

Biomarkers for the Diagnosis of Infective Endocarditis

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Infective endocarditis (IE) is a life threatening bacterial infection (1,2). IE has a mortality of almost 100% if left untreated. Early diagnosis and treatment with antibiotics and often surgery is therefore vital. With proper treatment, the mortality is still 15 –40% during the primary submission, depending on factors like localization, microbiological agents and treatment delay which correlates with poor prognosis (3). The diagnostic challenge is to determine if a febrile patient with either a positive blood culture or a suspected bacteremia has IE. At present the key diagnostic procedures are transthoracic and transesophageal echocardiography and in clinical practice there are no biomarkers, which can identify IE in patients with bacteremia.

The C-reactive protein (CRP) is an extremely valuable biomarker for inflammation, and is widely used in all patients suspected for IE — but it lacks sensitivity and specificity to distinguish patients having IE from patients having bacteremia without endocarditis (4,5).

The Procalcitonin (PCT) is the protein given most attention in the last decade as a putative biomarker for IE. The level of PCT is known to rise as a response to a pro-inflammatory stimulus, especially of bacterial origin. PCT has received substantial attention for its potential role in IE as compared to many other biomarkers. However, as the meta-analysis concluded PCT lacks sensitivity as well as specificity (6). A problem has been the difficulty of setting up a PCT threshold that can be clinically useful reflected by the variability among the included studies (3). Thus, PCT is not a useful biological marker, which can distinguish patients with bacteremia with or without IE (7).

Levels of NT-proBNP in the blood are being used for screening and diagnostics of heart failure, especially regarding ventricular wall stress and hypertrophy, and have increasingly been incorporated into the clinic in recent years. Elevated levels of NT-proBNP and BNP are both associated with left ventricular dysfunction, coronary artery disease and myocardial ischemia, and these studies substantiate that a high NT-proBNP is associated with higher risk of severity of disease and raised mortality. One would expect an increase in NT-proBNP to be associated with a more severe outcome, since it is a marker of an increased cardiac workload and heart failure and it is expected that an increase in NT-proBNP may indicate poorer prognosis in any cardiac condition (8,9).

The Cystatin C (Cys C) is a biomarker of kidney function. Recently, it has been studied as a marker of cardiovascular disease (10). One study assessed Cys C in IE-patients and found that increased

levels were associated with increased risk of short- and long-term mortality — especially in combination with age and mitral valve insufficiency (11). An increase of more than 20% from admission level after 14 days of treatment was a powerful indicator of increased 5-year mortality.

The Lipopolysaccharide-binding protein (LBP) is a soluble acute-phase protein produced predominantly in hepatocytes. LBP binds to bacterial surface lipopolysaccharide in Gram-negative bacteria and triggers an immune response by presenting the microorganisms to macrophages and dendritic cells. Its function is vital to the macrophage binding to the microorganism, inducing production of the pro-inflammatory cytokines IL-1, IL-6 and tumor necrosis factor- α (TNF α). Furthermore, LBP has also been investigated as a potential novel biomarker for IE (12,13). One study reported that an association between two specific single nucleotide polymorphisms (SNPs) seemed to signal that LBP has a function in IE development, and a role as a potential biomarker (12). Serial LBP measurement may provide an effective and useful tool for evaluating the response to therapy in IE patients. We found a strong correlation between LBP and CRP concentrations; LBP has a tendency to increase earlier in cases of reinfection (13).

The Troponins are biological markers of cardiac injury and poor outcomes after thrombotic events in the myocardium. Elevated cardiac troponin I (cTnI) and T (cTnT) in IE-patients had a higher risk of complications, including fatal outcome compared to cases with lower levels (14,15).

The S100 proteins (S100 calcium binding proteins A11, S100A11), adhesion molecules like E-selectin, ICAM-1, VCAM-1 on endothelial cell, and IL-6 showed a possibility as biomarkers of IE on a few studies (5,16,17).

In conclusion, in order to evaluate markers of IE it is important to compare patients having IE from patients having bacteremia without endocarditis. General markers of acute bacterial infections like CRP or PCT cannot be used to diagnose IE in patients with bacteremia. Potential markers, which seem promising for further investigations, include NT-proBNP alone or in combination with Cys C, LBP, troponins, S100A11, E-selectin (CD62E), VCAM-1 (CD54) and IL-6.

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