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Risk Factors for Vancomycin-Resistant Enteroccocci Colonization in Infants in Neonatal Intensive Care Unit

Research Article

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Abstract: We aimed to evaluate the risk factors for VRE colonization in neonatal intensive care units. In December 2007, we identified a neonate with VRE infection (urinary tract infection and we performed blood and stool cultures for VRE until the last colonized patient was discharged from our clinic. All the neonates hospitalized in NICU during December 2007 to January 2008. Active surveillance cultures for VRE fecal carriage was carried out in neonatal intensive care unit. Resistance to vancomycin was detected by the E-test method. Epidemiological data was recorded for all patients included in the study and was used for the risk factors. Totally 54 infants in NICU were screened for VRE colonization. Totally 11 infants (20%) were colonized with vancomycin-resistant enterococci. The average duration of all antimicrobial therapy was significantly longer in colonized patients. The infants who were hospitalized for more than 10 days were found to be significantly more colonized with VRE when compared to the infants with shorter hospital stay ($p<0.05$). There were no statistically significant differences between VRE colonized and non-colonized infants in respect to sex, to third generation cephalosporin usage, glycopeptide usage, presence of prematurity, presence of mechanical ventilation($p> 0.05$). The premature infants and the mature infants were under risk of VRE colonization. Longer duration of hospitalization and antimicrobial usage were the prominent risk factors. Since infants in neonatal intensive care units were under risk of infections, periodic active surveillance cultures should be combined with logical antimicrobial therapy.

Keywords: *Vancomycin resistant enteroccocci • Neonatal intensive care unit • Colonization*

1. Introduction

Multidrug-resistant organisms such as vancomycin-resistant enteroccocci (VRE) have emerged as important causes of nasocomial infections especially in high-risk group patiens [1]. Over the past decade, VRE increased its importance and intensity in nasocomial infections in USA [2-4]. Moreover National Nosocomial Infections Surveillance (NNIS) System of the Centers for Disease Control and Prevention (CDC) reported the emerging menace concerning especially in all participating intensive care units (ICUs); with this report 28.5% of enterococcal isolates causing infection were reported to be vancomycin resistant [1].

Emerging VRE colonization in neonatal intensive care units (NICU) has been reported more often than before [1,5-7]. Vancomycin usage, third-generation cephalosporin antibiotics, presence of central-venous catheters, increased length of hospital stay has been reported as risk factors for colonization in NICU [1]. Since asymptomatic VRE colonized patients could act as potential reservoirs for other patients via the hands of health care workers [1,8-11] persistent environmental VRE contamination were the extrinsic risk factors complicating the situation and hardening the control measures [1,12-15].

In December 2007, we identified a neonate with VRE infection (urinary tract infection). Because of risk of underestimating VRE colonization in our NICU, we

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performed blood and stool cultures for VRE until the last colonized patient discharged from our clinic. In this study we aimed to evaluate the risk factors for VRE colonization and described the interventions used to control VRE transmission in NICU.

2. Material and Method

Dr. Behçet Uz Children's Hospital, Izmir, Turkey is a 400-bed pediatric teaching hospital with annual outpatient visit exceeding more than 465 000 in 2007. The NICU is composed of 80 beds with 4000 inpatients. Approximately 350 patients were admitted in NICU annually. It is a reference center and the newborn admitted to our center were referred from nearby maternity clinics. All patients were born at other hospitals and transported to our NICU. NICU is divided into three main unites; one for premature patients and one for the patients who need life support and third for the mature infants.

2.1. Surveillane cultures

In December 2007, VRE was isolated from the urine sample of a febrile newborn who was diagnosed as urinary tract infection. Further investigations revealed that VRE isolate was Enterococcus gallinerium and we performed surveillance cultures until the last VRE colonized infant was discharged.

