Emergence of linezolid resistance in clinical isolates of vancomycin-resistant enterococci

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INTRODUCTION

Linezolid, an oxazolidinone antibiotic, was introduced early in 2000 as a new therapeutic option against Gram-positive cocci, including vancomycin-resistant enterococci (VRE). It acts by inhibiting protein synthesis through binding to the peptidyl transferase center of the 50S ribosomal subunit and preventing the formation of fMet-tRNA-30S ribosome-mRNA initiation complex. It is important to note the increase in the emergence of strains resistant to linezolid worldwide since it remains one of the few therapeutic options available to treat VRE.\[1-3\] They include linezolid-resistant Enterococcus (LRE) and linezolid and vancomycin-resistant Enterococcus. Recent studies from India reporting LRE in clinical isolates are a cause of concern.\[4,5\]

Case reports of three patients in 2002 from the UK, stated resistance in two isolates of Enterococcus faecium and one isolate of Enterococcus faecalis after linezolid therapy. The minimum inhibitory concentration (MIC) of linezolid for the resistant isolates was 64 mg/L in each case, where as the susceptibility breakpoint for linezolid is 4 mg/L. One of the isolates of E. faecium with low-level resistance to gentamicin and susceptible to ampicillin and glycopeptides was treated with intravenous vancomycin while other two patients were treated with quinupristin/dalfopristin. Typing by pulsed-field gel electrophoresis showed that resistance had developed in previously susceptible strains.\[2\]

In 2014, Kumar et al. reported the first case of high-level linezolid resistance in E. faecium from India (Kolkata), isolated from the blood culture of a hypoglycemic encephalopathy patient with no previous antibiotic exposure.\[8\] The isolate was sensitive to vancomycin, and had an MIC of 1024 μg/mL for linezolid. In 2015, Rai et al. from New Delhi have demonstrated a G2576T mutation (by Conjugation experiments) in E. faecium isolate from an 80-year-old patient on short-term linezolid therapy.\[9\] In this study, resistance to linezolid was observed both in infection and surveillance sites.

Linezolid resistance in VRE can be acquired by various suggested modes. First, an independent event of de novo selection of resistant mutants in colonizing/infecting VRE (patients who carried genetically unrelated strains). Second, possible patient to patient spread (patients who carried genetically related strains). Third, the emergence of LR mutants from linezolid intermediate (LI) VRE occurred during the linezolid therapy.

MECHANISM OF RESISTANCE

Known mechanisms of linezolid resistance in Gram-positive cocci include mutations in the 23S rRNA gene, acquisition of cfr and mutations of ribosomal proteins L3, L4, and L22.

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The G2576T mutation, the most common mechanism conferring resistance to linezolid, has been identified in the V domain 23S rRNA gene. However, resistance by this mechanism is nontransferable, and the spread of resistance can be limited by standard infection control measures. However, another mechanism of plasmid-mediated resistance due to the presence of cfr gene which is transferable among susceptible population and other bacterial species is a greater concern. It has been demonstrated in a human clinical isolate of *E. faecalis* from a 72-year-old diabetic women from Thailand, but not yet reported from India. This mechanism of transfer of resistance was first described in animals in China, and thus has a potential of dissemination both among humans and animals to humans conferring multidrug resistance. In India, the presence of cfr gene on transferable plasmid has been reported in clinical isolates of *Staphylococcus* species.[4,7]

**THERAPEUTIC USE OF LINEZOLID**

Linezolid is an easy option available as oral formulation to treat a wide spectrum of patients with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *S. aureus*, vancomycin intermediate *S. aureus*, and VRE. Acquisition of linezolid resistance is the latest disturbing event of this lineage and would limit the range of effective therapies available for life-threatening infections by these organisms. An additional concern is the risk of nosocomial spread of LR organisms.

National treatment guidelines laid down by National Centre for Disease Control (NCDC) in 2016 suggest usage of linezolid as an “alert antibiotic” only in cases of severe sepsis, clinical failure of all other classes of antibiotics over 48 hours, hypersensitivity/allergy to glycopeptides and severe immunosuppression. This emphasizes the importance of using linezolid with caution only in selected group of patients, switch to combination therapies wherever possible, keeping the duration of treatment as short as possible, screening of contacts and adhering to appropriate infection-control measures, including source isolation/cohorting and use of personal protective equipment.

**ROLE OF MICROBIOLOGY LABORATORIES**

Clinical microbiology laboratories should be aware of the emergence of resistance and should routinely test all VRE isolates for susceptibility to linezolid. CLSI breakpoints for enterococci should be carefully applied, and the strains with intermediate susceptibility (MIC = 4 μg/ml) should be considered at risk for developing linezolid resistance under antibiotic selective pressure. The presence of mutation in the single allele of 23S rRNA may not exhibit phenotypic linezolid resistance and therefore, it becomes imperative that such mutations with cryptic resistance need to be screened before linezolid therapy for development of frank resistance due to sequential mutations during therapy.[8]

There is a need to monitor prescription patterns in hospitals regularly and disseminate antimicrobial resistance data to the participating laboratories, clinicians, and policy makers to prevent the emergence of LI and LR cases of *Enterococcus* species in the hospital and community.

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**Conflicts of interest**

There are no conflicts of interest.

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