

Review Article

Linezolid resistant *Staphylococcus aureus*

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Received: 12 September 2014

Accepted: 24 September 2014

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ABSTRACT

Linezolid is the only antibiotic available as an oral formulation for resistant staphylococcal infections. It is effective in skin & soft tissue infections, nosocomial pneumonias including VAP, infective endocarditis and MRSA meningitis. It is also effective in the eradication of both nasal & throat colonization of MRSA. Its high bioavailability and post antibiotic effect, ease of switching to oral therapy during its use and the fact that it can be used in patients of all ages, also in patients with liver disease and poor kidney function and its increased effectiveness over glycopeptides makes this drug a precious drug in the treatment of resistant staphylococcal infections. Linezolid resistance in staphylococcus is defined as a linezolid MIC of ≥ 8 mg/L. Reported Linezolid resistance in India and elsewhere is 2-20%. There is clonal dissemination of Linezolid Resistant *Staphylococcus aureus* (LRSA) within or across health care settings which demands continuous surveillance to determine the emergent risk of resistance strains and to establish guidelines for appropriate use. Clinical laboratories should confirm any LRSA preferably by a second method, prior to using linezolid for serious infections. Effective surveillance, more judicious use of this antibiotic, avoiding linezolid usage for empiric therapy in hospital acquired staphylococcus infections, optimization of the pharmacological parameters of the antibiotics in specific clinical situation, decreasing bacterial load by timely surgical debridement or drainage of collections, use of combination therapies would prevent the emergence of resistance to linezolid in staphylococcus aureus.

Keywords: Linezolid, *Staphylococcus aureus*, Linezolid resistant staphylococcus aureus

INTRODUCTION

Linezolid is the first antibiotic of the oxazolidinone class approved for clinical use for resistant *Staphylococcus aureus*. It was approved by FDA due to the rising incidence of MRSA.¹ It is the only antimicrobial drug available which has proven high activity against multidrug resistant *Staphylococcus aureus* including the strains with reduced susceptibility to glycopeptides.²

MECHANISM OF ACTION OF LINEZOLID

Linezolid acts by inhibiting bacterial protein synthesis through binding to the peptidyl transferase centre of the 50S ribosomal subunit.³ Linezolid stops the growth and

reproduction of bacteria by disrupting translation of messenger RNA into proteins in the ribosome. It works on the first step of protein synthesis i.e. initiation unlike other protein synthesis inhibitors which inhibit elongation.⁴

CLINICAL USE OF LINEZOLID FOR STAPHYLOCOCCUS INFECTIONS

It is the only antibiotic with good activity against MRSA available as an oral formulation; making it desirable for outpatient treatment.⁵ It is safe and effective for use in children and newborns as well as adults. When administered for short periods, it is a relatively safe drug,

can be used in patients of all ages, in people with liver disease or poor kidney function.⁶

Though it has bacteriostatic effect *in vitro*, it behaves as a bactericidal antibiotic *in vitro* because it inhibits the production of toxins by staphylococci. It also has a post antibiotic effect lasting one to four hours for most bacteria, i.e. the bacterial growth is temporarily suppressed even after the drug is discontinued.⁷

Linezolid is more cost effective than comparable antibiotics like vancomycin because of the possibility of switching over from intravenous to oral administration as well as patients are stable enough without the need for dose adjustments.⁸

Because this drug has a novel structure and unique mechanism of action, it does not display cross resistance with other classes of antimicrobial agents. Moreover it has been proven to be effective in the treatment of MRSA infection in critically ill patients due to its acceptable safety profile for both intravenous and oral administration.⁹ It is widely used in critical care because of its antimicrobial spectrum, favourable short term safety profile, pharmacokinetics and effectiveness.¹⁰

It is more effective than glycopeptides & β lactam antibiotics in the treatment of skin and soft tissue infections caused by gram positive bacteria. It is cheaper and more effective than vancomycin in the treatment of diabetic foot infections.

It is recommended as the first line treatment for hospital acquired MRSA pneumonia along with vancomycin. Linezolid is superior to vancomycin against nosocomial pneumonia, particularly VAP caused by MRSA because the penetration of linezolid into bronchial fluids is much higher than that of vancomycin. Other advantages of linezolid are its high bioavailability because it allows easy switching to oral therapy and the fact that poor kidney function is not an obstacle to use.

Studies reveal linezolid to be a better therapeutic option for infective endocarditis caused by multidrug resistant grampositive bacteria. Linezolid is used as an alternative to vancomycin for MRSA meningitis and it is superior to vancomycin as suggested by studies.¹¹

It is effective in eradication of both nasal and throat colonization of MRSA.¹²

LINEZOLID RESISTANT STAPHYLOCOCCUS AUREUS

Both the clinical laboratory standards (CLSI) and European Committee on Antibiotic Susceptibility Testing [EUCAST] have defined linezolid resistance in staphylococcus as a linezolid MIC of ≥ 8 mg/L.¹³

