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A Potential Role of Hematologic Abnormalities as Prognostic Markers an Infective Endocarditis (IE)

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Opinion

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Abstract

Infective Endocarditis is a highly morbid disease whose diagnosis is largely based on the modified Duke Criteria. These criteria are mainly developed by expert opinion due to the low incidence of the disease, the low number of randomized trials, and the limited number of me-ta-analyses, making the evidence of their recommendations relatively low with major gaps. A prompt diagnosis of IE is crucial to avoid serious complications. However, the great clinical variability and non-specific manifestations, constitute diagnostic challenges. Hematologic abnormalities, especially anemia are frequently associated with IE. However, they have not been widely explored as potential diagnostic and prognostic parameters in IE patients. In this article, we explored the common hematologic abnormalities in IE patients and the available evidence of the impact of their changes on diagnosis and risk stratification in these patients.

Keywords: Infective Endocarditis; Diagnostic Guidelines; Diagnostic Challenges; Risk-Stratification; Hematologic Abnormalities

Abbreviations: IE: Infective Endocarditis; HF: Heart Failure; RBC: Red Blood Cell; DRE: Device-Related Endocarditis; PVE: Prosthetic Valve Endocarditis.

Introduction

Endocarditis is often defined as an infection of the endocardium, but it rarely includes noninfective causes, referring to sterile platelet and fibrin thrombi. The latter endocarditis sometimes provokes infective endocarditis and both types may lead to embolization and impaired cardiac function. The systemic consequences of endocarditis are primarily due to embolization of infected material or immune-mediated reaction often in chronic infection [1].

Infective Endocarditis (IE) is a highly morbid disease often presenting with non-specific symptoms, including anemia and systemic manifestations [2]. Although an improvement of radiologic diagnosis and treatment strategies have improved in recent years, the disease outcome is still poor.

Due to its high morbidity and mortality, a prompt diagnosis of IE is crucial to avoiding serious complications, including valvular regurgitation, heart failure (HF), embolic events, and sepsis. Investigations should start on suspicion in patients with fever with or without bacteremia and/or cardiac risk factors such as prior IE, a prosthetic valve or cardiac device, valvular or congenital heart disease, or noncardiac risk factors, including intravenous drug use, intravenous lines, immunosuppression, or a recent dental or surgical procedure [3].

Diagnosis has long been based on the modified Duke Criteria for which echocardiography and blood cultures are the cornerstones. Other imaging techniques, included in the ESC 2015 may increase diagnostic sensitivity and help detection of silent vascular phenomena and endocardial lesions [4]. Several refinements have been made to both the

major and minor Duke criteria, including the addition of elevated erythrocyte sedimentation rate or C-reactive protein, the presence of newly diagnosed clubbing, splenomegaly, and microscopic hematuria to the minor criteria. However, the current guidelines are largely developed on expert opinion because of the low incidence of the disease, the low number of randomized trials, and the limited number of meta-analyses, making the evidence of their recommendations relatively low with major gaps [4].

Various hematologic abnormalities are common in IE, with variable pathophysiologic mechanisms. However, they are not included as significant criteria of the modified Duke guidelines. Only small clinical studies exploring their diagnostic and prognostic roles are reported.

Therefore, in this article, we explore the frequent hematologic abnormalities associated with IE and the available evidence of the impact of these changes in the diagnosis and prognostic stratification of IE patients.

Clinical Presentation of Infective Endocarditis

Only in a minority of patients, diagnosis of IE is straightforward including those with a consistent history and classic manifestations: sustained bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunological vascular phenomena. However, in most patients, the classic history and physical findings may be few or absent. In acute IE, immunological vascular phenomena may not be as developed as in later stages of the more insidious subacute form of IE [5].

Some cases may have an indolent clinical course with non-specific symptoms, no fever, and atypical presentation of infective Endocarditis, such as elderly and immunocompromised patients, comprising challenging diagnoses. Therefore, risk factors for Endocarditis should prompt further evaluation to avoid delay in diagnosis and treatment [6,7].

The nonspecific presentation of infective endocarditis by symptoms such as fatigue, fever, or chest pain, calls for a broad workup.

Laboratory Abnormalities in Infective Endocarditis

In acute states, a laboratory workup includes a complete blood count that often shows leukocytosis, while subacute or chronic cases often may show normocytic anemia. Elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) are seen in around 60% of cases. A comprehensive chemistry panel should include electrolyte levels to detect any derangements requiring correction during the initial resuscitation [8].

