

Linezolid in Nasal Isolates of Staphylococci

C. Baragundi Mahesh¹, Telkar Anjana² and V. Sukanya Badami¹

¹S.N.M.C.Bagalkot, India.

²J.J.M. Medical college, Davangere, India.

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Linezolid is an oxazolidinone with antimicrobial activity against gram-positive bacteria indicated for the treatment of infections by multiresistant *Staphylococcus aureus* and coagulase-negative staphylococci, as well as penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci. Resistance has developed sporadically during therapy in both enterococci and *S. aureus*. Staphylococci colonised health care workers transfer staphylococci to patients they take care of and are a risk for hospital acquired infections. This study was carried out to primarily determine the prevalence of linezolid resistance in nasal staphylococcal isolates from health care workers. Study sample included 197 nasal staphylococci isolated from health care workers of our tertiary care hospital. Resistance to methicillin was detected by disc diffusion method of Kirby Bauer using 30 µg cefoxitin discs and Linezolid resistance was detected by disc diffusion method of Kirby Bauer using 30 µg linezolid discs according to CLSI 2011 guidelines. Out of 197 staphylococci isolated, 38(18.44%) were methicillin sensitive *S.aureus*, 45(21.84%) were methicillin resistant *S.aureus*. 63(30.58%) were methicillin sensitive coagulase negative staphylococci and 61(29.61%) were methicillin resistant coagulase negative staphylococci. In the present study, all (100%) staphylococcal isolates were sensitive to linezolid. Although reports of linezolid resistance are still uncommon and resistance rates are still low from reports of many studies, emerging linezolid resistance in staphylococcal isolates is a matter of great concern. Resistance surveillance studies among patients and screening of health care workers for linezolid resistant staphylococcal carriage should be conducted regularly to monitor resistance to linezolid. Paucity of newer antibiotics demands judicious use of linezolid to preserve its clinical utility.

Key words: Linezolid, Nasal carriage, Methicillin, Resistance.

Linezolid is an oxazolidinone with antimicrobial activity against gram positive bacteria indicated for the treatment of infections by multiresistant *Staphylococcus aureus* and coagulase negative staphylococci, as well as penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci.¹ It has replaced the antibiotics such as methicillin and vancomycin as gram positive bacteria develop resistance rapidly to them.²

Linezolid was discovered in 1990's and first approved for use in 2000. As of 2014, it along with tedizolid are the only marketed oxazolidinones.³

The mode of action of linezolid is different from that of other protein synthesis inhibitors which prevent protein synthesis at the chain elongation step. However, linezolid prevents the 50S subunit of prokaryotic ribosome to complex with the 30S initiation complex and inhibits protein synthesis at the initiation step. Studies have suggested that the expression of virulence factors in toxin producing *S.aureus* are especially sensitive to the inhibition of protein synthesis by linezolid.^{4,5} With this novel mechanism, it was thought that

* To whom all correspondence should be addressed.
E-mail: baragundimc@rediffmail.com

bacteria would never develop resistance to linezolid.⁶ Despite a decade of its clinical use, resistance to linezolid has remained stable and extremely low with only sporadic cases being reported mostly from USA and Europe.^{7,8}

The most common mechanisms for linezolid resistance are mutation to the 23S rRNA.^{9,10} The other less reported mechanism is the presence of a transmissible cfr (designated cfr for chloramphenicol–florfenicol resistance initially characterised from animal isolates) gene coding for an rRNA methyl transferase, found on plasmids and capable of horizontal transfer between staphylococci.¹¹

Since few Indian studies^{12,6} also have reported resistance to linezolid and staphylococci colonised health care workers (HCW's) transfer staphylococci to patients they take care of¹³ and are a risk for hospital acquired infections, the present study was done to know the linezolid resistance in nasal staphylococcal isolates from health care workers in a tertiary care centre in south India.

MATERIALS AND METHODS

The present study was conducted on 206 health care workers of whom 104 were medical students, 102 were paramedical personnel (technicians, nursing staff and nursing students). The subjects were selected by systematic random sampling. The standards of ethical committee on human experimentation were followed during the study. Consent was taken from all the subjects of the study. This was a cross sectional study.

Inclusion criteria

Health care workers of S.N.M.C and H.S.K.Hospital like laboratory technicians, attenders, Nursing staff, Nursing students, Medical students and interns.

Exclusion criteria

1. Subjects suffering from respiratory tract infection.
2. Subjects on antibiotic therapy.

Nasal swabs were collected from all the participants with a sterile cotton swab soaked in sterile saline by rotating the swab in both anterior nares consecutively. The swabs were processed immediately by inoculating on to sheep blood agar plates. The culture plates were incubated at 37°C for 24-48 hours. Staphylococci isolated were identified by standard microbiological techniques.

