A new world for the conquistadors?

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This editorial refers to ‘Abrasions of the outer silicone insulation of endocardial leads in their intracardiac part: a new mechanism of lead-dependent endocarditis’ by A. Kołodzinska et al., on page 903

In this issue of the Journal, Kołodzinska et al.1 report a very intriguing finding that the presence of abrasion in the intracardiac part of the leads was strongly associated with infection. Insulation defect was frequent in their population (64%) and was significantly higher on leads extracted for an infectious indication (91%). In multivariate stepwise analysis incorporating patient age, number of leads, lead age, number of prior procedures, time from the last procedure, and the presence of any abrasion in the intracardiac part was independently associated with infection with an odds ratio of 4.9 (95% confidence intervals, 1.5–15.4) for atrial leads and 21.7 (2.8–167.8) for ventricular leads. To explain such as a significant association between lead defects and infection, we have to go back to the mechanisms of device infections.

Mode of contamination

Two distinct mechanisms of contamination exist: (i) haematogenous contamination with seeding of the device from a distant source of infection or during a bacteraemia, e.g. valvular endocarditis; and (ii) local contamination of the pulse generator or leads during implantation of the device or any subsequent procedure on the pulse generator site. We do not know the exact proportion of device infections induced by haematogenous contamination but we have many plausible arguments to believe that this is a rare mechanism of contamination compared with local contamination.

Firstly, in haematogenous contamination, risk factors for infection mainly relate to the implant procedure particularly device replacement and multiple device revisions, early reintervention on the pulse generator site, procedure duration, pulse generator size and additional subcutaneous material, experience of the operator, and lack of antibiotic prophylaxis during the implant procedure.2 3

Secondly, infection occurring early after a surgical intervention is directly attributable to the procedure. The majority of device-related infections are diagnosed in the 24 months following implantation. In our series of 544 patients with device infection, the median time to the occurrence of infection was 7 months, with 83% of infections occurring within 24 months after implantation (unpublished data).

Thirdly, Staphylococcus epidermidis and the coagulase negative Staphylococcus (CoNS), known to be part of the normal skin microflora, are responsible for the great majority of infections. Da Costa et al.4 have compared bacteria found on systematic skin cultures during pacemaker implantation procedures with the bacteria responsible for device infections during follow-up and have shown that devices were infected by bacteria present on the skin during the implantation procedure. Therefore, we cannot explain the association between lead abrasion and lead infection by a haematogenous contamination mechanism occurring preferentially on damaged leads.

Contamination does not always induce infection

Three types of factors contribute to infection or so-called ‘virulence’: (i) microbial persistence factors, (ii) adherence factors, and (iii) biofilm formation. The primary attachment leads to a monolayered film of microorganisms involving multiple physicochemical, protein, and polysaccharide factors. The ability to attach to the device surface is probably a key factor in the occurrence of infection. The initial adherence factors are non-specific and are driven by physicochemical factors including van der Waal’s forces, hydrophobic interactions, and polarity. The type of surface determines the risk of infection, for example, adherence to a polyurethan lead is theoretically more difficult than it is to a silicon lead.

These factors are followed by more specific interactions between the microorganism, the device surface, and host proteins. These interactions are facilitated by multiple surface ‘adhesins’ termed as ‘microbial surface components reacting with adherence matrix molecules’ or MSCRAMM. These microbial surface components bind to various host extracellular matrix components including fibrinogen, fibronectin, or collagen present on the surface of the implanted material. These MSCRAMM are genetically
predetermined. The ‘virulence’ of some species can be explained by multiple MSCRAMM as for the Staphylococcus aureus. In contrast, CoNS do not have major factors of virulence. Genetic analysis revealed that the gene of the major autolysine AtEL and the gene Fbe encoding a fibrinogen-binding protein were involved in attachment of CoNS. In the second phase of biofilm formation, the attached bacteria proliferate and accumulate in a multilayered biofilm. A polysaccharide intercellular adhesin (PIA), which is functional in cell-to-cell adhesion is essential for biofilm accumulation. Synthesis of PIA depends on the gene icaADBC. Some other proteins are important in biofilm formation as the accumulation-associated proteins.

It is plausible that abrasions with an irregular surface and exposure of some metallic material facilitate the adherence of microorganisms. This could explain the relation between infection and the abrasion of the lead inside the pulse generator pocket. But if we retain the local contamination phenomenon, it remains difficult to explain how an abrasion of the intracardiac part of a lead influences the infection occurrence.

**Potential mechanisms**

The answer is perhaps in some other mechanisms: the microbial persistence factors and the latent infection with equilibrium between the human host and bacteria. Staphylococci have a capability of sequestration and antibody absorbing to survive in hostile conditions and some small-colony variants of S. aureus and CoNS have been involved in pacemaker infections, similar to recurrent infections in the bones, heart valves, lungs, and soft tissues. These small-colony variants grow slowly, have been found to persist inside of cultured cells (intracellular location), and can grow in anaerobic conditions. Their characteristics give them the ability to survive several days within phagocytes. Moreover, their membrane properties render some antibiotics (aminoglycoside) ineffective.

Latent device-related infection is a reality. Previous studies found asymptomatic bacterial colonization of pacemakers. Several hypotheses could explain the equilibrium between the human host and bacteria. When this balance is broken, either bacteria are destroyed or infection occurs. Many factors could influence this balance: the number of bacteria or the addition of a new infection, the virulence of bacteria and their ability to adapt to an unfavourable environment and the defence capacity of the host. Lead damage could influence the balance shifting it towards infection. When a bacterial material is introduced, the adherence capacity and the ability of biofilm formation give an advantage to some microorganisms during the course of colonization over the new surface. The capacity to survive and antibiotic resistance are also major factors. Some additional virulence factors associated with CoNS have been described. The poly-gamma-DL-glutamic acids protect S. epidermidis from innate host defences. Some other peptides such as epidermin, epilancin, and epilicidin are implicated in virulence of CoNS. These peptides are active against gram-positive bacteria and give a survival advantage against the competitor in the course of surface colonization. The abrasion is perhaps the discovery of a new territory to colonize in which there are advantages for the CoNS: best conditions for adherence, best protection against host defences, and mechanical conditions responsible for abrasion and unfavourable for host cell colonization.

**Conclusion**

This paper with its intriguing finding of the association between lead damage and infection is perhaps another proof of the equilibrium between the human host and bacteria. The bacteria involved in this equilibrium must have the ability to survive in hostile conditions. The abrasion would be a new territory for conquest by the bacteria leading to infection, but this hypothesis needs further validation.

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**References**