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Letter to the Editor

Increasing antimicrobial resistance is not inevitable: in reply to microbiological and antibiotic profile of osteomyelitis tertiary care hospital

Sir,

It was with interest and alarm that we read the report by Vijakumar et al regarding antimicrobial susceptibility patterns of pathogens isolated from patients with chronic osteomyelitis.[1] The authors reviewed 132 isolates from 100 patients managed in Davangere, Karnataka, South West India between January 2017-December 2019.

Notably, the authors report that for *Staphylococcus aureus*, the most commonly isolated pathogen, 75% of isolates were resistant to gentamicin, 81% to ciprofloxacin and 50% were methicillin resistant *Staphylococcus aureus* (MRSA). With regard to gram negative isolates the predominant species were Pseudomonas aeruginosa and *Acinetobacter baumanii*. Both pathogens are intrinsically highly antibiotic resistant, however a high number of the isolates reported in this study were in addition resistant to carbapenems (42.9% meropenem resistant Pseudomonas, 54.5% meropenem resistant acinetobacter). The authors report rising rates of antimicrobial resistance which they regard as inevitable, as a result of extensive antibiotic use. They advocate surveillance to monitor these changes in infection aetiology.

In 2019 we reported a comparison of microbiological findings and resistance profiles from patients surgically managed for osteomyelitis between 2001-2004 (184 patients) and 2013-2017 (157 patients) in Oxford UK.[2,3] Demographics of included patients and location of osteomyelitis were similar to those included by Vijakumar et al.[1] Infections with *Staphylococcus aureus* were also most common in both cohorts (31.3% for 2001-2004 cohort, 37.5% for 2013-2017 cohort). However, notably, the proportion of MRSA fell significantly over this 10-year period (30.8% vs 11.4% of *Staphylococcus aureus*, p=0.007) (Figure 1).[2] In a comparable cohort of patients with fracture-related infections (FRI) managed at our institution between Jan 2017 and Jan 2019 (167 patients, average age 51 (range 16-82), 23% female, 30.9% of all isolates were *Staphylococcus aureus*, of which 8.3% were MRSA.[4]

Similarly, Dudareva et al also report that rates of resistant gram-negative infections either measured as percentage of *Enterobacteriaceae* classified as extended spectrum beta lactamase producers (ESBL) or *Enterobacteriaceae* with the potential to over express AmpC type beta lactamases (ESCAPPM group) also fell during the study period (7.4% 2001-2004 versus 5.6% 2013-2017 for ESBL, and 44.4% 2001-2004 versus 35.2% 2013-2017 ESCAPPM) (Figure 1).[3] This is despite a slight increase in the percentage of the overall infections that were either *Enterobacteriaceae* (16.3% vs 23.3%) or non-fermenters, including *Pseudomonas*, (5.4% versus 7.3%) over this 10-year period. No carbapenems producing *Enterobacteriaceae* (CPE) were recorded in either cohort. In our FRI cohort, 5.7% of *Enterobacteriaceae* were ESBL, with a further 8.6% CPE. Of note the CPE isolates were from 2 patients both of whom had had their initial injury and fracture fixation outside the UK, in Greece and India.[4]

Two important messages must be taken from these comparisons:

Firstly, as observed by Dudareva et al the falling prevalence of MRSA osteoarticular infection mirrored the fall in MRSA bloodstream infections in the UK.[3,5] This decrease was likely to have been driven at least in part by national incentives for effective antimicrobial stewardship to reduce fluoroquinolone, cephalosporin and carbapenem prescribing across all infectious diseases. This observation highlights that increasing antimicrobial resistance is not inevitable. One of the benefits of effective antibiotic stewardship is that the increase in hospital-adapted multi-drug-resistant infections can be prevented.

Orthopaedic infections, such as FRI, are often caused by micro-organisms that are normally present on epithelial surfaces. The fewer antibiotics these populations are exposed to, the greater the evolutionary fitness cost they bear when continuing to express genes that confer antibiotic resistance. The fitness cost to bacteria is obvious: antibiotic resistance might involve the metabolic cost of synthesizing additional enzymes, or the nutritional disadvantage of maintaining reduced porin expression or efflux pump over-expression.

As soon as selection pressure from widespread antibiotic use is reduced, antibiotic-resistant bacteria start to be outcompeted by antibiotic sensitive strains. In countries where control of antibiotic prescribing is effective, the likelihood of resistant infection decreases with time.

Secondly, it is striking how variable the resistance patterns are for similar pathogens isolated from similar infections but separated only by country of origin and management. This comparison highlights the important regional differences in micro-organisms responsible for bone infections. Such differences are essential to consider when selecting empiric post-operative treatment for osteoarticular infections.

In summary, we agree that orthopaedic infection departments will benefit from surveillance audits of susceptibility patterns in common micro-organisms to inform optimal local prescribing. However, surveillance must go hand in hand with active anti-microbial stewardship. With effective antimicrobial stewardship, increasing antimicrobial resistance is not inevitable.

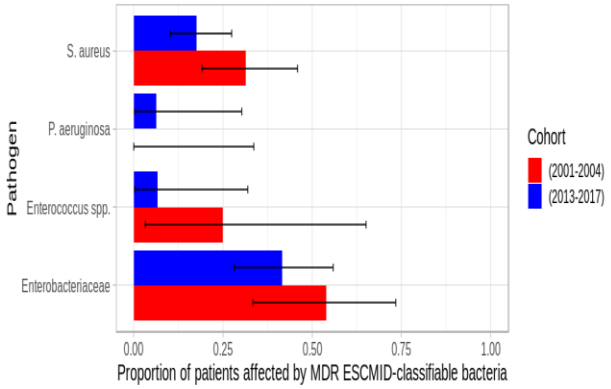

Figure 1: Comparison of microbiology between patients treated in 2001-2004 and 2013-2017 depicting the change in the proportion of patients affected by multi-drug resistant (MDR) ESCMID-classifiable bacteria. This demonstrates the reduction in both resistant *Staphylococci* (including MRSA) and resistant *Enterobacteriaceae* isolated over the 10-year period as described in the text. In addition, the reduction in the proportion of patients affected by MDR *Enterococcus* species isolated from patients managed at our institution over the same time period is shown. Adapted from Dudareva et al et al.[3]

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