

**A COMMENTARY ON THE DISPARATE PERSPECTIVES OF CLINICAL  
MICROBIOLOGISTS AND SURGEONS: *AD HOC* ANTIMICROBIAL USE.**

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## **Abstract**

Prosthetic joints and other orthopaedic implants have improved quality of life for patients world-wide and the use of such devices is increasing. However, while infection rates subsequent to associated surgery are relatively low (<3%), the consequences of incidence are considerable, encompassing morbidity (including amputation) and mortality in addition to significant social and economic costs. Emphasis, therefore, has been placed on mitigating microbial risk, with clinical microbiologists and surgeons utilizing rapidly evolving molecular laboratory techniques in detection and diagnosis of infection, which still occurs despite sophisticated patient management. Multidisciplinary approaches are regularly adopted to achieve this. In this commentary, we describe an unusual case of *Actinomyces* infection in total hip arthroplasty and, in that context, describe the perspectives of the clinical microbiology and surgical teams and how they contrasted. More specifically, this case demonstrates an *ad hoc* approach to structured eradication of biofilms and intracellular bacteria related to biomaterials, as reflected in early usage of linezolid. This is a complex topic as, and as described in this case, such accelerated treatment can be effective. This commentary focuses on the merits of such inadvisable use of potent antimicrobials amid the risk of diminishing valuable antimicrobial efficacy, albeit resulting in desirable patient outcomes.

## **Introduction**

North America has experienced significant declines in mortality secondary to infectious diseases.<sup>1</sup> In the European Union, incidence of severe sepsis, associated with multiorgan failure, is currently estimated as 90.4 cases per 100,000 population.<sup>2</sup> Not least, in bringing about improvements, have been the adoption of enhanced infection control practices, efficacious antimicrobial therapies, advanced molecular-based laboratory methodologies and sepsis management protocols.<sup>3</sup> Indeed, direct links have been demonstrated between time required for pathogen identification and infectious illness outcomes.<sup>4</sup> In response, use of molecular-based laboratory technologies has become more common, leading to more rapid microbial identification, susceptibility testing, reduction in empiric antimicrobial use, faster application of targeted therapies and, overall, enhanced patient care.<sup>5</sup>

Despite these advances, surgical practice can require decision-making with respect to treatment of nosocomial or procedure-related infections, often in the absence of laboratory data regarding the nature of causative organisms, whether those infections are monomicrobial or polymicrobial, and their relative sensitivities to available bacteriostatic or bacteriocidal agents. There is, therefore, an imperative that clinical and molecular microbiologists determine accurate etiological diagnoses enabling selection of the most appropriate antimicrobial treatments. However, while laboratory analysis is underway, surgical teams may decide to engage in broad spectrum empiric treatments, using parenteral or oral therapy, as well as consideration of further surgical management.

In the case of orthopaedic surgery, specifically, the use of prosthetic joints and other

implants has been associated with relatively low levels of infection (<3%).<sup>6</sup> Focusing more keenly on total hip arthroplasty, or hip replacement, reports of infection classify occurrence based on the timing of incidence: “early” within one month of procedure, “delayed” within a year, and “late” at any time after that.<sup>7 8</sup> Such infections are considered a serious complication<sup>9</sup>, with “early” and “delayed” infection typically due to perioperative bacterial contamination, whereas “late” incidence is understood to be predominantly blood-borne.<sup>7 10</sup>

### **The Case**

Prosthetic joint infections typically result from monomicrobial contamination by *Staphylococcus aureus* or *S. epidermis*, with much fewer cases associated with any other species.<sup>11 12 13 14 15</sup> In this case, a 71 year old man had presented 9 years following hip arthroplasty with hip pain and elevated inflammatory markers (erythrocyte sedimentation rate of 71 mm/h and c-reactive protein of 65 mg/l).<sup>7</sup> Imaging techniques indicated that there was evidence of osteolysis, subsequent biopsies of adjacent tissue confirmed presence of *Actinomyces israelii*. Treatment involved removal of the prosthesis, insertion of vancomycin-loaded bone cement spacer, intravenous antimicrobials, and eventual re-implantation with a new prosthesis. There has been no recurrence of infection to date.

