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# Daptomycin susceptibility in *enterococci* isolated from urinary samples in a tertiary care hospital

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ABSTRACT

**Introduction:** *Enterococci* are gram positive cocci encountered in various human infections.The most striking feature of *enterococci* is their relative and absolute resistance to variety of antibiotics.Vancomycin resistant *enterococci* (VRE) were first described in late 1980 and the incidence of nosocomial infections by VRE being 11.9% in Asia Pacific and 35.5% in U.S. Daptomycin is a lipopeptide antibiotic with bactericidal activity .

**Objective:** To study the daptomycin susceptibility in *enterococci* isolated in urinary samples.

**Results:** A total of 76 strains of *enterococci* were isolated during the study period.25 (33%) were identified as *E.faecium* and 51 (67%) as *E.faecalis.* Most of the Enterococcal isolates (82.8%) were resistant to Norfloxacin followed by 71% being resistant to tetracycline and 76% of isolates were sensitive to nitrofurantoin. Most of the *E.faecium* isolates were multidrug resistant. Of the 76 *Enterococci* isolated only 2(2.63%) were VRE and both the VRE strains isolated were *E.faecium*. There was no resistance to linezolid including the VRE strains. All the isolates 76 (100%) were sensitive to daptomycin including the VRE strains.

**Conclusions:** Our study mainly focused on susceptibility of enterococcal isolates in urinary samples to daptomycin which has bactericidal activity against gram positive organisms including multidrug resistant strains. This study shows growing concern for increasing antibiotic resistance in enterococcal isolates and treatment of these infections with daptomycin is invited as there are only few reports of daptomycin non susceptible *enterococci* (DNSE).



## 1. Introduction

*Enterococci* are gram positive cocci arranged in pairs and short chains, which in the Lancefield scheme are included in Group D streptococci which includes both *enterococcal* and non-*enterococcal* speices.[1] From 1980 *Enterococci* were classified in their own genus due to presence of sufficient differences from other *Streptococci* which contains at least 12 species[2] and this classification has been modified constantly, with several species being added like *E.faecalis, E.faecium, E.cecorum, E.columbae, E.saccharolyticus, E.dispar, E.sulfureus, E.seriolicida and E.flavescens.*[3] *Enterococci* are facultative anaerobes that can grow under the extreme conditions like in the presence of 6.5% NaCl, pH 9.6, temperature ranging from $10^0$C to $45^0$C, presence of 40% bile and they also can hydrolyse esculin and L-pyrroldonyl $-\beta$-naphthol .[4] These are a part of normal flora of gastrointestinal tract, oral cavity and vagina in humans. *E.faecalis* (80-90%) and *E.faecium* (5-10%)are the predominant species encountered in various human infections like urinary tract infections (UTI), bacteremia, endocarditis, catheter related infections, wound and soft tissue infections, meningitis, respiratory tract infections, neonatal sepsis, intra abdominal and pelvic infections.[5] *Enterococci* are not virulent intrinsically like *Staphylococcus aureus* and *Streptococcus pyogenes* but several factors have been described like extracellular surface protein (Esp) which contribute to the pathogenesis and

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colonization in humans and these strains contain esp genes which encode for these proteins.[6,7] *E.faecalis* has fsr locus due to which it expresses quorum sensing system for production of extracellular serine proteases and gelatinase (Gel E) which are associated with enhanced enterococcal virulence by helping them in dissemination. The same fsr locus also codes for biofilm formation in *E.faecalis* which helps to colonize and infect urinary and vascular catheter and heart valves.[8] Some strains of *E.faecalis* also produce plasmid mediated haemolysins though the role of haemolysin production in enterococcal pathogenicity in humans is not determined.[9]The most striking feature of *enterococci* is their relative and absolute resistance to a variety of antibiotics which are commonly used to treat infections with gram positive organisms.[10,11] (Table 1 )

Apart from intrinsic resistance to various antimicrobial agents in *Enterococci*, the acquired resistance is mediated by genes encoded on plasmids or transposons. *Enterococci* have efficient methods of transferring resistance genes not only between themselves but also to different organisms. Tolerance to cell wall active agents also leads to acquired resistance. Enterococcal isolates without prior antibiotic exposure are killed by cell wall active agents but a brief exposure to these drugs may be enough to develop tolerance[12] and due to the above reasons combination therapy with cell wall active agents along with aminoglycosides is advised especially in cases of endocarditis or meningitis which generally require bactericidal therapy. There is also development of High level aminoglycoside resistance (HLAR) in enterococcal isolates due to mutations in ribosomes and production of aminoglycoside modifying enzymes which is plasmid mediated.[13,14]Vancomycin Resistant Enterococci (VRE) were first described in late 1980's, followed by identification of different phenotypes where resistance to vancomycin is due to production of a ligase with an altered specificity which will result in formation of cell wall precursors ending in D-alanine-D-lactate rather than D-alanyl-D-alanine which is the main target for vancomycin.[15] Strains exhibiting VanA phenotype show high level resistance to vancomycin and teicoplanin.Van B strains exhibits moderate to high level resistance to vancomycin but are susceptible to teicoplanin. Van C phenotype is seen in *E.gallinarum* and *E.casseliflavus*.[16] The genes of which are located on chromosomes and are not transferred and Van D and Van E are described in *E.faecium* which exhibit moderate level of resistance to vancomycin and teicoplanin.[17]The incidence of nosocomial infections by VRE is increasing being 11.9% in Asia Pacific and 35.5% in U.S[18]and the Centre for Disease Control has also made several recommendations to help the control of spread of VRE strains within hospitals.[19]