2.2. Bacterial Strains

Rectal swab specimens for culture surveillance of VRE were obtained from newborns in the NICU. VRE isolation was carried out in chromogenic medium (containing alpha-Glucosidase & beta-Galactosidase) supplemented with 8-mg/L vancomycin (Chrom ID, Biomerieux). After 24-48 hours of incubation at 35ºC, the plates were re-examined for VRE. Identification of VRE species was performed by the Rapid ID 32-strep (Biomerieux).

Routine antibiograms for enterococci, performed with the Phoenix System (Becton–Dickinson), were confirmed by a disc diffusion method on Mueller–Hinton agar (Bio-Rad, Marnes-La-Coquette, France). A panel of 22 antimicrobial agents was tested: penicillin G, oxacillin, amoxicillin, piperacillin, imipenem, kanamycin, streptomycin, gentamicin, cefotaxime, erythromycin, clindamycin, pristinamycin, levofloxacin, rifampicin, fosfomycin, tetracycline, linezolid, chloramphenicol, nitrofurantoin, co-trimoxazole, vancomycin and teicoplanin. MICs of vancomycin and teicoplanin were determined by Etest (AB BIODISK, Solna, Sweden) according to the manufacturer's instructions.

2.3. Management strategies

Rigid Contact precautions were maintained for all VRE-positive patients until three rectal screenings at weekly intervals were negative according to the recommendations of the Centers for Disease Control and Prevention. Because of open unit type conditions of the NICU, we placed VRE-colonized infants (cohort) in a room together. We also formed two other rooms for infants who were not colonized with VRE. There was no restriction of new patient admittance since our hospital is a reference center. We routinely performed rectal swab from the infants transferred from other institutions. Rectal swab cultures were taken once a week from all patients hospitalized in the NICU. Environmental cultures were performed in areas adjacent to VRE-colonized patients. We have cleaned all of the surfaces with 500-ppm sodium hypochlorite for 3 times a day until last infant with VRE colonization discharged from the NICU. Also usage of alcohol-based hand-rub solutions was strongly encouraged in NICU.

3. Results

From December 2007 to January 2008, totally 54 infants (except from the index case) who were hospitalized in NICU were screened for VRE colonization and/or VRE infection. VRE was isolated in the index case culture of one patient. Totally 11 infants (20%) were found to be colonized with VRE. Further characterization of the species revealed that none of isolated VRE was *enterococcus gallinarium*. *Enterococcus faecalis* and *Enterococcus faecium* were the isolated species. Since we could not perform further molecular typing; we could not determine the genes responsible No blood stream infection due to VRE species were observed in colonized patients and no deaths due to VRE were present in NICU.

The mean age of the infants was 18,95±15,78 days (age range 1 to 72 days). There were 26 female (48,1%) and 28 (51,9%) male patients hospitalized during that period. During this period 44,4% of the patients were premature while 55,6% of the cases were term infants.

3.1. Risk factors for VRE colonization

Totally 11 infants (20%) were found to be colonized with VRE. The spectrum of diseases of the infants were wide and listed in Table 1. Six of the colonized newborn was female while five patients were male. There was no significantly difference in terms of mean age and gestational ages between the infants with gastrointestinal VRE colonization and non-colonized patients. The

Table 1. Demographic features of the infants colonized with VRE.

	Age (days)	Gender (M/F)*	Gestational week	Birthweight	Hospital stay (days)	Primary disease	
1.	Case	31	F	38	1600	23	Broncho pulmonarydysplasia
2.	Case	28	F	40	2300	21	Chronic Lung Disease
3.	Case	14	M	38	3000	14	Congenital adrenal hypoplasia
4.	Case	13	F	40	3630	13	Asphyxia
5.	Case	10	M	40	3200	10	Congenital pneumonia
6.	Case	14	M	38	5100	13	Congenital Heart Disease
7.	Case	52	M	26	1180	42	Respiratory distress syndrome
8.	Case	12	F	28	1100	11	Respiratory distress syndrome
9.	Case	22	M	27	1350	22	Respiratory distress syndrome
10.	Case	25	F	38	4000	15	Broncho pulmonarydysplasia
11.	Case	52	F	26	1180	52	Chronic Lung Disease, sepsis

average duration of over all antimicrobial therapy was significantly longer in VRE colonized patients (6,8±3,6 days) when compared to non-colonized patients (4,3 ± 2,8 days)(p< 0,05). The infants who were hospitalized for more than 10 days were found to be significantly more colonized with VRE when compared to the infants with shorter hospital stay(p<0.05).