HISTORY AND PREVALENCE OF LINEZOLID RESISTANT STAPHYLOCOCCUS AUREUS

Linezolid resistance in bacteria was first detected in 1999. Linezolid resistant Staphylococcus aureus was first isolated in 2001.¹⁴ The first linezolid resistant strain of MRSA was reported in a Spanish hospital during an outbreak.¹⁵ Global surveillance studies report <1% of Staphylococcus aureus as linezolid resistant. But, a study conducted by Lyra et al. in Karnataka, India, the Linezolid resistance was observed in about 5.7% of MRSA isolates.¹⁶ Another study conducted in South India by Rajadurai pandi reported LRSA in 2% of MRSA.¹⁷ Similar incidence of 2.2% was reported by Norma et al from Mexico.¹⁸ Harcharan singh et al. reported 20.3% LRSA in Rajasthan.¹⁹ Resistance rates to linezolid was 85.7% in MRSA isolates as reported by Shahnaz et al. from Iran.²⁰

MECHANISM OF LINEZOLID RESISTANCE IN STAPHYLOCOCCUS AUREUS

The mechanisms responsible for linezolid resistance in Staphylococcus aureus isolates are: mutations in the domain V region of one or more of the five or six copies of the 23S rRNA gene, acquisition of the plasmid-mediated ribosomal methyl transferase cfr gene and deletions or mutations in the ribosomal protein L3 of the peptidyl transferase centre. Substitutions in ribosomal protein L4 of the PTC have also been reported in LRSA strains derived from laboratories.³

Resistance develops to linezolid as a result of a point mutation known as G2576T in which a guanine base is replaced with thymine in basepair 2576 of the genes coding for 23S ribosomal RNA. This is the most common mechanism of linezolid resistance in staphylococci.²¹ Resistance to linezolid in Staphylococcus aureus is probably acquired following the prior linezolid exposure.²² Studies revealed high linezolid resistance in PSICU. Other studies reveal clonal dissemination of LRSA within or across health care settings.²³

RISK FACTORS FOR LRSA

Many reported cases of linezolid resistant Staphylococcus aureus infections have been associated with deep organ involvement, the presence of foreign device and/or prolonged therapy with linezolid usually more than 3 weeks and nosocomial outbreaks.²⁴

SURVEILLANCE FOR LRSA

Linezolid is a clinically valuable option as a form of therapy. There is a widespread clonal dissemination of LRSA within and across health care settings. Therefore continuous surveillance is necessary to determine the emergent risk of resistance strains and to establish guidelines for appropriate use of linezolid.²⁵

LAB TESTING FOR LRSA

Susceptibility testing for linezolid resistance should be done prior to using linezolid for serious infections.²⁶ E test, disc diffusion, VITEK 2, agar dilution, microscan, broth macrodilution, PFGE and PCR are the various methods used to detect LRSA.²⁷

LZD resistance may be underreported based on technical hurdles in laboratory interpretation of both MIC and disc diffusion results. Inter-user interpretation of linezolid disc diffusion zones and MIC end points for staphylococci varied significantly, even among seasoned technologists. These problems would arise if a single method of laboratory testing is used for detecting Linezolid resistance. To address this concern, it is advisable that clinical laboratories confirm any LRSA preferably by a second method, prior to using linezolid for serious infections.

Staphylococcus species showing inhibition zone size ≥ 21 mm with a 30 μg disc is considered as LZD sensitive and ≤ 20 mm was considered as resistant. When testing for linezolid, disc diffusion zones should be examined using transmitted light. Organisms with resistant results by disc diffusion should be confirmed using an MIC method. Isolates with an MIC ≤ 4 mg/L are considered susceptible to linezolid and isolates with an MIC ≥ 8 mg/L are resistant as per CLSI 2013 breakpoints.²⁸ In E test an MIC of 4 $\mu\text{g}/\text{ml}$ is suggestive of LSSA and 8 $\mu\text{g}/\text{ml}$ LRSA.²⁹

TREATMENT

Treatment options for LRSA are limited, but based on current *in vitro* susceptibility data, LRSA remain universally susceptible to vancomycin, daptomycin and tigecycline. Prestinomyin is 75% sensitive to LRSA.¹⁹

PREVENTION OF LRSA

As suggested by studies, dissemination of cfr gene in hospital settings would compromise the effectiveness of linezolid in the future.

Some of the measures to prevent the emergence of resistance to linezolid in Staphylococcus aureus are to decrease the bacterial load by timely surgical debridement or drainage of collections and optimization of the pharmacological parameters of the antibiotics in specific clinical situation. Another strategy includes the use of combination therapies which lack proper evaluation in severe infections.³⁰

CONCLUSION

Linezolid is a reserve antibiotic that should be used sparingly so that it will remain effective as a drug of last resort against potentially intractable staphylococcal infections because of its cost-effectiveness, acceptable

safety profile for both IV and oral administration. It is a promising agent for MRSA nasal and throat colonization. Increased prevalence of linezolid resistance in MRSA isolates warrants a more judicious use of this antibiotic. Linezolid usage for empiric therapy in hospital acquired staphylococcus infection should be avoided. Antibiotic susceptibility testing for all staphylococcus isolates before using linezolid is recommended. It is advisable that clinical laboratories confirm any LRSA preferably by two methods of testing prior to using linezolid for serious infections. Prescribing antibiotics with a different mode of action, effective surveillance, rational use of antibiotics may reduce the increasing selection pressure for resistance to linezolid.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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DOI: 10.5455/2320-6012.ijrms20141103
Cite this article as: Gandham P. Linezolid resistant *Staphylococcus aureus*. *Int J Res Med Sci* 2014;2:1253-6.