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Anti-Microbial Susceptibility Pattern of Linezolid in Various Clinical Isolates

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Abstract

The literature review is suggestive of good efficacy of Linezolid (Oxazolinedione derivative) against gram positive bacteria only. However it is deficient regarding its susceptibility in various clinical isolates. Therefore, the current study was planned to identify the susceptibility pattern of Linezolid in various isolates. Total 748(n) specimens were included in this study**.** Out of which 144(n) yielded positive growth. For microbiological culture proceedings all recommended CLSI – 2014 (Clinical and laboratory standard institute) guidelines were followed. The linezolid having 30µgm disc potency was used to assess its susceptibility. The clearing zone diameter of ≥21mm was considered sensitive. Data was recorded and analyzed by using SPSS version 20 for statistical inference. For numerical variables, frequencies were calculated in terms of percentages. The results of current study showed that 84.2% gram-positive and 45.6% gram-negative organisms were sensitive to linezolid. The efficacy of linezolid is more for gram-positive i.e 84.2% as compared to gram-negative 45.6%.

1 Introduction

The Linezolid belongs to a group of Oxazolidinone group of antibiotics. In the year 2000, it was licensed by FDA (Food and Drug Administration) for the treatment of severe infections like MRSA (Methicillin resistant *Staphylococcus aureus*) infections. This is considered as a most common cause of complicated nosocomial infection having high morbidity rate.[1] Furthermore, same organization also emphasized that this drug harbors good efficacy for the management of severe and complicated nosocomial pneumonias, skin and soft tissue infections caused by MRSA strains[2,3]**.** Even the large scale clinical trials revealed that this drug is very effective for the management of severe gram-positive infections[4]**.**

The mode of action involves inhibition of protein synthesis by binding to 23S rRNA in the catalytic site of the 50S ribosome[4]**.** Despite having this bacteriostatic property, this drug revealed successful outcomes in the management of severe infections[5]**.** The recommended duration of linezolid management is 28 days due to it's haematological side effects like thrombocytopenia and neurological problems[6]**.**

A study report by *Fu J et al* in 2013 described that upon comparison with Vancomycin and Teicoplanin, linezolid has better efficacy for the treatment of gram positive infections[7]**.**

There are many latest studies available showing the efficacy of linezolid for the successful management of complicated gram positive infections like MRSA. However, the studies on its efficacy for gram negative infections are deficient. Therefore, the current study was planned to assess the susceptibility pattern of linezolid for both gram positive and gram negative isolates in our setup.

2 Materials and Methods

The current study was conducted at Pathology department of Al Nafees Medical College & Hospital, Islamabad, Pakistan. The duration of this study was two years, from 01st Oct 2013 to 01st Oct 2015.

For ethical considerations, an informed consent was taken from all the patients prior study proceedings. Convenient sampling technique was adopted for the study proceedings. Total 748 specimens (indoor and outdoor) received for culture and sensitivity in microbiology section, were included in the study. While the samples of non-willing patients were excluded from the study.

The recommended protocols for microbiological sample processing and CLSI -2014 (clinical and laboratory standard institute) guidelines were followed. The duration of sample processing for urine, HVS (high vaginal swabs), pus, stool, and sputum were 03 days. While for Blood cultures it was 07 days. Blood agar, Macconkey's agar and CLED (cysteine lysine electrolyte deficient media) were the culture Medias used for this study.

On first day the inoculation for blood, HVS, sputum, stool and pus specimens, were done on Blood agar and Macconkey's agar. While CLED agar was used for urine specimens. The bacteriuric strips were used to collect the urine specimens for inoculation on CLED agar. The plates were then incubated at 37^0C for 24 hours. After wards, the remaining urine specimens were transferred in the test tubes for 05 minutes centrifugation at 3000rpm. The supernatant was removed and deposits were used for direct microscopy to detect the presence of pus cells. The pyuria was than correlated with bacteriuria for further processing.

The second day proceedings include the diagnosis of significant colonies by gram staining and biochemical tests. The linezolid having 30µgm disc potency was used to detect the susceptibility pattern on Mueller Hinton agar on the same day.

On third day, biochemical tests and drug susceptibility were interpreted as per recommended CLSI guidelines, and the reports were finalized. As per CLSI guidelines the linezolid disc having the zone diameter of $\geq$21mm was considered sensitive. While $\leq$21mm zone diameter was considered as resistant.

While for all blood cultures the processing was done uptil 07^{th} days.

SPSS Version was used for statistical inference. Frequencies and percentages were the numerical variables extracted by using the SPSS version 20.

