G58: Is there a role for phage lysins in treatment of patients with orthopedic infections?

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Response/Recommendation:
Based on minimal clinical data, the use of phage lysins holds promise for treatment of patients with periprosthetic joint infections (PJI).

Level of Evidence: Limited

Rationale:
Bacteriophages (phages) are natural viruses that specifically infect bacteria. Virulent phages have the ability to destroy a targeted species by replicating inside the bacterial host. This process is associated with the production of various enzymes, by the virus itself, during the replication process inside the bacteria. These phage-encoded enzymes are hydrolases, endolysins (also called lysins), and depolymerases (1). Some of these enzymes, by themselves, have antibacterial and/or anti-biofilm activities, and are called "enzybiotics", as they are enzymes with antimicrobial activity, or "direct lytic agents" (2,3). As a consequence, outside the use of phages, production of engineered recombinant phage enzymes is of interest as: (i) from a microbiological perspective, they possess anti-bacterial and anti-biofilm properties, with a broader spectrum in comparison with phages; (ii) from a biotech point of view, the production process and the protein itself could be patented, unlike a natural phage (1).

Of note, in 2022 the WHO categorized phages and phage-related proteins as key members of the non-traditional antibacterial agents that need to be urgently developed, especially due to their activity on priority pathogens responsible for the worldwide spread of antimicrobial resistance. These non-traditional antibacterial agents in the pipeline have been updated in the WHO 2023 report, and two lysins called CF-301 and SAL-200 were listed (4).

We reviewed all documented cases of bone and joint infections treated with phage lysin in English-language publications since 2010. Only one paper, published in 2021 was found (5). Authors reported the use of the CF-301 lysin (exebacase),a recombinantly produced lysin, that demonstrated antibiofilm activity *in vitro* against staphylococcal species (6,7). In this paper, arthroscopic debridement and implant retention with local administration of CF-301 (LysinDAIR procedure) followed by suppressive tedizolid as salvage therapy was described in four elderly patients with recurrent multidrug-resistant *S. epidermidis* periprosthetic knee infection with no further surgical or antimicrobial therapeutic options. All had multiple previous prosthetic knee revisions without prosthesis loosening; three had experienced a relapse despite previous suppressive antibiotics following an open debridement, antibiotics, and implant retention (DAIR) procedure; two had clinical signs of septic arthritis; the two others had a sinus tract. No adverse events occurred during and after the treatment course. All patients received the same primary antibacterial therapy, followed by tedizolid 200 mg/day as suppressive therapy. At 6 months, recurrence of the sinus tract occurred in the two patients with sinus tract at baseline. After >1 year

follow up, the clinical outcome was favorable in the other two patients with total resolution of clinical signs of septic arthritis even if microbiological persistence was detected in one of them. Given the severity and refractory nature of these infections, any favorable clinical outcome was unexpected.

Following this paper, other patients were treated in the phage referral center for the management of complex bone and joint infections in Lyon, France with ongoing follow up (unpublished data). A single-center, randomized control trial evaluating CF-301-108 was launched in 2023, but stopped prematurely due to the bankruptcy of the sponsor.

Based on: (i) the WHO report about non-traditional agents and the need to develop phages and phage-related proteins to face antimicrobial resistance; (ii) the phage lysins *in vitro* activity, and especially their lytic and anti-biofilm activity; and (iii), the single scientific paper available in the literature about clinical use of lysins, we concluded that phage lysins are of interest in patients with PJI. The development of phage lysins, and their clinical evaluation in acute or chronic PJI need further research for developing evidence-based recommendations about their potential adjuvant role in the management of PJI treated with a conservative approach.

References

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