QUESTION 7: What is the role of the microbial synergy in polymicrobial infections?

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Response:

In polymicrobial infections, a complex environment may be formed in which microbiological interactions exist between microorganisms. Scientific evidence exists to show that combinations of bacterial species may exist whereby these can protect each other from antibiotic action via the exchange of virulence and antibiotic resistance genes, and this may be evident in adverse outcomes for polymicrobial orthopaedic implant-related infections. It is also probable that polymicrobial infections may be more likely in patients with poor immunity and tissue healing.

Level of Evidence: Strong

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Post Meeting Rationale:

The authors felt that the original question was not suitable for a proper systematic review. Therefore a structured review, focusing on the understanding of differences in clinical outcomes and mechanisms of microbial synergy was performed . Pubmed was performed from inception to April 2017. Search words were "Polymicrobial", "Infection" and "synergy" with no restrictions. This yielded 94 publications. After review, selection and inclusion of relevant references, 18 studies were included as references.

Varying incidences for polymicrobial infections have been reported with reported rates ranging from 6% to 37% [1–5]. The literature consistently demonstrates that patients with a polymicrobial infection demonstrate inferior treatment outcomes. Tan et al. reported that patients with polymicrobial PJI had a higher failure rate (50.5%) compared with monomicrobial (31.5%) and a higher rate of amputation (odds ratio [OR] 3.80), arthrodesis (OR 11.06), and mortality (OR 7.88) compared with patients with monomicrobial PJI [2]. Similarly, Wimmer et al. demonstrated that the infection free rate after two years was 67.6 % for polymicrobial infections vs. 87.5 % for monomicrobial infections in a series of 77 polymicrobial PJIs [6]. In addition, Marculescu et al. demonstrated that the 2-year cumulative probability of success of polymicrobial PJIs was 63.8% compared to 72.8% for monomicrobial PJIs [7].

There are several explanations for the increased rate of failure in patients with polymicrobial PJI. Some explanations include that polymicrobial infection include the following: the association with a sinus tract or a soft tissue defect, the frequent presence with difficult to treat organisms such as Enterococcus spp and Gram negatives [2,7,8], increased comorbidities [2,7], and microbial synergy.

Microbial synergy is defined as an interaction of two or more microbes in an infection site that results in enhanced disease by creating a more favorable condition for one another, compared to

infections containing a single organism [9,10]. While microbial synergy results in an enhancement of the disease, real experimental data supporting this phenomenon is still limited [12–14], which may be attributed to the complex and dynamic web of interactions that occur in natural systems [15]. Several mechanisms of microbial synergy have been proposed in order to explain microorganisms interactions during polymicrobial infections: 1) metabolite cross-feeding: reported as the consumption of metabolic end-products by one of the microbial communities involved and optimization of local environment with the metabolic end-products [9,18,19]; 2) dedicated signaling systems: capacity of many microorganisms to communicate and coordinate activities as a group through low molecular weight signals, called "quorum sensing" [20]; 3) stimulation of resistance to the immune system: production of chemical substances that induce resistance to immune system like outer membrane proteins that inhibits immune pathways [9,18]; 4) suppression of the immune system by commensal bacteria: promotion of growth environment for commensal pathogens [9,21,22]; 5) direct contact: formation of biofilm by membrane-bound structures (adhesins) between microbes [23,24] and 6) increased virulence of the organisms: production of substances that enhance the virulence of other bacteria [9].

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