3 Results

Total 748 (n) specimens received in microbiology section of the pathology department from 01^{st} Oct 2013 to 01^{st} Oct 2015. Out of which 144(n) yielded significant growth. This is shown in table 1. The distribution showed a maximum number of positive urine cultures seen in 62.5% (n=90) cases. Next in sequence were the cultures of pus i.e 13.1% (n=19), high vaginal swabs (HVS) i.e 11.1 % (n=16), sputum i.e 6.2% (n=09), blood i.e 4.1% (n=6), and lastly the stool i.e 2.7% (n=04). This is shown in table 1.

Table 1: Distribution of positive specimens from Oct 2013 – Oct 2015 (N=133) OUT OF 748 specimens

Specimens	Total Number of Positive Cultures (N=144)	
	(n)	(%)
Urine	90	62.5
Pus	19	13.1
High vaginal swabs (HVS)	16	11.1
Sputum	09	6.2
Blood	06	4.1
Stool	04	2.7

Out of the total 90 (62.5%) positive urine specimens most common isolate was *Escherichia coli* seen in 44.8% (n=44). Next in sequence was *Klebsiella pneumoniae* i.e 18.8% (n=17) and *Pseudomonas aeruginosa* i.e 14.4% (n=13). This is shown in table 2.

Out of the total 19 (13.1%) positive pus specimens most common isolate was *Staphylococcus aureus* seen in 36.8% (n=07). This was followed by *Pseudomonas aeruginosa* i.e 21% (n=04), *Klebsiella pneumoniae* and *Proteus vulgaris* i.e 15.7% (n=03), each. This is shown in table 2.

Out of the total 16 (11.1%) positive HVS specimens most common isolate were *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* 25% (n=04), each. This was followed by *Proteus vulgaris* 18.7% (n=03), *Neisseria gonorrhea* and *Streptococcus agalactiae* in 12.5% (n=02) each. This is shown in table 2.

Out of the total 09 (6.2%) positive sputum specimens most common isolate was *Klebsiella pneumoniae* 44.4% (n=04), each. This was followed by *Morganella morganii* i.e 33.3% (n=03), and *Streptococcus pneuminiae* in 22.2% (n=02) each. This is shown in table 2.

For the total 06 (4.1%) positive blood cultures, *Salmonella typhi* was the commonest pathogen seen in 83.3% (n=05) cases. While for 04 (2.7%) positive stool cultures, *Escherichia coli* was isolated in 100% (n=04) specimens. This is shown in table 2.

One hundred and twenty five (n=125) organisms were gram negative (86.6%). Out of which 45.6% (n=57) organisms were sensitive to linezolid. While 56% (n=70) were resistant. However, 19 (13.1%) were the gram-positive organisms. Out of those 84.2% (n=16) organisms were sensitive to linezolid while 15.7% (n=03) organisms were resistant. This distribution is shown in table III.

Table 2: Commonly prevalent organisms (N= 144)

Organisms	Urine		Pus		HVS		Sputum		Blood		Stool	
	n = 90	%	n = 19	%	n = 16	%	n = 09	%	n = 06	%	n=04	%
Escherichia coli	44	48.8	02	10.5	01	6.25	-	-	01	16.6	04	100
Klebsiella pneumoniae	17	18.8	03	15.7	04	25	04	44.4	-	-	-	-
Pseudomonas aeruginosa	13	14.4	04	21.0	04	25	-	-	-	-	-	-
Staphylococcus saprophyticus	06	6.6	-	-	-	-	-	-	-	-	-	-
Proteus vulgaris	04	4.4	03	15.7	03	18.7	-	-	-	-	-	-
Serratia	04	4.4	-	-	-	-	-	-	-		-	-
Morganella morganii	02	2.2	-	-	-	-	03	33.3	-	-	-	-
Staphylococcus aureus	-	-	07	36.8	-	-	-	-	-	-	-	-
Streptococccus pneumoniae	-	-	-	-	-	-	02	22.2	-	-	-	-
Neisseria gonorrheae	-	-	-	-	02	12.5	-	-	-	-	-	-
Streptococcus agalactiae	-	-	-	-	02	12.5	-	-	-	-	-	-
Salmonella typhi	-	-	-	-	-	-	-	-	05	83.3	-	-

For gram-negative organisms highest sensitivity i.e 80.5% was seen in *Morganella morganii*. This was followed by *Proteus vulgaris* 70%, Escherichia coli 55.7%, *Serratia marcescens* 50% and *Pseudomonas aeruginosa* in 33.3% cases respectively. This is shown in table 3.

For gram positive isolates highest sensitivity was seen i.e 100% for *Staphylococcus saprophyticus*. This was followed by *Staphylococcus aureus* 85.7%, *Streptococcus agalactiae*, and *Streptococcus pneumonia* in 50% each. This is shown in table 3.

4 Discussions

The management of MRSA and VRSA always remained a challenging task for the health professionals around the globe. Literature review had shown that the prevalence of MRSA associated nosocomial infection in China, Korea and Japan are 60%. In Europe, it is 45% and in United States, it is 35%[9,10].

