# CASE REPORT

# VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM VANA* PHENOTYPE: FIRST DOCUMENTED ISOLATION IN INDIA

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Abstract. In recent years, vancomycin-resistant enterococci, especially *Enterococcus faecium* has emerged as an important nososcomial pathogen and represents a serious threat to patients with impaired host defences. We report infection with vancomycin-resistant *Enterococcus faecium* in a 3-year-old child with patent ductus arteriosus. The organism, isolated from a central venous catheter tip, exhibited a high-level resistance to vancomycin (minimum inhibitory concentration ≥256 μg/ml) and was also resistant to teicoplanin. The child probably died due to sepsis from this highly resistant organism. To the best of our knowledge, this is the first reported isolation of *VanA* phenotype *Enterococcus faecium* in India.

## INTRODUCTION

Enterococci have evolved over the past few decades from being harmless intestinal commensals of little clinical significance to becoming the second or third most common pathogens associated with nosocomial infection (Low *et al,* 1995; Jones *et al*, 1997). Serious enterococcal infections are often difficult to treat since the organisms have a tremendous capacity to acquire resistance to penicillin, high concentrations of aminoglycosides and vancomycin, thus drastically limiting therapeutic options. Vancomycin resistance is undoubtedly the greatest concern and is associated with severe underlying disease, compromized host defences, indwelling urinary or central venous catheters (CVC), prolonged hospitalization and administration of multiple antibiotics (especially vancomycin and cephalosporins) (Low *et al,* 1995; Cetinkaya *et al,* 2000). The emergence of vancomycin-resistant enterococci poses a serious threat to hospitalized patients with impaired host defences. We report the isolation of vancomycin-resistant *Enterococcus faecium* in a child with patent ductus arteriosus who was on vancomycin and cephalosporin therapy.

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## CASE REPORT

A 3-year-old girl with patent ductus arteriosus (PDA) was hospitalized with a history of fever, cough and increasing difficulty in breathing for four days duration, poor feeding and altered sensorium for one day. On examination, she was febrile, had a pulse rate of 178/minute, a respiratory rate of 68/minute and a blood pressure of 132/56 mm Hg. Respiratory examination showed decreased air entry into the lungs, rhonchi and bilateral rales.

Laboratory studies revealed a hemoglobin level of 7.8 g/dl; other hematological parameters were within normal limits. Chest X ray showed cardiomegaly, bilateral infiltrates and prominent hila. Echocardiogram revealed a large PDA (6.5mm) with large left to right shunting. Cerebrospinal fluid examination revealed no abnormalities. A diagnosis of congenital heart disease (PDA) with congestive cardiac failure and pneumonia was made.

Initially, empiric therapy with parenteral cefotaxime, amikacin and cloxacillin was administered along with supportive treatment in the form of bronchodilators and digoxin. Despite therapy, there was no clinical improvement. Her respiratory distress worsened with worsening saturation. The child was intubated and placed on mechanical ventilation for respiratory failure.

On the second hospital day (HD), she had cardiac arrest but was resuscitated. Her blood

cultures drawn on admission grew methicillin resistant *Staphylococcus aureus*. In view of poor response, antibiotic therapy was switched to parenteral vancomycin, piperacillin/tazobactam and amikacin. As the child continued to worsen, the possibility of fungal sepsis was considered and fluconazole was added to the regimen. However, the child continued to have spikes of fever. Her hemodynamic and renal status also deteriorated. Fluconazole therapy was withdrawn on HD 16 and parenteral cefepime was added. PDA ligation was performed on the 24$^{th}$ day of hospitalization and was complicated postoperatively by hypertension and pleural effusion. A sodium nitroprusside drip was started and pleural drainage done. The patient developed puffiness of face and persistent bilateral rales on the 2$^{nd}$ postoperative day. Peritoneal dialysis (PD) was initiated as the child developed severe metabolic acidosis in the presence of altered renal function. During the 27$^{th}$ cycle of PD, the patient developed oxygan desaturation, so PD was stopped and fluid drained; this led to transient improvement. However, the patient's hemodynamic and respiratory course continued to deteriorate and she died on the 29$^{th}$ day of hospitalization.

The PD catheter tip and blood cultures obtained at the time of discontinuation of PD were sterile, but a semiquantitative culture of the central venous catheter tip grew a significant count (more than 15 colonies) (Maki *et al*, 1977) of *Enterococcus faecium*. The identification of the isolate was done by standard methods (Facklam and Teixiera, 1998) and confirmed by API 20 Strep (BioMërieux-Vitek, USA). By standard Kirby-Bauer disc diffusion method, the isolate was resistant to penicillin, erythromycin, high-level gentamicin, meropenem, ciprofloxacin, vancomycin and teicoplanin but susceptible to linezolid. The isolate possessed high-level resistance to vancomycin; the minimum inhibitory concentration (MIC) of the strain to vancomycin was ≥256 μg/ml by E test (AB Biodisk, Solna, Sweden). Based on its high-level resistance to vancomycin and resistance to teicoplanin, the strain was designated as belonging to *VanA* phenotype.