Anemia is the most common hematologic abnormality in subacute bacterial Endocarditis, recognized in 29% of patients and is associated with higher mortality [9]. However, most clinical studies do not emphasize its significance, particularly in cases where antibiotic therapy for an undiagnosed febrile illness may mask symptoms and signs of the disease. Anemia and other hematological abnormalities may occasionally overshadow the more familiar manifestations of bacterial Endocarditis. Therefore, a comprehensive investigation of anemia is necessary as early as possible [10].

Diagnostic Guidelines and Criteria: The diagnostic strategy should be both sensitive for disease detection and specific for its exclusion across all forms of the disease [5].

The modified Duke criteria, which have a reported sensitivity of 70%–80%, may misclassify some patients with confirmed IE by pathological criteria, as possible IE. This is primarily related to lower sensitivity in patients with blood culture-negative IE (BCNIE), prosthetic valve endocarditis (PVE), and device-related endocarditis (DRE) [11].

Diagnostic Gaps and Challenges: Several laboratory investigations and biomarkers have been evaluated in sepsis/sepsis syndromes and endocarditis, reflecting the complex pathophysiology of the disease process, including pro- and antiinflammatory processes, humoral and cellular reactions, and both circulatory and end-organ abnormalities. However, due to their low sensitivity and specificity, they are not included in major diagnostic criteria and are only used to facilitate risk stratification. For example, Sepsis severity may be indicated by the degree of leucocytosis/leucopenia, granulocyte shifts to the left, CRP and procalcitonin levels, ESR, and markers of end-organ dysfunction (lactatemia, elevated bilirubin, thrombocytopaenia and changes in serum creatinine concentration) [12]. Specific parameters are also used in surgical scoring systems [Sequential Organ Failure Assess-ment (SOFA) score], including bilirubin, creatinine, platelet count, and creatinine clearance [European System for Cardiac Operative Risk Evaluation (EuroSCORE) II]. The pattern of increase in inflammatory mediators or immune complexes may also support the diagnosis of IE, e.g. the finding of hypocomplementaemia and elevated antineutrophil cytoplasmic antibody in endocarditis-associated vasculitis [12].

Prognosis and Risk Stratification

The in-hospital mortality for IE can reach up to 30%. High-risk patients can be identified as those with specific patient characteristics (age, PVE, or comorbidities), IE

complications (heart failure, renal failure, septic shock, or brain hemorrhage), echocardiographic findings (abscess, significant valve destruction, or pseudoaneurysm), and specific cultured organisms (S aureus, fungi, and non-Haemophilus spp, Actinobacillus spp, Cardiobacterium hominins, Eikenella Corrodens or Kingella spp (non-HACEK) Gram-negative bacilli) [13].

Early and accurate risk assessment is crucial in patients with infective endocarditis (IE). However, only very limited studies have evaluated the prognostic role of clinical risk parameters. Hematologic abnormalities have been investigated as predictors of mortality risk- in cardiac intensive care unit (CICU) patients.

In a study by Meshaal, et al. [14] the neutrophil-to-lymphocyte ratio (NLR) and plate-let-to-lymphocyte ratio (PLR) were reported as independent predictors of worse prognosis in many infectious and cardiovascular diseases. Elevated NLR, TLC, neutrophil percentage, serum creatinine, and CRP levels were associated with higher hospital mortality and morbidity in IE patients. Reduced lymphocyte and platelet counts were similarly, strong indicators of hospital mortality in these patients. Therefore, calculating the NLR directly from a CBC upon admission may assist in early risk stratification of patients with IE.

Anemia is another predictor of clinical risk in IE, suggesting its potential value as a non-specific marker of poor outcomes in cardiac intensive care unit (CICU) patients

Anemia is common in acutely ill cardiac patients, with a prevalence of 19% and 48% in patients with acute coronary syndrome (ACS) and acute heart failure (HF), respectively, and is associated with higher short-term and long-term mortality. Anemia with elevated red cell distribution width (RDW), or mean corpuscular volume (MCV), is reported as an adverse prognostic factor in patients with cardiovascular disease and critical illness. It has been reported as an independent predictor of adverse cardiovascular events, bleeding, and mortality in those patients. Elevations of red cell distribution width (RDW) and mean corpuscular volume (MCV) are similarly associated with worse outcomes in patients with acute cardiac disease. These easily-available hematologic data can be applied as adverse outcome risk predictors in CICU patients. However, further studies are needed to explore the underlying pathophysiology of hematologic changes in acute illness patients; a specific etiology versus a reflection of illness severity [15].

