Linezolid use in sepsis due to methicillin-susceptible *Staphylococcus aureus*

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Sir,

We read with interest the correspondence from De Bels et al. We given the tissue penetration data available on the two agents in question, however, it is not surprising that linezolid proved to be successful where vancomycin had failed in a case of septic arthritis. We present a similar case, but of methicillin-susceptible *Staphylococcus aureus* (MSSA)-induced sepsis, which only responded to antimicrobial therapy after linezolid had been added to a regimen of flucloxacillin, fusidic acid and gentamicin. Whilst linezolid’s capacity to reduce *S. aureus* virulence factor expression has been described previously, it has not been reported to date in a clinical setting.

A 57-year-old man was admitted to hospital complaining of back pain and lower limb weakness. He had undergone two spinal operations in the past: cervical discectomy 9 years previously and lumbar discectomy 5 weeks prior to this presentation. MRI of the spine revealed degenerative disc disease in the cervical and lumbar

regions with spinal stenosis and disc protrusion respectively at C5-6 and L3-4. On admission he had a raised white cell count of 14 000/mL with an erythrocyte sedimentation rate of 77 mm/h. Liver function tests and urea and electrolytes were normal. Three days post-admission, he became febrile and profoundly hypotensive, with a concurrent deterioration of his renal and liver functions. He was transferred to the intensive care unit (ICU) for haemodynamic support. Examination revealed bilateral inflamed elbows and an inflamed right knee, which were presumed to be the source of sepsis. The working diagnosis at this point was metastatic infection from his operative wound. However, inspection of the wound revealed no evidence of infection and MRI of the spine revealed no underlying abscess. He was commenced on broad-spectrum antimicrobial therapy of benzylpenicillin, vancomycin, gentamicin and piperacillin/tazobactam. Blood drawn for culture on admission to ICU yielded MSSA. His antimicrobial therapy was rationalized to high-dose flucloxacillin (2 g every 4 h), fusidic acid (500 mg every 8 h) and gentamicin (3 mg/kg) daily, with daily monitoring of gentamicin levels. However, he remained febrile; his inotrope requirement increased and he required haemodialysis. There was no apparent source for continued infection: repeat blood cultures were sterile; chest X-ray was clear; joint washouts were performed, and were sterile despite the use of enrichment techniques. However, these washouts were performed after antimicrobial therapy had been commenced. Trans-oesophageal echocardiogram and CT abdomen were normal. No definitive source of infection was identified. His clinical condition continued to worsen. On day 4 of his ICU admission, intravenous linezolid 600 mg 12-hourly was commenced (Figure 1). His intravascular devices were changed: line tips were sterile. Within

![Figure 1. Inotrope requirements.](https://academic.oup.com/jac/article-abstract/57/1/150/914997)
16 h, his fever settled and he was weaned off inotropic support. After 72 h of continued improvement, linezolid and gentamicin were ceased in an endeavour to reduce his antimicrobial burden. Within 18 h of this change in therapy, he deteriorated, as measured by an increasing inotrope requirement (Figure 1). Linezolid was recommenced and his intravascular devices were again changed (line tips sterile). His clinical progress thereafter was slow but continuous. He was discharged to the ward 2 weeks later.

We believe that linezolid played a significant role in the recovery of this patient. Given that the patient continued to deteriorate despite appropriate MSSA therapy—which succeeded in sterilizing blood drawn for culture—we suggest that the possibility of the clinical improvement being related to an anti-toxin effect of linezolid has to be considered. Gemmell and Ford\(^1\) have shown that sub-MIC linezolid concentrations impair production of coagulase, \(\alpha\)-haemolysin and \(\beta\)-haemolysin: these virulence factors are likely to play a role in the infection process. Bernardo \textit{et al}.\(^5\) have also reported the effects of subinhibitory concentrations of linezolid on the secretion of the \textit{S. aureus} virulence factors. Nakamura \textit{et al}.\(^5\) have described a case of invasive group A streptococcus infection successfully treated with linezolid, whereas Coyle \textit{et al}.\(^6\) have documented the effect of linezolid on the release of streptococcal pyrogenic exotoxin A.

In the present case, the absence of specific assays and measurements of inflammatory mediators and virulence factors means that all we can do at this point is hypothesize. However, given the \textit{in vitro} data, it is not unreasonable to assume that some of this anti-toxin activity is maintained \textit{in vivo}, as is the case with clindamycin. Therefore, whilst currently invaluable almost solely in the treatment of resistant Gram-positive infections such as methicillin-resistant \textit{S. aureus}, linezolid may yet have a broader role to play in the treatment of Gram-positive sepsis.

**Transparency declarations**

No declarations were made by the authors of this paper.

**References**


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**Comment on: Evidence-based review of antifungal prophylaxis in neutropenic patients with haematological malignancies**

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Sir,

A recently published JAC review claims to have found ‘unambiguous evidence’ in the field of antifungal prophylaxis.\(^1\) In our view this topic is too complex to allow such a simple conclusion. This review by Glasmacher \textit{et al}. shows several short comings that require further comment and some additional clarification.

In 2003, we collected evidence available from all published major clinical trials on antifungal prophylaxis and applied the standard evidence grading system of the Infectious Diseases Society of America.\(^2\) It is the decisive strength of this review that available data were listed in detail extensively for the first time, thus facilitating the reader’s assessment of single trials.\(^3\)

Glasmacher \textit{et al}. claim that our review on this topic recommened no indication for the use of any kind of antifungal prophylaxis. Unfortunately, the authors failed to quote our conclusions adequately. We clearly recommend prophylaxis with fluconazole 400 mg once daily in patients undergoing allogenic stem cell transplantation. It is the only regimen based on ‘Good evidence to support a recommendation for use’ and ‘Evidence from ≥1 properly randomized, controlled trial’ (category A I).\(^2\) Furthermore, we concluded—and still do so—that data advocating the prophylactic use of itraconazole are less conclusive (category B I). The evidence for the use of any antifungal agent in subjects receiving conventional chemotherapy is poor to support prophylaxis (category C I).\(^3\)

We agree with the authors that most single trials do not achieve an adequate statistical power to detect a statistically significant difference between placebo and antifungal prophylaxis. However, we disagree that this problem can only be overcome by cumulative meta-analysis to answer the question of antifungal efficacy. This is mainly due to an enormous heterogeneity in patient population and their risk factors for fungal infections treated within different clinical trials. Meta-analysis has, in our opinion, a potential usefulness in the design of future trials when previous results are inconclusive, but cannot replace them. Obviously, this problem can only be