### **The Microbiologist Perspective**

*Actinomyces israelii* is a filamentous Gram-positive anaerobic bacterium, is considered

only opportunistically pathogenic,<sup>16</sup> and is frequently isolated from the gastrointestinal tract, bronchi, oral cavities and female genital tract.<sup>14 17</sup> Pathogenesis most commonly involves dental caries or gingival disease, with infections of the lung or abdomen being the next most common. *A. israelii* infection in hip replacement is extremely rare with only 3 previous reported cases in the literature, associated with contamination at the time of surgery<sup>13</sup>, dental work without antibiotic prophylaxis<sup>14</sup>, and intravenous drug abuse<sup>17</sup>. In the present case, infection occurred with Type 2 diabetes mellitus the dominant risk factor.

For the reasons outlined above, *Actinomyces* infection was not initially suspected in this case. Indeed, aspirate from the painful hip joint was devoid of microbes (Figure 1) and it was only following culture of biopsies from periprosthetic tissue that *A. israelii* was detected. The microbiological process (Figure 1) involved 10 days anaerobic incubation on blood agar and use of biochemical kits (bioMérieux® API®). Laboratory assays demonstrated susceptibility to penicillin, teicoplanin, vancomycin, ciprofloxacin and linezolid. These results corresponded broadly with expert recommendations for antimicrobial therapy<sup>18 19</sup> including prolonged high doses of parenteral penicillin, followed by oral penicillin / amoxicillin or tetracyclin, erythromycin, doxycycline or clindamycin if penicillin is not an option.<sup>20</sup>

### **The Surgeon Perspective**

An empirical antimicrobial approach was adopted (Figure 2). A vancomycin-loaded cement spacer was put in place and intravenous teicoplanin administered until the

infectious agent was identified and susceptibility to vancomycin was confirmed by the clinical microbiology team, at which point teicoplanin was discontinued. The subsequent therapeutic approach deviated from recommended anti-actinomycosis protocols,<sup>20</sup> through relatively long-term (28 day) use of linezolid, due to the following factors:

- Requirement for eradication of infection before any re-implantation could occur
- Recognition that biofilm formation, initially associated with the pathogenesis of catheter-related infection but now considered a key aspect of many biomaterial-related microbes, may be involved.<sup>21</sup> This was potentially indicated by the lack of recoverable bacteria from the aspirated synovial fluid.
- Linezolid has demonstrated efficacy against most Gram-positive pathogens, including multidrug-resistant staphylococci.<sup>22 23</sup>
- Linezolid has been shown to accumulate rapidly in bone, with reported efficacy in a broad range of orthopaedic infections.<sup>24</sup>

## **Discussion**

Amongst the primary roles of the clinical microbiologist are guidance and support of surgical teams, and selection of appropriate diagnostic investigations and antimicrobials, as warranted.<sup>5</sup> In this case, the recommended antibiotic treatment profile, based on susceptibility testing, included teicoplanin and vancomycin. However, the imperative for the surgical team was eradication of *Actinomyces* associated with bone prosthesis. In that context, linezolid was a suitable antimicrobial due to its proven ability to achieve high

concentrations in bone,<sup>24</sup> and so the patient was administered a four week oral course (2x 600 mg day<sup>-1</sup>).

From a clinical microbiologist perspective, this course of treatment would be undesirable as linezolid is generally reserved for treatment of multidrug-resistant microbes. Worryingly, although resistance to linezolid is difficult to generate *in vitro*,<sup>23</sup> emergence of *cfr*-related *in vivo* resistance has been reported<sup>25 26 27</sup> in addition to only bacteriostatic activity against staphylococci and *Enterococcus* spp.<sup>28</sup> Indeed, pharmacodynamic studies provide evidence of low AUC<sub>24</sub>/MIC related to high numbers of therapeutic failure,<sup>28</sup> including orthopaedic applications.<sup>29 30</sup> Of even greater concern to the clinical microbiologist, however, are reports of adverse events associated with relatively long-term use of linezolid,<sup>31 32</sup> analogous to the four week regimen in this case (although linezolid is approved for treatment of that duration).

