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EDITORIAL

Antimicrobial rationing in orthopaedic surgery

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The use of prophylactic systemic antibiotics in the perioperative period has been shown to reduce postoperative infections following arthroplasty procedures,[1,2] tumour surgery,[3] and trauma procedures.[4] In open fractures, the administration of systemic broad-spectrum antibiotics has been shown to be a more important factor in minimizing the risk of infection than timing of surgical debridement.[5,6] Local antibiotic prophylaxis using bone cement has been shown to reduce the risk of deep postoperative infection following arthroplasty surgery significantly.[7-9] More recently a systematic review and meta-analysis found that local antibiotic prophylaxis resulted in a four-fold relative risk reduction in fracture-related infection following open limb injury.[10] The World Health Organization (WHO) recommends preoperative screening and eradication in orthopaedic surgery of not only methicillin-resistant *Staphylococcus aureus* (MRSA) but methicillin-sensitive *S. aureus* (MSSA).[11] Evaluation of these strategies has shown them to be both effective[12-15] and acceptable to patients.[16] An economic analysis estimated that national *S. aureus* screening programmes could potentially save up to $900 million in total treatment costs annually in the USA and UK.[17]

Even with therapeutic antibiotic use there has been an evolution in practice. The administration of combination therapies (local and systemic routes) has become more popular, despite the paucity of published evidence. Combination therapies are thought to work by: 1) broadening the spectrum of activity; 2) utilizing synergistic effects; 3) preventing resistance mechanisms from evolving; 4) enhancing intracellular penetration; and 5) limiting the expression of bacterial toxins and other virulence factors.[18] Meta-analyses of clinical trials evaluating antibiotic combinations in periprosthetic joint infection (PJI) have reported that the available literature is currently too heterogeneous to draw any clinically useful conclusions regarding optimal regimens.[19,20] Yang et al[21] have compared the effectiveness of a gentamicin and vancomycin (GV)-loaded articulating spacer in two-stage revision with a vancomycin, meropenem, and amphotericin (VMA)-loaded cement spacer. It was postulated that a high percentage of gentamicin resistance within cultured isolates (22/78) was the reason the VMA combination was found to be more effective at eradicating PJI (11/62 vs 1/52). However, it should be noted that from the preoperative and intraoperative samples 20/62 and 9/52 cases were culture-negative in the full GV and in full VMA protocols, respectively, despite fulfilling the Musculoskeletal Infection Society (MSIS) criteria for PJI.[22] One explanation for these culture-negative samples could be the presence of viable but non-culturable pathogens. This is a cellular state characterized by low metabolic activity and failure to grow on routine bacteriological media.[23] Known inducers of the viable but non-culturable state include: starvation; non-physiological ambient temperature; osmotic stress; hypoxia; heavy metals; and antimicrobial and disinfectant challenges.[24-27] A critical feature is that nutritional stimulation, known as resuscitation in this field of microbiology, can restore metabolic activity and culturability.[25,28] It has been hypothesized that in vivo resuscitation of quiescent cells may be responsible for recalcitrant biomaterial infections.[29] The biofilm phenotype, as often displayed by common biomaterial pathogens, is physiologically akin to the viable but non-culturable state, therefore inadequate resuscitation during laboratory culture may result in false negative results.[30] The phenomenon of viable but non-culturable

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states should therefore be taken into account when considering whether infection has been eradicated.

The looming global crisis of antimicrobial resistance[31,32] threatens to halt elective biomaterial-associated procedures.[33,34] Careful antimicrobial stewardship is essential to decelerate the emergence of resistance to currently available drugs, and thus preserve their efficacy. One approach is to explore alternative bactericidal agents for the treatment of biomaterial-associated infections.[35-41] A further approach is to implement antimicrobial stewardship interventions. Evaluations of these interventions have demonstrated their efficacy in reducing rates of both infection and colonization with antimicrobial-resistant bacteria.[42-44] The prevalence of carbapenem (e.g. meropenem)[45,46] and glycopeptides (e.g. vancomycin)[47,48] resistance is increasing globally and their use should be restricted, unless absolutely necessary, to maintain their efficacy. The WHO recognizes carbapenems and glycopeptides as 'critically important' antimicrobials.[49] Carbapenem and glycopeptide sparing, when clinically and microbiologically appropriate, is therefore a key goal of antimicrobial stewardship programmes. The injudicious use of critically important antimicrobials should be questioned.[50] Their incorporation into local treatment protocols should only be implemented following a review of the institution's bacterial epidemiology and justified by local resistance profiles as carried out by Yang et al.[21]

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