## DISCUSSION

The case described here has several features in common with those reported for VRE earlier (Low *et al,* 1995; Cetinkaya *et al,* 2000). The patient had severe underlying disease, was cardiologically compromized, had an indwelling central venous catheter, was hospitalized for a long period of time and was administered multiple antibiotics, notably vancomycin and cephalosporins. Thus, she was at risk of acquiring VRE. The VRE strain in the present case was isolated from a CVC tip; we speculate that the patient probably had CVC-associated bloodstream infection with the highly resistant organism which may have contributed to the fatal outcome.

It is important to speciate enterococcal isolates from clinical samples because, while most isolates of *E. faecalis* are inhibited by concentrations of penicillin or ampicillin (1 to 8 μg/ml) easily achievable in humans, isolates of *E. faecium* are more resistant to penicillins, requiring an average of 16 to 64 μg/ml to inhibit growth, although some isolates are even more resistant (Murray, 1997). *Enterococcus faecium* strains as compared to *E. faecalis* display a higher degree of drug resistance to multiple other antibiotics as well, including ampicillin, gentamicin, ciprofloxacin, vancomycin and teicoplanin (Murray, 1997; Udo *et al* 2003). Failure to recognize the resistant strains may result in inadequate antibiotic therapy with its attendant morbidity and mortality.

Resistance to vancomycin in enterococci can be divided into six phenotypic groups: five are acquired (*VanA, VanB, VanD, VanE* and *VanG*) and one VanC is an intrinsic property of less commonly isolated species, such as *E. gallinarum*, *E. casseliflavus*, and *E. flavescens* (Fines *et al,* 1999; Cetinkaya *et al,* 2000; McKessar *et al*, 2000). *VanA* phenotype is the most commonly encountered and confers high-level resistance to vancomycin and teicoplanin. Resistance in *VanB* isolates results in moderate-level resistance to vancomycin. This is very similar to *VanA*, except that these isolates remain susceptible to teicoplanin. Although *E. faecium* accounts for most VRE isolates, *VanA* and *VanB* phenotypes can be found in both *E. faecalis* and *E. faecium*. *VanC* confers low-level vancomycin resistance and is not associated with resistance to teicoplanin. *VanD* phenotype is manifested by moderate resistance to vancomycin and low-level resistance or susceptibility to teicoplanin. *VanE* (Fines *et al,* 1999) and *VanG* (McKessar

*et al*, 2000) phenotypes recently described in *E. faecalis,* confer low- and moderate-level of resistance to vancomycin, respectively, while retaining susceptibility to teicoplanin.

Enterococci are commensal inhabitants of the gastrointestinal tract (GIT) Broad spectrum antibiotic coverage, such as seen in the present patient, exerts antibiotic selection pressure on these bowel inhabitants resulting in increased survival and overgrowth of the resistant population. VRE may thus colonize the GIT or skin and subsequently result in infection. Although resistant strains appear to arise from the patient's endogenous flora, VRE may spread through direct contact with contaminated environmental surface and hands of health care workers (Murray, 1997; Cetinkaya *et al,* 2000). We can only speculate about the source of this strain, as neither the skin/rectal swabs nor environmental samples could be taken. The skin or rectal swabs could not be taken as the patient died before the culture report of the isolation of VRE could be communicated to the attending physician.

Vancomycin-resistant enterococci are slowly emerging as significant pathogens in India (Mathur *et al,* 2003; Taneja *et al,* 2004). However, most of the VRE reported earlier are of *VanB* or *VanC* phenotype (Karmarkar *et al*, 2004; Taneja *et al,* 2004). In India, *VanA* VRE has been reported only in *E. faecalis* (Mathur *et al,* 2003). This is the first documented isolation of vancomycin-resistant *E. faecium* of VanA phenotype in India.

The primary therapeutic options for patients with VRE infection include quinupristin/dalfopristin which, is active against most strains of *Enterococcus faecium*, and linezolid which is active against *E. faecium* and *Enterococcus faecalis* (Linden, 2002). Because comparative data are extremely limited, the optimal treatment of patients with VRE infection is uncertain. Some VRE strains (most often *E. faecalis*) are susceptible to ampicillin (Linden, 2002) which is the preferred therapy in these cases. However, susceptibilities to quinupristin/dalfopristin or linezolid should not be assumed but should be confirmed by susceptibility testing.

This case report as well as earlier reports of vancomycin-resistant enterococci are a reminder that these potentially lethal organisms may become endemic to India if appropriate infection control procedures, judicious use of antibiotics and screening programs are not implemented immediately.

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