Is flucloxacillin monotherapy sufficient for the treatment of skin and soft tissues infections in plastic surgery?

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Dear Sir/Madam,

Skin and soft tissue infections (SSTIs) are commonly managed by plastic surgeons throughout the UK particularly in upper limb and in burns. With an ageing population, and an increasing number of immunocompromised and critically ill patients, the incidence of SSTIs is rising. An important cause of morbidity and mortality, correct recognition and management is vital. *Staphylococcus aureus* and beta-haemolytic streptococci (Group A, C and G predominantly) are the most common causative pathogens of SSTIs and accordingly prompt, and appropriate, antimicrobial therapy forms the mainstay of treatment along with strict elevation and early surgical debridement (if indicated). There are increasing pressures to improve antimicrobial stewardship with growing concerns surrounding antimicrobial resistance and with cost saving implications to decrease the financial burden on the National Health Service (NHS).

Anecdotally we have found that flucloxacillin and benzylpenicillin (or penicillin V, if administered orally) are often co-prescribed empirically in the management of SSTIs. We believe this practice has arisen from traditional prescribing habits trying to target staphylococci with flucloxacillin and streptococci with penicillin, but this is not supported by a strong evidence-base. We are concerned that this dual antimicrobial therapy regimen is associated with increased healthcare costs and a greater likelihood of non-concordance in patients.¹ We believe that flucloxacillin monotherapy would suffice as first line empirical therapy for the treatment of SSTIs in most departments across the UK based on review of the currently available evidence.

The only related randomised controlled trial (RCT) found in the literature compared intravenous flucloxacillin monotherapy with intravenous flucloxacillin and benzylpenicillin dual therapy in the context of treating lower limb cellulitis in the emergency department (n = 81).² This RCT found no significant difference between either treatment group in terms of the number of doses taken to achieve a clinical response, reduction in the size (diameter) of infection, decreases in body temperature and visual analogue scale (VAS) pain scores.²

Rationale for flucloxacillin monotherapy and its sufficiency for treatment of SSTIs is based on evidence that high dose flucloxacillin exerts antistreptococcal activity in addition to targeting staphylococci, thereby rendering the coprescription of benzylpenicillin (or penicillin V) unnecessary.^{1,2} Flucloxacillin has a minimum inhibitory concentration (MIC) breakpoint of 0.06 mg/L against Group A beta-haemolytic streptococci.³ Bergan et al initially characterized the pharmacokinetics of intravenous administration of 2 g flucloxacillin by serially sampling peripheral lymph and skin blister fluid. They demonstrated a flucloxacillin concentration above the Group A streptococci MIC at all intervals up to 10 hours post dose.⁴ Furthermore, samples from skin blister fluid demonstrated a prolonged half-life when compared to serum samples (11.0+/-4.1 hours versus 2.1+/-0.9 hours).⁴ Skin blister fluid concentration can be used as a surrogate for tissue interstitial fluid concentration. Given that betalactam activity is measured by the 'time above MIC' principle, when examining the pharmacokinetics of flucloxacillin in the context of soft tissue infections, monotherapy is sufficient to achieve the requisite time-above-MIC for antistreptococcal activity. We should also note dual antibiotic prescription increases the beta-lactam exposure of patients and thus increases their risk of penicillin related

side-effects including neutropenia, nephropathy and reduced seizure threshold. Furthermore, the addition of intravenous benzylpenicillin to flucloxacillin had no effect on all-cause mortality at any time point in a previous retrospective study.⁵

However, there are caveats and caution that must be taken by clinicians when prescribing antimicrobials in this setting including: patient factors (those with penicillin allergy and pre-existing co-morbidities), microbiological factors (geographical microbiological variance, previous microbiological sensitivities and growth and cases of methicillin resistant *Staphylococcus aureus* (MRSA)) and wound factors (infected animal bites, necrotising skin infections and when underlying bony structures are involved).

This brief review of related literature suggests that there is no benefit of co-prescribing flucloxacillin and benzylpenicillin (or penicillin V) when managing SSTIs in plastic surgery. We therefore recommend that clinicians use high-dose flucloxacillin monotherapy in this setting initially given its ability to exert antistreptococcal activity, reduced costs, and greater likelihood of patient compliance.

Conflict of interest

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