$\beta$ lactamase producing strains of *E.faecium* were found initially in 1980 and these strains were isolated in USA also.[20]

Based on invitro activity, Quinpristin/dalfopristin are used only against *E.faecium* as *E.faecalis* is intrinsically resistant. Linezolid is active against both *E.faecalis* and *E.faecium* in vitro and is used successfully even in infections caused by VRE and also in cases where Quinpristin/dalfopristin therapy has failed.Linezolid being a bacteriostatic agent should be used with caution in cases of infective endocarditis or meningitis with *enterococci* where in such situations an bactericidal agent may be preferred.

Daptomycin is a lipopeptide antibiotic which is a fermentation product of *Streptomyces roseosporus* which was described in 1980's.[21] This drug acts by binding to cell membrane of gram positive organism in a calcium dependent process and disrupts the bacterial cell membrane potential without entering into the cytoplasm.[22,23]It's in vitro activity is dependent on calcium ions. So 2003 NCCLS guidelines have recommended to add calcium to standard Cation Adjusted Muller Hinton broth (CAMHB) for microdilution susceptibility testing.[24]Daptomycin also inhibits organism embedded in biofilm. Daptomycin has bactericidal activity against stationary phase bacteria and also good in penetrating into biofilm and reducing the bacterial growth.[25]Daptomycin is effective in treatment of complicated skin and soft tissue infections, blood stream infection with *Staphylococcus aureus* and also has bactericidal activity against VRE which is approved by Food and Drug Administration (FDA).[26] As a bactericidal agent it is also used in treatment of deep seated infections like infective endocarditis. Higher doses of daptomycin may be beneficial in treatment of invasive VRE infections.[27]Daptomycin non susceptible Enterococci (DNSE) were seen before clinical use and during clinical trials also.[28]Though there are a lot of case reports of DNSE , only one study has reported the rate of daptomycin non susceptibility in VRE isolates as 15%.[29] According to Clinical Laboratory Standards Institute(CLSI) guidelines, minimum inhibitory concentration (MIC) breakpoint of daptomycin for *Enterococci* is $\leq$4 mg/l.[30]Epidemiological data states that 99.9% of *E.faecalis* and 99.8% of *E.faecium* isolates are sensitive to daptomycin[31] and decreased daptomycin susceptibility may be attributed to suboptimal dosing. Pharmacokinetic and pharmacodynamic dose response experiments reveal that a minimum dose of 8mg/kg/day of daptomycin is sufficient for its bactericidal activity.[32]Studies have revealed that mutations in various metabolic pathways may lead to non-susceptibility to daptomycin but still the mechanism of its resistance is not well understood.[33–35]

Accordingly the aim of the present study is to determine the in vitro susceptibility of *Enterococci* isolated from urine samples to daptomycin by determination of MIC using E-test strips.(Himedia Labs, Mumbai)

**Table 1:** Showing intrinsic and acquired drug resistance in *enterococci*

| Antimicrobial resistance in *Enterococci* |
|---|
| **Intrinsic resistance** 1. Aminoglycosidic aminocyclitols(low level) 2. $\beta$- Lactams(relatively high MICs) 3. Lincosamides (low level) 4. Trimethoprim –sulfamethoxazole (in vivo only) 5. Quinpristin/dalfopristin (E.faecalis) |
| **Acquired resistance** 1. Aminoglycosidic aminocyclitols(high level) 2. $\beta$- Lactams (altered PBPs) 3. Cell wall active agents (tolerance) 4. Fluoroquinolones 5. Lincosamides (high level) 6. Macrolides 7. Penicillin and ampicillin 8. Tetracyclines 9. Vancomycin |

## 2. Materials and Methods

This is a prospective observational study conducted in the department of Microbiology, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation from March 2019 to December 2019 after approval from Institutional ethical committee.

