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Research Article

TEICOPLANIN RESISTANCE IN GRAM-POSITIVE BACTERIAL ISOLATE: AN EMERGING THREAT

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ABSTRACT

Objectives: Development of antimicrobial resistance in microorganism isolated from blood stream infection constitutes a major concern about their treatment. Teicoplanin is a glycopeptide antibiotic used in the treatment of infection caused by Gram-positive bacteria. This study was planned to determine Teicoplanin resistance in the Central India and recommend policy changes for prevention of the future resistance to the higher antibiotics.

Methods: A total of 1855 septicemia suspected blood samples were studied. The blood culture samples were processed and identified in the microbiology laboratory according to the Clinical and Laboratory Standards Institute guidelines. Antibiotic susceptibility test was done using Kirby B disk diffusion method.

Results: About 39.5% of blood culture samples showed positive growth for organism. We observed high teicoplanin resistance (29.5%) among Gram-positive isolates, predominantly (53%) in the *Enterococcus* species.

Conclusion: Teicoplanin resistance has emerged tremendously in the present study. Hence, attention is required about this serious issue otherwise very limited choice of antibiotics will be available for treating infections in the future.

Keywords: Teicoplanin, Blood culture, Sepsis, Gram-positive bacteria, Drug resistance.

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INTRODUCTION

Teicoplanin is a glycopeptide antimicrobial agent which has almost similar antimicrobial spectrum as Vancomycin. It is active against infections caused by Coagulase Negative *Staphylococcus* (CONS), various *Enterococcus* species, Methicillin-Resistant *Staphylococcus Aureus,* and in some cases Vancomycin Resistance Staphylococci [1]. It is a bactericidal agent against susceptible Gram-positive bacterial strains and may be effective in Clostridium difficile-associated diarrhea and pseudomembraneous colitis.

Teicoplanin binds with the D-Alanyl-D-alanine terminals of cell wall precursor units and thus inhibits bacterial cell wall synthesis. Teicoplanin does not penetrate the outer membranes of Gram-negative bacteria because of their large molecular size [2]. The Minimum Inhibitory Concentration (MIC) of teicoplanin for *Staphylococcus*, *Streptococcus pneumonia*, viridians/non-viridians streptococci and Enterococci is 0.01–1 µg/ml whereas the MIC for Corynebacterium species, anaerobic Gram-positive cocci, and Listeria species is 0.25-2 µg/ml [3]. Teicoplanin has a fused ring structure contain a mixture of five major (A2-1–A2-5), four minor (RS-1–RS-4), and two carbohydrates (mannose and N-acetylglucosmine) compounds. Major and minor components contain a third carbohydrate moiety-Beta-D-glucosamine, all share same core of glycopeptides termed as teicoplanin A3-1 [4]. Antibacterial activity of Teicoplanin is affected by its protein binding capacity, it is highly bound by plasma proteins (90–95%). Teicoplanin has a long serum elimination half-life, (up to 100 h) with normal renal function in adult patients [5].

Vancomycin and Teicoplanin both have different antimicrobial activity, lipophilic activity, and pharmacokinetic properties with almost similar structures. Teicoplanin binds as a monomer whereas Vancomycin forms a dimer. Teicoplanin antibiotic susceptibility testing for CONS can be problematic because of poor diffusion of the molecule in solid media and effect of the medium used [6]. Glycopeptides intermediate *S. aureus* (GISA) isolates MIC range (4–16 µg/ml) have been recovered from patients after prolonged glycopeptides exposure in the recent years from most parts of the world. Glycopeptides resistance intrinsically arises due to frequent exposure, multiple mutations, and/or alterations in gene expression [7].

The purpose of our study was to determine the Teicoplanin-resistant among isolates from bacteremia or septicemia in the Central India and recommend strategy for the prevention of Teicoplanin resistance in the future.

METHODS

A cross-sectional observational study was conducted on 1855 blood culture isolates at Gandhi Medical College and associated Hamidiya Hospital, Bhopal, Madhya Pradesh, India, a 1000 bedded tertiary care hospital in the Central India.

All the blood samples were withdrawn and collected using strict aseptic measures and sent for culture and sensitivity testing to the clinical bacteriology laboratory. Blood culture was done by conventional blood culture method (BHI broth). Thereafter, bacterial isolates identification was performed from colony morphology, gram staining, and biochemical tests.