The surgeon-led patient-centred care commented on here focused on efficacy of treatment appropriate to an elderly man. Since approximately 1996, management of similar cases have employed both two-stage surgery (i.e., removal of infected prostheses – sometimes use of antibiotic-loaded spacers – eradication of causative pathogens followed by replacement of devices) and intracellular antimicrobials to avoid relapse due to potential harbouring of bacteria within periprosthetic fibroblasts.<sup>33</sup> That was the approach adopted in this case, oral linezolid facilitating outpatient-based treatment and, importantly for the elderly patient, markedly reduced discomfort for him and his family.

In conclusion, advances in molecular technologies for rapid species identification and susceptibility testing are mitigating the protracted incubation times associated with conventional microbiology, facilitating quicker diagnosis and reduction in exposure of

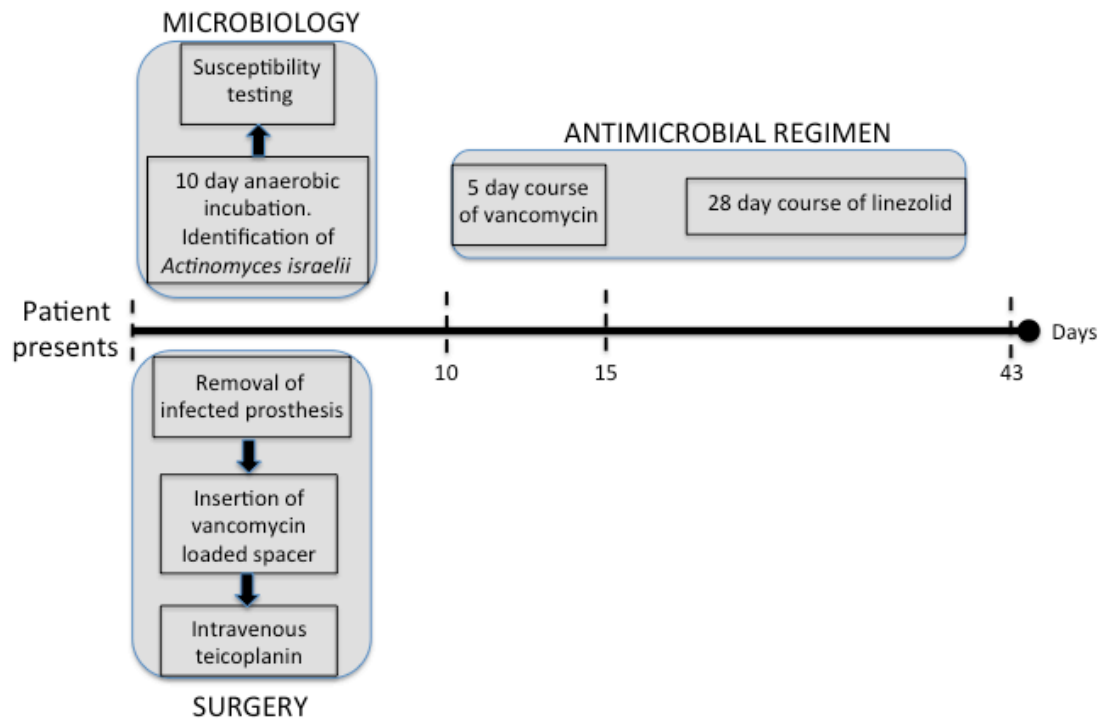
patients to empiric therapy in favour of targeted antimicrobial use. In the specific case described here, the use of the linezolid proved successful, with no adverse events evident. However, it is probable that double-blind, randomized trials of linezolid in orthopaedic settings are necessary to clarify its efficacy and, therefore, suitability for use.



**Figure 1** X-ray showing translucency surrounding the femoral component of the prosthesis. Aspirate was negative for infection. Subsequent analysis of the acetabulum proved positive for *Actinomyces Israelii*.

**X-Ray Image to be inserted here**

Figure 2



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