

# Biomarkers in infections related to cardiac implantable electronic devices

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## RELATED ARTICLE

by Ząbek et al,  
see p. 918

Infections related to cardiac implantable electronic devices (CIEDs) are one of the most feared complications of device therapy associated with significantly increased healthcare costs, morbidity, and mortality. For de novo CIED implantation, the risk of infection is 0.5% to 1.0%; however, the risk can increase up to 5% for generator changes or upgrades.<sup>1</sup> The burden of CIED infection is increasing as patients with CIEDs are now older, have more comorbidities, and receive more complex devices than in the past.<sup>2</sup>

Device pocket infection, or local infection, is the most common infectious complication associated with the use of CIEDs. Diagnosing local infection is challenging, as most patients present with few or mild symptoms and sometimes without any localizing signs. The diagnosis requires a suspicious clinician, detailed patient history, and focused physical examination. Often, the physical examination findings of erythema, pain, warmth, swelling, induration, tenderness, or fluctuation are the only indicators of local infection.<sup>3</sup> Conversely, the identification of lead-dependent infective endocarditis (LDIE) is usually more clear and diagnostic workup more standardized with the application of the modified Duke criteria.

In both conditions, the complete removal of the device and lead, accompanied by tailored antibiotic therapy, is the gold standard treatment. The extent of an infection, local versus systemic, defines not only the duration of the antibiotic treatment but also the prognosis. The 1-year mortality rate for patients with local infection is less than 10%, whereas patients with “possible” or “definitive” LDIE face 1-year mortality rate in excess of 20% and 30%,

respectively.<sup>4,5</sup> The mortality rate rises to 55% to 65% in patients with LDIE managed with conservative or inadequate treatment.<sup>6</sup>

Thus, the early recognition and accurate diagnosis of CIED infections and their extent are crucial to facilitating an appropriate therapy, preventing endocarditis in patients with local infection, and optimizing outcomes in patients with LDIE. On the contrary, the importance of excluding local infection or LDIE cannot be overlooked, as it will prevent unnecessary surgical pocket exploration and patient anxiety.

Given the significance of the differentiation of LDIE, local infection, and no infection, it is important to have an easily accessible, noninvasive tool that assists with this differentiation. Some biomarkers could be promising in this role.<sup>3</sup>

In this issue of *Kardiologia Polska (Kardiologia Pol)*, Ząbek et al<sup>7</sup> present prospective data on inflammatory markers in 640 patients with CIED undergoing transvenous lead extraction. From October 2011 to December 2018, they enrolled 63 patients (9.9%) with LDIE, 61 patients (9.5%) with local infection, and 516 controls (80.6%) with noninfectious indications. Their aim was to assess the diagnostic value of white blood cell (WBC) count and C-reactive protein (CRP) level in patients with local infection and LDIE.

Their major findings were threefold. Firstly, WBC count was similar in the local-infection group and control group; secondly, WBC count and CRP level were significantly increased in the LDIE group compared with the local-infection group; and finally, the CRP level was superior to WBC count in identifying LDIE. The test characteristics for CRP and WBC, respectively, were: sensitivity (84% vs 46%), specificity (82%

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vs 95%), positive predictive value (34% vs 52%), negative predictive value (NPV) (98% vs 94%). Although the mean CRP levels exceeded the established cut-off values in the local-infection group, they were only slightly higher than in the control group and are unlikely to be of use in day-to-day clinical practice.

It is well known that in the majority of patients with local infection, WBC count and CRP level are normal and therefore are of limited diagnostic value.<sup>8,9</sup> The present study confirms this observation but extends upon it to identify WBC count and CRP level as useful biomarkers to identify patients with LDIE in the local-infection population. In cardiac device pocket infection, normal serum WBC and CRP levels may be explained by the localized nature of the infection, isolated from the systemic circulation to some extent by the fibrous capsule of the pocket. An important take-home message from the article is that normal CRP level and WBC count do not exclude local infection.

Our own group have shown that higher serum levels of high-sensitivity CRP are seen in local infection when compared with controls.<sup>3</sup> We also did not see a difference in CRP levels between the local-infection and control groups. Although high-sensitivity CRP is becoming more widespread, its use still remains predominant in the realm of research and the authors should be congratulated on their investigation of cost-effective and widely available biomarkers to aid differentiation between local infection and LDIE in the real-world setting.

Currently, the CRP level is not considered a diagnostic criterion for LDIE, as it is not specific and may be elevated in the context of viral infections, a recent surgery, or trauma. CRP concentrations do tend to be the highest in acute *Staphylococcus aureus* infections, a frequent offending pathogen in CIED infections.<sup>10</sup> However, CRP does have a role in assessing response to antimicrobial therapy in a patient with infective endocarditis.<sup>11</sup>

The current study highlights the excellent NPV of the 2 assessed biomarkers in differentiating local infection from LDIE with a NPV of 94% for WBC and 98% for CRP, suggesting that WBC and CRP can be used as rule-out criteria for LDIE. In short, negative inflammatory markers in patients with a clinical local infection make LDIE exceedingly unlikely. Elevated inflammatory markers in a patient with a definite local infection should initiate further investigation as per the European Society of Cardiology Guidelines for the management of infective endocarditis.<sup>12</sup>

The authors should be congratulated for highlighting the importance of the high NPV for WBC and CRP in LDIE. These simple, widely available biomarkers can aid in excluding a more extensive infection in patients with local infection,

which has implications for treatment decisions and patient prognostication. Finally, the study confirms the important point that inflammatory markers have no role in ruling out an isolated local infection.

## ARTICLE INFORMATION

**DISCLAIMER** The opinions expressed by the author are not necessarily those of the journal editors, Polish Cardiac Society, or publisher.

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