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Review

A systematic review of biomarkers in the diagnosis of infective endocarditis

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ABSTRACT

Timely diagnosis of bacterial infective endocarditis (IE) is crucial, as mortality remains high in this severe bacterial infection, currently without any distinct biological markers. Our goal was to evaluate potential diagnostic biomarkers by reviewing current literature. The MEDLINE, Embase and Scopus databases were searched for articles published from 1980 through June 2015 restricted to English, Norwegian, Danish and Swedish. Eighteen studies qualified, providing a review of the most promising candidates for future studies. Several studies are inconclusive, since they are characterized by using improper control groups. Patients with IE have bacteremia, and control groups should therefore be patients with bacteremia without IE. Based on current research, N-terminal-pro-B-type natriuretic peptide (NT-proBNP) alone or in combination with Cystatin C (Cys C), lipopolysaccharide-binding protein (LBP), troponins, aquaporin-9 (AQP9), S100 calcium binding protein A11 (S100A11), E-selectin (CD62E) and VCAM-1 (CD54) and interleukin-6 (IL-6) are potential biomarkers for future studies.

1. Background

Infective endocarditis (IE) is a life threatening bacterial infection [1,2]. Cardiac valves can be destroyed which leads to heart failure [3] and vegetations can embolise to the brain and other organs. 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 [4]. 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. 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 [5,6]. The average diagnostic delay of IE is reported to be approximately 30 days [4]. Any diagnostic biomarker, which could reduce the time from IE onset to diagnosis, and thereby start of correct treatment, would have the potential to reduce mortality.

IE is initiated by bacterial adhesion to cardiac valves, and subsequently bacteria invade and destroy the valve and form vegetations consisting of bacteria, fibrin clots, inflammatory proteins and leukocytes [1]. The aim of this study was to review the literature for proteins which have the potential to be used as biomarkers of heart valve infection, destruction and formation of vegetations, which could be selected for further analyses as markers of IE.

2. Literature search

The MEDLINE, Embase and Scopus databases were used to identify publications relevant to the topic. The MEDLINE database was searched using PubMed with the search string ((("Endocarditis"[Mesh]) OR "Endocarditis")) AND (("Biological Markers"[Mesh]) OR ("Biological Markers" OR "biomarkers")). Embase was searched with the following search string: ('endocarditis'/exp OR 'endocarditis') AND ('biological marker' OR 'biomarker') AND [1988–2015]/py. Scopus was searched using the search string (endocarditis) AND ("biological marker*" OR "biomarker"). We restricted our search to studies published in English, Norwegian, Danish and Swedish including all articles published from 1980 through June 2015. Articles not fulfilling these criteria were excluded, resulting in a total of 256 articles with abstract after removal of duplicates. Screening based on study type, titles and abstracts excluded 191 irrelevant articles, 40 case reports and 15 conference papers resulting in 10 remaining studies. Reference lists of retrieved papers were also searched for relevant studies, which resulted in eight additional studies being included. Eighteen articles were included for review.