The current study results concluded that 84.2% (n=16) gram-positive organisms were sensitive to linezolid. While 15.7% (n=03) organisms were resistant. This finding is in favour of study results conducted by *Leach KL et al* (2011). He narrated that the linezolid is only effective for the management of gram-positive infection[4]. A meta-analysis review reported by *Fu et al*, showed increased effectiveness of linezolid on comparison with Vancomycin and Teicoplanin for managing complicated gram positive infections[7]. The better tissue penetration, equivalent bioavailability and lack of cross resistance are the important factors, ranking this drug higher up, as compared to vancomycin[8]. The effectiveness of linezolid seen in the current study can be further strengthened by comparison with three meta-analysis review reports conducted in 2008, 2009, and 2010[11-13].

However, this finding is not in accordance with another meta-analysis review report, which narrates equal effectiveness of linezolid and Vancomycin for the management of complicated gram-positive infection[14]. Another published report for the year 2015 showed that both drugs are equally effective for severe gram-positive infections especially MRSA cases[15].

Table 3: Susceptibility pattern of linezolid

Organisms	Total		Sensitive		Resistant	
	n = 144	%	n	%	n	%
Gram negative organisms 86.8% (n=125)						
Escherichia coli	52	36.1	29	55.7	23	44.2
Klebsiella pneumoniae	28	19.4	06	21.4	22	78.5
Pseudomonas aeruginosa	21	14.5	07	33.3	14	66.6
Proteus vulgaris	10	6.9	07	70	03	30
Salmonella typhi	05	3.4	01	20	04	80
Morganella morganii	05	3.4	04	80	01	20
Serratia marcescens	04	2.7	02	50	02	50
Neisseria gonorrheae	02	1.6	01	50	01	50
Total			**57**	**45.6**	**70**	**56**
Gram positive organisms 13. 1% (n=19)						
Staphylococcus aureus	09	4.8	08	88.8	01	11.1
Staphylococcus saprophyticus	06	4.1	06	100	00	--
Streptococcus agalactiae	02	1.3	01	50	01	50
Streptococccus pneumoniae	02	1.3	01	50	01	50
Total			**16**	**84.2**	**03**	**15.7**

For gram positive isolates highest sensitivity was seen i.e 100% for *Staphylococcus saprophyticus*. This finding is different from two published reports showing that linezolid is a drug of choice for managing the *Staphylococcus aureus* infections[14,15].

This was followed by *Staphylococcus aureus* 85.7%, *Streptococcus agalactiae*, and *Streptococcus pneumonia* in 50% each. This is different from the study results by *Gu et al* conducted in 2013. He narrated that linezolid is not effective for the management of infections by *Staphylococcus aureus* and MRSA cases[16].

The results of current study showed that 45.6% organisms were sensitive to linezolid. While 56%(n=70) were resistant. For gram negative organisms highest sensitivity i.e 80.5% was seen in *Morganella morganii* . This was followed by Proteus *vulgaris* 70%, *Escherichia coli* 55.7%, *Serratia marcescens* 50% and *Pseudomonas aeruginosa* in 33.3% cases respectively. This finding is different from the study results by *Livermore et al* (2003). He concluded that except Moraxella, species rest all gram negative organisms are resistant to linezolid. [17] This is also different from the published report by *Rose et al* (2011). He described that linezolid is only effective against gram positive bacteria[16,18].

The recommended guidelines by WHO for the year 2006 recommended linezolid for the multi drug resistant (MDR) and extremely drug resistant (XDR) tuberculosis cases[19,20]. This is strengthened by the study report of *Agyeman A et al* (2016). He narrated that linezolid usage has proven good results when used for MDR and XDR tuberculosis cases[21].

The susceptibility pattern of linezolid extracted from current study will be helpful and a guide for initiating the prophylactic management decisions in various circumstances.

5 Conclusion

The linezolid sensitivity for gram-positive organisms is 84.2%. While for gram-negative organisms, it is 45.6%. The efficacy of linezolid is more for gram positive as compared to gram negative.

6 Recommendations

Linezolid can be used for the management of severe infections by gram negative isolates.

The studies with larger sample size are required to assess the efficacy of linezolid for gram negative organisms.

Inclusion of linezolid in the management of MDR and XDR cases.

7 Conflict of interests

There are no conflicts on interests regarding the publication of this manuscript.

8 Author's contributions

- ZH is the corresponding Author. Contributed in writing the abstract, methodology & result writing, along with final formatting of entire manuscript.
- AN initiated the idea of study, supervising the all laboratory microbiology technicalities, and final proof reading of manuscript.
- BKT wrote the introduction and discussion along with the references adjustment as per Vancuover style.
- LLK recorded the data on SPSS and its analysis along with summarizing the tables for Results.

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