Pathogenesis of Anemia and Red Blood Cell Abnormalities in IE

Anemia, the commonest hematologic abnormality in IE is multifactorial. It varies in degree and mechanism between subacute and acute Endocarditis and sometimes with the type of infection [16]. Most commonly, the anemia is non-regenerative and rarely hemolytic [17]. Severe anemia may divert attention initially toward a hemorrhagic gastroenterological or a primary hematologic disease, thus delaying IE investigations and diagnosis [18].

The Type and Mechanism of Anemia in IE may Include one or more of the Following: Normocytic and normochromic anemia without reticulocytosis is reported in about 70-90% of IE patients. The common pathogenic factor of this anemia is a chronic infection and inflammation [2]. The absence of reticulocytosis may point to a component of bone marrow suppression due to the bacteria or its toxins. Another potential explanation is intramedullary ineffective hematopoiesis. Iron deficiency anemia due to intravascular hemolysis may occur later [19].

Hemolytic anemia is much less common and can result from intravascular or extravascular events. Several mechanisms may induce hemolytic anemia, including fragmentation hemolysis re-lated to turbulent flow caused by vegetation and abnormal valve structures, which produces shearing stress on the red blood cells, hyper splenic sequestration, production of anti-erythrocyte antibodies, and production of circulating immune complexes. Anti-erythrocyte antibodies may arise by crossreaction between invading microorganisms and erythrocytes, leading to their destruction in the spleen. Circulating immune complexes may also induce thrombotic thrombocytopenic purpura (TTP)-like syndrome and red cell fragmentation [20].

An autoimmune hemolytic process may also occur, supported by spherocytes in the peripheral blood, splenomegaly, and a positive Coombs test. An alteration of red cell antigenicity may underly the production of anti-erythrocyte antibodies [21].

Intravascular hemolysis is the primary mechanism of hemolytic anemia and may result from mechanical trauma, complement fixation, and toxic damage to RBCs. The hallmark of valve failure is the presence of regenerative anemia with schistocytes on a blood smear. The RBCs lysis in the circulation, releasing hemoglobin into the plasma will lower serum haptoglobin levels. Therefore, low serum haptoglobin and hemoglobinuria are two additional laboratory tests that can support the detection of intravascular hemolysis.

Extravascular hemolytic destruction by splenic macrophages can result from the sequestration of schistocytes caused by mechanical damage to the RBCs associated with the vegetative lesions or antibody-coated erythrocytes [17].

Hemolytic anemia associated with hypertrophic obstructive cardiomyopathy (HOCM) with left ventricular outflow tract (LVOT) obstruction, mostly with co-existing infectious endocarditis, highlights the importance of considering infectious causes in managing hemolysis, especially in a patient with cardiac anatomical deformities when persistent surveillance for sub-acute Endocarditis is imperative.

Other Etiologic Factors for Anemia in IE: The type of organism may sometimes induce unique abnormalities. Currently, *Staphylo-coccus aureus* is the most prevalent organism in IE accounting for ~26.6% of all cases, followed by Viridans group streptococci at 18.7%, other streptococci at 17.5%, and enterococci at 10.5%. Certain microorganisms may be associated with specific pathogenic mechanisms. Mechanical damage to red blood cells (RBCs) has been reported with A chromobacter *xylosoxidans* resulting in intravascular hemolysis or splenic removal of damaged RBCs [17]. A. israelii infection has been reported as a cause of anemia in IE patients with native valve vegetation [22].

Effect of Therapy

Therapeutic drugs used in IE may contribute to anemia, such as Ceftriaxone and linezolid, via different mechanisms. Including hemolysis and bonemarrow suppression [23].

Conclusion

Although hematologic abnormalities are common in association with IE, they have not been widely studied as potential markers for diagnosis and risk stratification of IE patients. Anemia and changes in red cell indices which are the commonest blood abnormality in these patients showed promising results in small clinical studies as predictors of adverse outcomes. However, the evidence available at present is low to justify inclusion in standard diagnostic criteria.

Future Directions

The variability in clinical presentations, predominantly non-specific, and the lack of strong evidence for the diagnostic and prognostic impact of certain diagnostic parameters in IE call for large clinical studies, with a representative from various etiological and prognostic clinical groups. This may necessitate multicenter and follow-up collaborative studies. Regular updating and implementation of newly obtained data are important to hasten early diagnosis and risk stratification.

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