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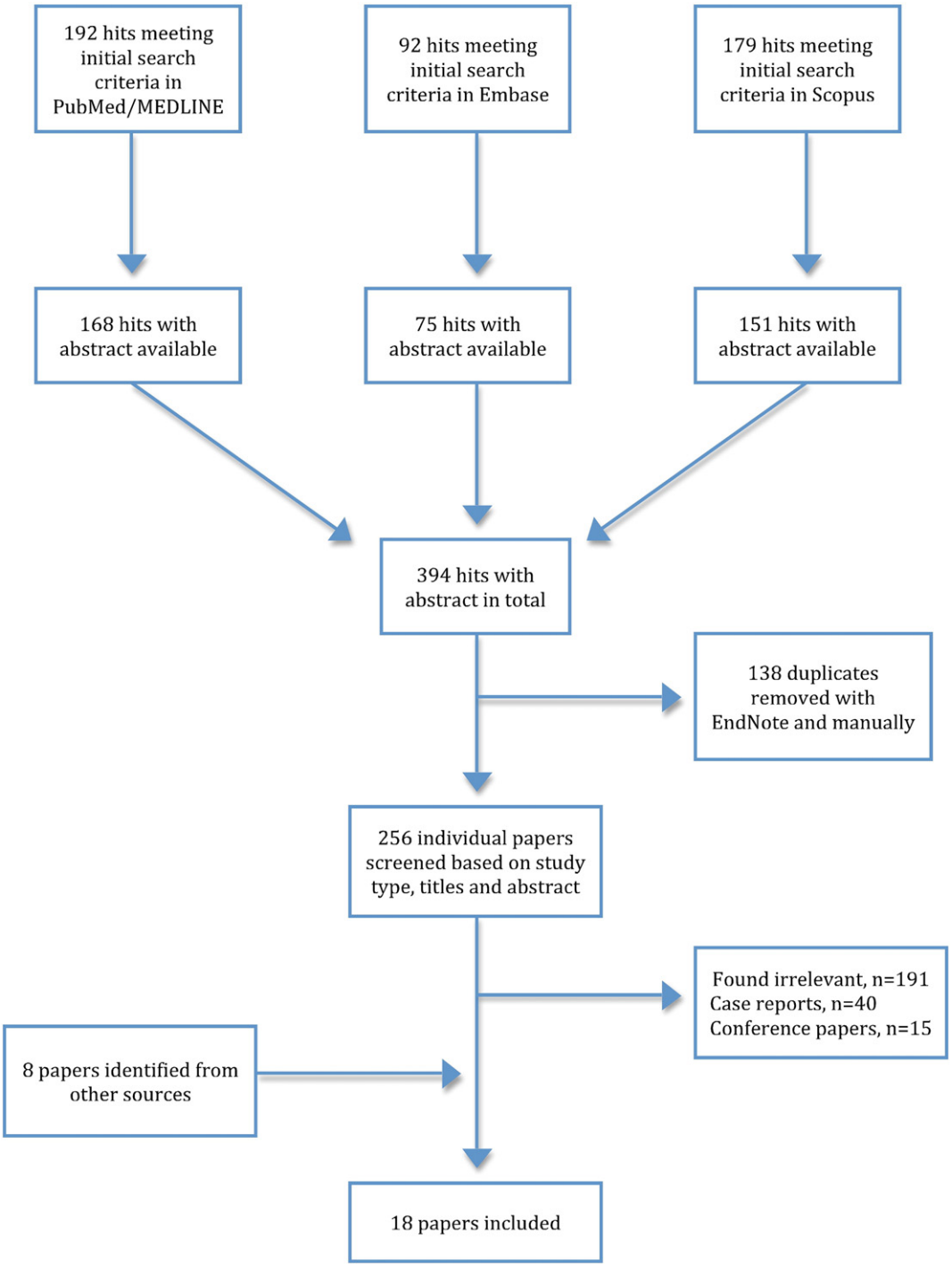

Fig. 1. Strategy for inclusion of articles in the study.

A flow chart illustrating the inclusion process is presented in Fig. 1. The methodological quality of all included articles was assessed by modifying a set of 13 criteria from Kmet et al. [7]. Each criterion was given 0, 1 or 2 points giving a total maximum score of 26 (100%). Studies with bacteremic patients as controls were rated higher than studies using control patients with other diagnoses or healthy donors, respectively. The 18 papers had a median score of 19 (73%) with a range from 17 (65%) to 22 (85%).

The included studies focused on biomarkers able to distinguish patients with fever, with or without IE, and biomarkers predicting surgery or early mortality. Our primary focus was on biomarkers from human tissues, either from heart valves or blood samples, without any discrimination in regards to the analytic method.

3. Review of putative biomarkers studied

Eighteen papers were included for review according to our criteria (Fig. 1). For detailed study information, see Table 1.

3.1. Procalcitonin (PCT)

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 proinflammatory stimulus, especially of bacterial origin. Several studies in recent years, have presented the hypothesis that PCT might be a useful biomarker in IE cases. PCT-values tend to increase