

Increase in linezolid resistance in staphylococci in the private sector in Western Cape Province, South Africa

To the Editor: Concerns about increasing antimicrobial resistance secondary to the COVID-19 pandemic have been raised previously.^[1] We report a marked increase in linezolid resistance in predominantly coagulase-negative staphylococci in the private sector in Western Cape Province, South Africa (SA), in the past 18 months.

Based on data extracted from the Pathcare laboratory information system, the number of linezolid-resistant staphylococci isolated from blood increased from 25 in 2019 to 49 in 2020 and to 72 in the first 6 months of 2021. *Staphylococcus epidermidis* and *Staphylococcus capitis* accounted for the vast majority of these isolates, with only 2 other coagulase-negative staphylococci and a single *Staphylococcus aureus* isolate reported over the 2.5-year period. The relative contributions of linezolid-resistant *S. epidermidis* and *S. capitis* also changed, from roughly equal numbers in 2019 (11 and 13 isolates, respectively) to a predominance of *S. capitis* in 2021 (24 and 46 isolates, respectively), even though *S. capitis* is far less commonly isolated than *S. epidermidis*. The proportion of linezolid-resistant *S. capitis* increased from 5.9% in 2019 to 22.5% in 2021, while there was only a modest increase in proportions of linezolid-resistant *S. epidermidis* from 1.5% to 3.6%.

Further analysis suggests that the patients with linezolid-resistant isolates were admitted at >10 different private hospitals in the Cape metropole, although they were disproportionately concentrated in a small subset of these hospitals.

Personal communication suggests that similar patterns and levels of linezolid resistance have been noted at other private laboratories in Gauteng and KwaZulu-Natal provinces. In contrast, linezolid resistance has not been observed in the public sector in the Western Cape, or at a national level.

Linezolid is an oxazolidinone antibiotic with activity against Gram-positive organisms such as staphylococci, enterococci and streptococci.^[2] Linezolid acts by inhibiting the initiation of protein synthesis on the bacterial ribosome. Although initially described as having a unique mechanism of action and no cross-resistance, the binding site is in fact partly shared with other antibiotics with a related mechanism of action, such as clindamycin and chloramphenicol. Linezolid was first introduced in 2000. In recent years, multiple mechanisms of resistance have been described, including target site changes due to mutations or modifications of the 23S rRNA subunit or of neighbouring ribosomal proteins, as well as increased efflux of antibiotic out of bacterial cells. While some resistance is due to chromosomal mutations, some is mediated by acquired genes present on plasmids, e.g. the *cfp*, *optrA* and *poxA* genes.

S. capitis, one of the coagulase-negative staphylococci and part of the normal skin flora, is considered relatively avirulent, though there have been occasional reports of infection, e.g. osteomyelitis, prosthetic joint infection and prosthetic valve endocarditis. Infections are usually due to diverse strains, but in the past two decades a unique clone of *S. capitis* has been associated with late-onset sepsis in neonatal intensive care units (ICUs) worldwide.^[3] This NRCS-A clone is often associated with vancomycin heteroresistance, although not with linezolid resistance, perhaps because linezolid is not used in neonates owing to concerns of mitochondrial toxicity. More recently, linezolid-resistant clones have been described in adult ICUs in Europe^[4] and in China.^[5] Further investigation is required to determine whether the linezolid-resistant *S. capitis* isolates in the Western Cape and other provinces are clonally related or not, and to elucidate the underlying mechanism(s) of resistance.

Although the indications for the use of linezolid are primarily treatment of skin and soft-tissue infections as well as pneumonia, we have observed that it is commonly used in ICUs in the private sector

for empirical treatment of sepsis, including potential central-line sepsis. We hypothesise that in the setting of the COVID pandemic, with large numbers of long-stay ICU patients with indwelling lines, overuse of linezolid has possibly facilitated an increase in linezolid-resistant *S. capitis*. The chief concern is that linezolid resistance may also spread to the more virulent pathogen, *S. aureus*. It is noteworthy that the single linezolid-resistant *S. aureus* bloodstream isolate reported here was isolated from a patient who had previously experienced bacteraemia with a linezolid-resistant *S. epidermidis*.

For the treatment of central-line sepsis, we therefore encourage the prompt removal of indwelling lines, and avoidance of antibiotic therapy in the absence of persistent bacteraemia post line removal or other complications. Consideration should be given for antibiotic lock therapy, when the catheter is retained. Preferred antibiotics for the treatment of methicillin-resistant staphylococcal line sepsis include vancomycin, with linezolid regarded as an alternative agent. Once the patient's condition has stabilised and antibiotic susceptibilities are known, an oral agent such as trimethoprim-sulfamethoxazole or linezolid could be administered.

Linezolid is recommended for the treatment of methicillin-resistant *S. aureus* (MRSA) pneumonia, and empirical treatment of suspected hospital- or ventilator-acquired pneumonia (HAP or VAP), especially in patients with COVID-19, is probably driving some of the linezolid prescribing. We would encourage clinicians to critically reassess the need for linezolid in such patients, given the relatively low rates of MRSA infections in Cape hospitals (Pathcare data show that only 12% of *S. aureus* isolates from all specimen types were cloxacillin resistant in 2021), as well as the inherent limitations in the accurate diagnosis of VAP in the setting of COVID. The consequences of liberal use of antimicrobials will have an adverse impact on health outcomes far beyond COVID.

Acknowledgements. We thank M Chaplin for assistance with data extraction.

Author contributions. CB analysed the data and wrote the draft. MS and WL contributed to development of the discussion and revision of the document.

C Bamford

Pathcare, East London, South Africa; Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, South Africa
colleen.bamford@pathcare.org

M Senekal

Pathcare Reference Laboratory, Cape Town, South Africa

W Lowman

Pathcare Vermaak, Gauteng Province, South Africa; Wits Donald Gordon Medical Centre, Johannesburg, South Africa; Department of Clinical Microbiology and Infectious Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

- Chibabhai V, Duse AG, Perovic O, Richards GA. Collateral damage of the COVID-19 pandemic: Exacerbation of antimicrobial resistance and disruptions to antimicrobial stewardship programmes? *S Afr Med J* 2020;110(7):572-573. <https://doi.org/10.7196/SAMJ.2020.v110i7.14917>
- Ament P, Jamshed N, Horne J. Linezolid: Its role in the treatment of Gram-positive, drug-resistant bacterial infections. *Am Fam Physician* 2002;65(4):663-671.
- Laurent F, Butin M. *Staphylococcus capitis* and NRCS-A clone: The story of an unrecognized pathogen in neonatal intensive care units. *Clin Microbiol Infect* 2019;25(9):1081-1085. <https://doi.org/10.1016/j.cmi.2019.03.009>
- Butin M, Martins-Simões P, Pichon B, et al. Emergence and dissemination of a linezolid-resistant *Staphylococcus capitis* clone in Europe. *J Antimicrob Chemother* 2017;72(4):1014-1020. <https://doi.org/10.1093/jac/dkw516>
- Ding L, Li P, Yang Y, Lin D, Xu X. The epidemiology and molecular characteristics of linezolid-resistant *Staphylococcus capitis* in Huashan Hospital, Shanghai. *J Med Microbiol* 2020;69(8):1079-1088. <https://doi.org/10.1099/jmm.0.001234>

S Afr Med J 2021;111(11):1031. <https://doi.org/10.7196/SAMJ.2021.v111i11.16147>