Teicoplanin sensitivity testing was performed by Kirby-Bauer's disk diffusion method using Mueller Hinton agar plates as per Clinical and Laboratory Standards Institute guidelines [8]. Inoculums of 0.5 McFarland standards were poured on Mueller-Hinton Agar plates and a 30 µg Teicoplanin disk was applied. All plates were incubated for 16–20 h at 35–37°C temperature. A zone size more than 15 mm was taken as susceptible and <15 mm as resistance.

Data analysis

The proportion and percentage, confidence interval of the resistant isolates was calculated using graph pad software. The confidence intervals below are calculated using the so-called "exact" confidence intervals, computed by the method of Clopper and Pearson which are based on a relationship between the F distribution and the binomial distribution.

Ethical consideration

The study was approved by Institutional Ethical Committee of Gandhi Medical College and associated Hamidiya hospital, Barakattullah University Bhopal M.P. Ethical guidelines given by the Declaration of Helsinki were adhered to throughout the study.

RESULTS

Table 1 shows geographical distribution of blood culture cases. Total of 1855 blood samples were received from different wards including medicine, pediatric, surgery, and burn. The maximum number of samples was received from pediatric wards followed by other department such as medicine, surgery, orthopedic, and burn. Out of 1855 blood sample received, 732 turn out to be positive for growth of bacteria (Table 2). The positive rate was found to be 39.4%.

Table 1: Districts-wise distribution of positive and total blood culture cases

District	Positive cases (%)	Total cases
Bhopal	415 (40.5)	1025
Raisen	102 (35.6)	286
Vidisha	74 (37.4)	198
Sehore	86 (40.3)	213
Rajgarh	37 (43.5)	85
Hoshangabad	18 (37.5)	48
Total cases	732 (39.5)	1855

Table 2: Age-wise distribution of blood culture samples (n=1855)

Age	Growth	No growth	Total
Infant (<1 year)	226	338	564
Children (1–12)	165	242	407
Adolescent (13–18)	102	157	259
Adult (18–49)	111	188	299
Old (>50 years)	128	198	326
Total	732	1123	1855

Table 3: Frequency of bacterial isolates obtained from blood sample (n=732)

S. No	Bacteria isolated	Number	Percentage	Confidence Interval
1	Klebsiella	317	43.3	0.3968–0.4698
2	*E. coli*	121	16.5	0.1391–0.1942
3	Pseudomonas	76	10.3	0.0827–0.0952
4	NLFGNB	54	7.3	0.0559–0.0952
5	NLFGNB	36	4.9	0.0347–0.0674
6	Acinabactor	6	0.8	0.0030–0.0178
7	Staphylococcus	87	11.8	0.0963–0.1445
8	CONS	20	2.75	0.0168–0.0419
9	*Enterococcus*	15	2	0.0115–0.0336

Table 4: Resistance pattern to Teicoplanin

Bacteria	No. of resistant isolates	% of resistant isolates	Confidence interval
Staphylococcus	20 (n=87)	23	0.1464–0.3325
CONS	8 (n=20)	40	0.1912–0.6395
Enterococcus	8 (n=15)	53	0.2659–0.7873
Total	36 (n=122)	29.5	0.2180–0.3844

Frequency of total blood isolates (Table 3 and Figure 1)

Of 732 positive culture Gram-negative strain accounts for 610 (83.33%), whereas Gram-positive strain was found to be 122 (16.66%). The isolated Gram-negative isolates include Klebsiella 317 (43.3%), *E. Coli* 121 (16.5%), Pseudomonas 76 (10.3%), the non-lactose fermenting Gram-negative bacteria 54 (7.3%), Citrobacter 36 (4.9%), and Acinatobacter 6 (0.8%). The Gram-positive bacteria isolated includes *S. aureus* 87 (11.8%), CONS 20 (2.7%), and *Enterococcus* 15 (2%).

Resistance to teicoplanin (Table 4)

The resistance to Teicoplanin among different Gram-positive bacterial isolates was found to be in staphylococcus 20 (23%), CONS 8 (40%), and *Enterococcus* 8 (53%).