All urinary samples received in the microbiology laboratory were processed as per standard protocols by inoculating them onto sheep blood agar, MacConkey agar and Cysteine Lactose Electrolyte Deficient (CLED) agar, incubated at 35-37$^0$C for 18-24 hours. Any growth which showed non - hemolytic colonies of 0.5-1mm on Sheep blood agar, small yellow coloured colonies on CLED agar and magenta pink colonies on MacConkey agar were identified as *Enterococci*. Further smears from the colonies were gram stained which showed Gram positive cocci in pairs and short chains. Genus *enterococcus* was identified by negative catalase test, positive bile esculin hydrolysis, growth on 6.5% sodium chloride agar and positive heat tolerance test. Speciation into *E.faecalis* and *E.faecium* was done based on growth at 4$^0$C and fermentation of sugars like arabinose, sorbitol and raffinose. The strains which didn't grow at 4$^0$C and didn't ferment arabinose were identified as *E.faecalis*. The strains which grew at 4$^0$C and fermented arabinose were identified as *E.faecium*.

All the enterococcal isolates were subjected to routine antibiotic sensitivity testing on Muller Hinton Agar (MHA) by Kirby Bauer disc diffusion technique by using the antibiotics vancomycin (30$\mu$g), linezolid (30$\mu$g), piperacillin-tazobactum (100/10$\mu$g), norfloxacin(10$\mu$g), nitrofurantoin(300$\mu$g), penicillin (10 units), ampicillin (10$\mu$g), tetracycline(30$\mu$g) and erythromycin(15$\mu$g).(Himedia Labs , Mumbai)

All the isolates were further subjected to Epsilometer testing (E-test) of daptomycin according to the manufacturer's guidelines on MHA. Daptomycin E- test is capable of showing MIC ranging from 0.016 -256mcg/ml MIC was read where the ellipse intersects the MIC scale on the strip and interpreted according to CLSI guidelines.[30] (Fig 1)

## 3. Results

A total of 76(100%) non duplicate strains of *Enterococci* were isolated during the study period of which 25 (33%) were identified as *E.faecium* and 51 (67%) as *E.faecalis*.

Most of the Enterococcal isolates (82.8%) were resistant to Norfloxacin, followed by 71% being resistant to tetracycline and 76% of isolates were sensitive to nitrofurantoin. Most of the *E.faecium* isolates were multidrug resistant.(Table 2) Of the 76 *Enterococci* isolated only 2(2.63%) were VRE and both the VRE strains isolated were *E.faecium*. There was no resistance to linezolid including the VRE strains. (Table 2) All the isolates 76 (100%) were sensitive to daptomycin including the VRE strains. (Table 3)

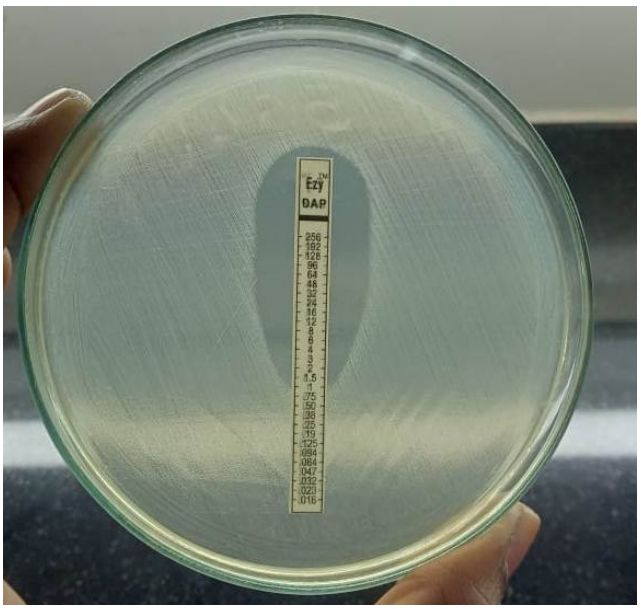


**Fig. 1:** Showing E test ofDaptomycin susceptible *enterococci*

## 4. Discussion

*Enterococci* are natural inhabitants of oral cavity, gastrointestinal tract and female genital tract of both humans and animals. They have now emerged as important nosocomial pathogens. *E.faecalis* and *E.faecium* are the two species which are most commonly isolated of which *E.faecalis* accounts for about 80%. In U.S.A, E.faecalis accounts for 12% of all the nosocomial infections especially UTI.[36–38]

Vancomycin remains the main stay for treatment of enterococcal infections; increase in emergence of vancomycin resistance *enterococci* is of concern as treatment of infections with VRE is difficult. The prevalence

