomarkers and described as a potential marker of infection, but yet not routinely used. PCT has been considered as an effective marker of bacterial sepsis, and as such, is providing a new tool for early diagnosis (Harbarth et al. 2001). PCT is stable in samples, and the assay is relatively easy to perform - with moderate to quite high costs (ca. €10, with a ca. €45 share to be paid by the patient). As compared to CRP, PCT has more rapid kinetics in terms of production and clearance. So, PCT may be better to identify sepsis at an earlier stage, to assess the severity of sepsis, and to monitor its progress (Castelli et al. 2004).

However, also in the absence of evidence of infection elevations of PCT serum concentrations have been observed, limiting its usefulness in the clinical diagnostic assessment (Dorge et al. 2003). In an aim to clarify the ambiguity regarding the diagnostic accuracy of PCT in sepsis diagnosis in severely ill patients, Tang and collaborators recently conducted a systematic review and meta-analysis (Tang et al. 2007). The authors found

that the diagnostic performance of PCT was low, and could not reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response in this patient cohort. As such, Tang and collaborators could not lend support to the widespread use of PCT testing to diagnose sepsis in severely ill patients (Tang et al. 2007). However, PCT probably has the best potential in guiding anti-infective treatment, more particularly in shortening the duration of therapy, because of several advantages over other inflammatory markers, including CRP, tumor necrosis factor-, interleukine-1 and 6 which may be only increased briefly (Nobre et al. 2008; Christ-Crain et al. 2006).

General Thoughts

The biomarkers currently available in the critical care setting lack sensitivity and specificity so the diagnosis of sepsis cannot exclusively be made based on the presence of one of these biochemical parameters alone. Nonetheless, the best potential can probably found in either combining several markers together into a predictive algorithm or by following their respective trends over time rather than single determinations (Vandijck et al. 2007c; Vincent and Abraham, 2006). The dynamics of biomarker serum concentrations have prognostic implications, as persistently elevated or increasing concentrations can be associated with adverse outcomes. Conversely, decreasing biomarker concentrations suggest a favourable outcome (Muller et al. 2007).

Given the relatively high costs associated with biomarker determinations and considering increasing cost constraints in healthcare, estimated expenses do not justify systematic application of biomarker determinations in all severely ill patients (Vandijck et al. 2007a). On the other hand, taking in mind the overuse of anti-infective agents, a well-considered use of biomarkers in well-selected severely ill patients might help to shorten duration of treatment and/or may as such avoid the unnecessary use of anti-infective agents. Consequently, this policy might result in a decrease in the sideeffects related to the use of anti-infectives, lower costs, and reduce emergence of drug resistance (Vandijck et al. 2008a; 2008b). Similarly, earlier diagnosis of septic patients will allow earlier antiinfective management, which on its turn will improve patients' outcome. As well, the latter may save money otherwise allocated to the higher use of resources due to extra therapies, and longer length of critical care and hospital stay because of sepsis-related complications.

Conclusion

As with all diagnostic tests, biomarkers must also be interpreted in the context of a careful clinical and microbiological assessment. To date, a 100% specific biomarker for sepsis is yet to be found - the major limitation includes false-positive and false-negative results, and the time-kinetics of the test, with its' substantial clinical and cost implications. Considering the scarceness of resources in healthcare, currently there is no evidence for routinely using biomarkers. However, in well-selected patients, single determinations, but in particular their respective evolutions over time may significantly help to monitor one's progress and may as such, help a physician to more rapidly intervene - with better clinical and economic outcome as a result.

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