DISCUSSION

Our study showed that 732 (39.4%) out of 1855 total samples were positive for presence of bacteria which is almost similar to Khanal *et al.* [9] and Sharma *et al.* [10], who reported positive blood cultures accounting for 44–33.9%, respectively but some other studies showed lower prevalence like Mehdinejad *et al.* [11], Vanitha *et al.* [12]., Kalpesh Gohel *et al.* [13], and Mehta *et al.* [14] reported 5.6%, 8.3%, 9.2%, and 9.9%, respectively. Higher prevalence rate (39.4%) in our study may be due to emerging of multidrug-resistant bacterial strains and inadequate or rational use of antibiotic. Probable reasons for variation in blood culture positivity rate are amount of blood taken, administration of antibiotic therapy before blood collection, nature of population, epidemiological difference of the etiological agents, and different areas of study. Gram-negative bacteria were tremendous (83.3%) in the present study which was similar to Vaghela *et al.* [15], Paul *et al.* [16], and Santwana Pandey *et al.* [17]. However, this contrasts with other studies where Gram-positive organisms were predominant like Belay *et al.* [18], Muley *et al.* [19], Pan *et al.* [20], and Sorsa *et al.* [21]. This variation of blood culture isolates may be due to various factors such as geographical location, seasonal variation, and endemicity of etiological agents.

In our study, we observed high prevalence of Teicoplanin resistance in CONS strain 40% which was concordance to Bertin *et al.* [22] and Lallemand [23] but in discordance to our study many other observers showed very low prevalence to Teicoplanin resistance like Schlegel *et al.* [24] and Julie *et al.* [25].

Teicoplanin resistance in *S. aureus* strain was 23% reported in the present study in contrary to that other authors like Szymanek-Majchrzak *et al.* [26] and Shuchi Kaushik *et al.* [27] showed very high resistance 76.6% and 66%, respectively. Nidhi Pal *et al.* [28] and Vanitha

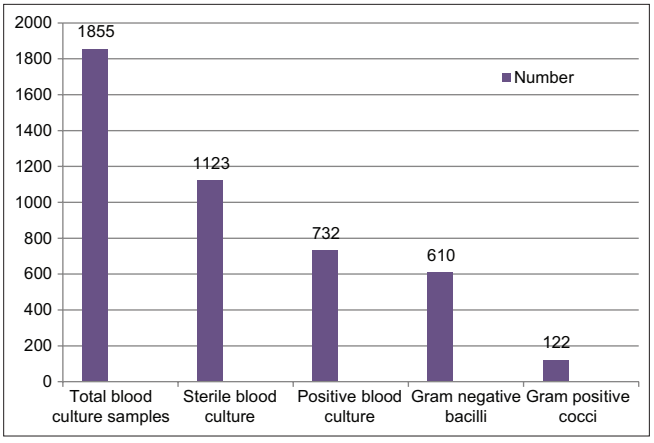

Figure 1: Growth profile of the blood culture samples

et al. [12] observed very low Teicoplanin resistance. The present study found that *Enterococcus* were highly resistance to Teicoplanin 53% in discordance to that Palewar *et al.* [29] and Gupta *et al.* [30] reported very low resistance to Teicoplanin.

In the present study, we were reported 39.5% Teicoplanin resistance in overall Gram-positive isolates in the Central India which was clinically and statically significant in because the majority of the previous studies in the Central India like Koksal *et al.* [31], Tripathi *et al.* [32], and Sodani *et al.* [33] reported 100% susceptibility to Teicoplanin

The increasing Teicoplanin resistance in the present study could be due to unregulated or widespread use of the drug in the empirical treatment protocol, altered virulence factor expression, and altered autolytic properties of the resistant organism.

CONCLUSION

Teicoplanin is a reserve antibiotic for multi-drug-resistant staphylococci or Enterococci and therefore emergence of Teicoplanin resistance is a serious concern. This mandates judicious use of antimicrobials and a strict antibiotic policy on a large scale to decrease or prevents further Teicoplanin resistance.

RECOMMENDATIONS

Recommendation of policy changes in the future for prevention of antibiotics resistance are as under:

- Health-care professionals should be educated about antibiotics resistance and its consequences
- Antibiotics should be used judiciously
- Appropriate antibiotics should be used only after culture-sensitivity reports
- Control of substandard and counterfeit uses of antimicrobials
- All health-care facilities should have an antibiotic monitoring committee, a strict antibiotic policy which is updated periodically
- All health-care facilities should maintain detailed records regarding antibiotics use and resistance patterns.

CONFLICT OF INTEREST

Authors have no known conflicts of interest to declare.

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