**Table 2:** ShowingAntibiotic susceptibility of *Enterococci* isolated (N=76)

| **Isolate** | ***E. faecium* ( 25 isolates)** | | ***E. faecalis* (51 isolates)** | |
|---|---|---|---|---|
| Antibiotic | Susceptible No (%) | Resistant No (%) | Susceptible No (%) | Resistant No (%) |
| Penicillin | 3 (22) | 22 (88) | 37 (73) | 14(27) |
| Ampicillin | 4(16) | 21(84) | 42(83) | 9(17) |
| Erythromycin | 2(8) | 23(92) | 28(55) | 23(45) |
| Piperacillin-Tazobactum | 4(16) | 21(84) | 37(73) | 14(27) |
| Nitrofurantoin | 13(52) | 12(48) | 45(88) | 6(12) |
| Norfloxacin | 1(4) | 24(96) | 12(24) | 39(76) |
| Tetracycline | 6(24) | 19(76) | 16(32) | 35(68) |
| Vancomycin | 23(92) | 2 (8) | 51(100) | Nil (0) |
| Linezolid | 25 (100) | Nil (0) | 51(100) | Nil (0) |

**Table 3:** Showing vancomycin and daptomycin susceptibility

| **Isolate** | ***E. faecium* (25 isolates)** | | ***E. faecalis* (51 isolates)** | |
|---|---|---|---|---|
| Antibiotic | Susceptible No (%) | Resistant No (%) | Susceptible No (%) | Resistant No (%) |
| Vancomycin | 23(92) | 2 (8) | 51(100) | Nil (0) |
| Daptomycin | 25(100) | Nil (0) | 51(100) | Nil (0) |

of VRE is low in Europe (4%) but is high in North America (33%). In India the prevalence of VRE range from 0-30%.[39,40]

Although *E.faecalis* causes about 80% of infections, resistance to ampicillin and vancomycin is uncommon. But *E.faecium* is frequently resistant to ampicillin and vancomycin, according to the surveillance data 83% of isolates are vancomycin resistant.[41] So currently available treatment for VRE and options to prevent increase in incidence of VRE are linezolid, tigecycline, daptomycin and also newly approved drugs like Tedizolid and oritavancin. The data about the efficacy of these drugs is being limited but resistance to these drugs has also been reported . Some authors have proved the role of combination antibiotic therapy in cases especially in VRE with various combinations like daptomycin and linezolid; daptomycin and ampicillin; daptomycin, gentamycin and $\beta$-lactams; Quinpristin – Dalfopristin and ampicillin etc. Limited data is available about the efficacy of daptomycin in vitro activity in urinary isolates of *enterococci* and ours is a single center prospective observational study conducted to know the invitro activity of daptomycin on urinary isolates of enterococci.

In the present study out of the 76 isolates of *enterococci* 25(33%) were *E.faecium* and 51(67%) were *E.faecalis*.

Of the 76 *Enterococci* isolated only 2(2.63%) were VRE .All the isolates were sensitive to daptomycin including the VRE strains .Studies from India which mainly focused on daptomycin susceptibility in VRE isolates showed 100% susceptibility to daptomycin and surveillance in U.S hospitals showed greater than 99.5% susceptibility to daptomycin.[28,42,43]

For over a period of 7 years Sader et al evaluated the invitro activity of daptomycin against clinical isolates of *enterococci* in 34 centers in Europe, Turkey and Isarel and found that the prevalence of VRE was 9.4% and all the isolates (100%) were susceptible to daptomycin.[44]

A study conducted at a tertiary care hospital in turkey, 52 enterococcal strains from clinical samples showed 100% susceptibility to daptomycin.[45] Similar to these results, in our study all the enterococcal strains were susceptible to daptomycin. There is only 0.6% non susceptibility of daptomycin in enterococci according to recent studies.[26]

## 5. Conclusion

Daptomycin is a cyclic lipopeptide antibiotic with potent bactericidal activity against gram positive organisms including multidrug resistant strains. Vancomycin remains the main stay of treatment for serious enterococcal infections. But due to inadvertent use of vancomycin there is emergence of VRE since late 1980's. This study shows growing concern for increasing antibiotic resistance in enterococcal isolates and treatment of these infections with daptomycin is invited as there are few reports of daptomycin non susceptible enterococci (DNSE).

Our study mainly focused on susceptibility of enterococcal isolates in urinary tract infections to daptomycin. Mode of action of daptomycin is different from glycopeptides and its activity is not influenced by Van genes of enterococci. Daptomycin is primarily eliminated by kidney and approximately 52% is excreted into urine after intravenous administration.

To conclude all the strains of *enterococci* isolated from urine samples were susceptible to daptomycin irrespective of sensitivity to vancomycin hence daptomycin can be used as a safe and effective alternative drug to treat enterococcal infections including VRE which has been showed by

various studies using CLSI breakpoint of $\leq$4 mg/l. However the yield of daptomycin has to be increased by combined work of various disciplines like genetics and biochemical engineering to reduce the cost of large scale production of daptomycin. So we believe that daptomycin is a valuable treatment option for UTI's, the usage of which can reduce the rates of VRE infections.

## 6. Conflict of Interest

None.

## 7. Source of funding

None.

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