There were no statistically significant differences between VRE colonized and non-colonized infants respect to sex, to third generation cephalosporin usage, glycopeptide usage, presence of prematurity, presence of mechanical ventilation (p> 0.05). Also VRE colonization rates did not change in very low birth weight and low birth weight infants (p> 0.05) when compared to normal weight infants.

4. Discussion

Vancomycin-resistant enteroccocci has become an important nasocomial pathogen and thread for the last decade [7]. From its initial discovery in 1986, VRE has been reported worldwide [1,2,16] mostly responsible for colonizations, and less often as a nasocomial pathogen [17,18]. Ten years later from its recovery, VRE was reported from our country [19] with growing intensity. In our clinic, during this period VRE colonization rate among infants were 24%. Although reports concerning VRE colonization in NICU were rare, one study from Turkey reported that 8 of 110 neonates who were screened for VRE, was found to be colonized with VRE (7,2%)[6] and another study from Germany reported VRE colonization as 13,1% [20].

Although early neonatal colonization with enterococci was reported [20-24], in our clinic the youngest infant with VRE colonization was 10 day-old and 20% of the non-colonized patients were younger than 1 week of age.

Although risk factors for colonization in adult patients including usage of vancomycin, third generation cephalosporin usage, organ transplantation, intensive care unit admission and length of hospital stay were well defined [25-28]; studies concerning risk factors for colonization in NICU was limited. Duration of hospital stay, use of vancomycin, third-generation cephalosporins, and central venous catheters were reported as the risk factors in NICU [7]. In our study duration of total antimicrobial therapy in VRE colonized patients were significantly longer as compared to negative cases. This finding was not suprising, since antimicrobial therapy increases the enterobacteriaceae colonization by decreasing population of anaerobic bacteria [29,30]. Although recent meta-analysis had showed prior vancomycin usage a 4,5 fold increased risk of VRE colonization [31], no relationship between VRE colonization and antecedent vancomycin usage was found in our study.

Length of hospital stay was one of the most identified factors, which were associated with VRE colonization [32-36]. In our study we have found that VRE colonization was highly associated with hospitalizations for more than 10 days as reported before. Longer hospitalization stay increases the chance of replacement of the gastrointestinal flora with more resistant bacteria and also chance of acquiring nasocomial infections which would require more frequently broad-spectrum antibiotics including especially glycopeptides.

Prematurity had been reported as an important risk factor for VRE colonization in NICU [20,37]. Hufnagel et al reported that prematures(especially premature patients younger than 32 gestational weeks were more likely to be colonized with VRE when compared to mature infants [20] and in another study prematurity was reported as an independent risk factor for VRE colonization [37]. Although prematures formed 44% of our patients in NICU, VRE colonization rates were

not higher when compared to mature infants. The exact mechanisms for increased incidence of VRE colonization in premature infants were not completely explained. Requirement of longer hospitalization in premature infants, tendency of clinicians for using broad-spectrum antibiotics in premature infants and high ratio of invasive procedures could be the predisposing factors for colonization with multidrug resistant microorganism. Although our study number was small, the rate of VRE colonization in premature infants was not higher when compared to mature infants. This could be due to the nearly equal hospital durations in two groups since the median hospital stay for prematures was not longer than mature infants in our study (because of the complexity of the diseases of mature infants).

In conclusion, not only the premature infants but also mature infants were under risk of VRE colonization. Longer durations of hospitalization and antimicrobial usage were the prominent risk factors. Since infants in NICU were more susceptible to infections, periodic active surveillance culture should be combined with logical antimicrobial therapy.

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