Methicillin resistance and linezolid resistance were detected by Kirby–Bauer disc diffusion test following CLSI 2011 guidelines.¹⁴ Methicillin resistance was detected by 30 µg cefoxitin disc and zone size of ≥ 22 mm was taken as sensitive and zone size of ≤ 21 mm was taken as resistant. Linezolid resistance was detected by 30 µg linezolid disc and zone size of ≥ 21 mm was taken as sensitive and zone size of ≤ 20 mm was taken as resistant.

RESULTS

A total of 197 staphylococci were isolated from 206 HCWs. Both *Staphylococcus aureus* and coagulase negative staphylococci were isolated from few HCW's. Of the 197 staphylococci, 38(18.44%) were MSSA (Methicillin sensitive

Table 1. Linezolid resistance among staphylococcal isolates

Methicillin Resistance	Medical Students	Paramedical Personnel	Total n=206(%)	Linezolid resistance. (%)
MSSA	24	14	38 (18.44)	0 (0)
MRSA	12	33	45 (21.84)	0 (0)
MSCONS	47	16	63 (30.58)	0 (0)
MRCONS	19	42	61(29.61)	0 (0)
Total	92	105	197	0 (0)

MSSA – Methicillin sensitive *Staphylococcus aureus*.

MRSA – Methicillin resistant *Staphylococcus aureus*.

MSCONS – Methicillin sensitive coagulase negative staphylococci.

MRCONS – Methicillin resistant coagulase negative staphylococci.

Staphylococcus aureus), 45(21.84%) were MRSA (Methicillin resistant *Staphylococcus aureus*), 63(30.58%) were MSCONS (Methicillin sensitive coagulase negative staphylococci), and 61(29.61%) were MRCONS(Methicillin resistant coagulase negative staphylococci). In the present study all staphylococcal isolates were sensitive to linezolid.

DISCUSSION

Among staphylococci, *S.aureus* is the most virulent and is associated with a wide spectrum of diseases.¹⁵ The other group of staphylococci, the coagulase negative staphylococci (CONS) are also pathogenic, when host immunity is compromised. More over CONS may donate its drug resistance to *S.aureus*, thus acting as a reservoir of drug resistance.¹⁶

Nasal carriage of staphylococci among HCW's is a risk factor for nosocomial infections with these bacteria.¹⁷

Linezolid is a therapeutic option for skin, soft tissue infections and pneumonia caused by multidrug resistant gram positive bacteria. Linezolid is extensively used in critical care facilities because of its broad spectrum of activity, short term safety profile. Although bacteriostatic in action, its bioavailability is 100% even with oral administration with excellent tissue distribution, that leaves an option for early oral switch from intravenous administration.

In the present study, none of the methicillin sensitive or resistant staphylococcal isolates showed resistance to linezolid. Similar to the present study, Tenguria R et al have reported 100% sensitivity to linezolid among community and hospital associated methicillin sensitive *S.aureus* and methicillin resistant *S.aureus* from north India.¹⁸ Similarly Indian network for surveillance of antimicrobial resistance (INSAR) group, India has also reported no resistance to linezolid among *S.aureus* isolates from 15 Indian tertiary care centres from Jan 2008 to December 2009.¹⁹ Aghazadeh M et al in their study from Iran have also reported 100% sensitivity to linezolid among all methicillin sensitive and resistant *S.aureus* isolates.²⁰

First reports of linezolid resistance in coagulase negative staphylococci from India (as

claimed by authors) were published by Peer MA et al in 2009-2010 from Kashmir India, in two patients of whom one was burn male patient and other was female patient who had intracranial bleeding.²¹ Vinodh Kumaradithyaa A et al have reported one *S.aureus* isolate resistant to linezolid by Kirby–Bauer disc diffusion test among nasal isolates from surgical unit staff in 2009 in Tamilnadu, India.¹² Twelve (23.52%) linezolid resistant *S.aureus* were detected by Kirby–Bauer disc diffusion, Ezy MIC strip test and VITEK-2 (MIC) among 51 *S.aureus* isolates from pus samples from dirty wounds of orthopaedic patients by Thool V.U et al in their study published in July 2012 from central India.⁶

Endimiani A et al have reported emergence of linezolid resistant *S.aureus* from 8 of 77 cystic fibrosis patients who had received prolonged linezolid therapy previously in Cleveland from 2000-2006.²² Emergence of methicillin and linezolid resistant *S.epidermidis* in Portugal hospital between May-November 2012, is reported by Barros Mariana et al.²³

A study by Arias CA et al has revealed that disc diffusion test or E test might not detect cfr-mediated linezolid resistance when standard procedures are followed and that a longer time of incubation may be needed.²⁴ Therefore it is advised to use MIC testing or molecular methods, when ever possible.

Although reports of linezolid resistance are still uncommon and resistance rates are still low, emerging linezolid resistance in staphylococcal isolates is a matter of great concern. Resistance surveillance studies among patients and screening of HCW's for linezolid resistant staphylococcal carriage should be conducted regularly to monitor resistance to linezolid. Paucity of newer antibiotics demands judicious use of linezolid to preserve its clinical utility.

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