DOI: 10.4274/tpa.46.61

Hospital acquired bloodstream infections in neonatal intensive care unit

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Summary

Aim: The aim of this study was to evaluate the risk factors for term and preterm newborns, etiological agents, antibiotic susceptibility and rate of hospital acquired bloodstream infections among newborns hospitalized in our Neonatal Intensive Care Unit during the year of 2008.

Material and Method: The medical records of patients were evaluated retrospectively. The risk factors for term and preterm babies were evaluated by multivariate logistic regression analysis.

Results: During the one year period, 807 patients were hospitalized for longer than 72 hours. A total of 97 hemocultures were found to be positive. Among hemoculture positive newborns, 65.6% were found to be preterm and 34.4% term. The most common microorganisms identified were coagulase negative staphylococci and Klebsiella pneumonia. Blood stream infection rate, catheter related blood stream infection rate and ventilator associated pneumonia rate were found to be 5;9:1000 days, 9.6:1000 days and 13.8:1000 days, respectively. Glycopeptide resistance was not observed among gram positive microorganisms. Length of hospital stay, mechanical ventilation and presence of catheter were risk factors for hospital acquired infections. The mortality was found to be 12.5% among newborns with positive hemocultures.

Conclusions: Hospital acquired infections are important causes of morbidity and mortality in neonatal intensive care units. The decrement of risk factors in term and preterm newborns would help to improve the outcome. *(Turk Arch Ped 2011; 46: 130-6)*

Key words: Hospital acquired infection, microbiological agents, newborn, risk factor

Introduction

Infection is one of the most common diseases which causes neonatal mortality worldwide arising primarily or as a complication of another disease. Most infections occur in neonatal intensive care units (NICU) (1). In a prospective study related to bloodstream infections in NICU in USA, the rate of confirmed bloodstream infection was found to be 11.2%. It was reported that this rate was higher in babies who needed intensive care and the mortality rate was reported to be 16% (2).

Bloodstream infection is the most commonly seen nasocomial infection. It has been reported with a rate of 7-14/1000 in term babies and with a rate of 50-162/1000 in very small for gestational age babies (3). In prevention of nasocomial infections, the most important factors include flora of the delivery room and NICU, number and knowledge of healthcare personnel, infection control methods applied and politics of antibiotic usage. Antibiotics which are started ampirically when infection is suspected should be selected considering the effective surveillance results of the unit. Frequent use of the same antibiotics may cause microorganisms to develop resistance in the long term (4,5).

This study was performed to form a basis for practices which will decrease nasocomial infections by investigating the rate of nasocomial bloodstream infections, demographic properties of term and preterm subjects who had infection, the infectious agents, antibiotic sensitivity and risk factors.

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Material and Method

In our hospital, approximately 5000 deliveries occur yearly. The NICU of our hospital is one of the most important neonatal centers in Istanbul with 10 tertiary level, 20 secondary level and 8 primary level beds. Two neanatologists, two neonatology subspeciality residents, four pediatric residents and five nurses work during the day and one neonatology subspeciality resident, one pediatric resident and three nurses work at night. To prevent spread of infections infection control methods including monitoring and education of hand washing methods, providing alcohol based disinfectants for each patient, seperation of infected and colonized patients are being practiced. Infection control methods are being monitored closely both in written and verbal forms, cooperation with infection control committee accompanied by effective surveillance data is being exercised and results are being shared with healthcare workers. If hemoculture is negative and there is no clinical finding of sepsis, antibiotic treatment is discontinued prematurely. In patients with a positive hemoculture, antibiotic treatment is being reevaluated according to the result of the antibiogram.

This retrospective cohort study was performed between January 1st 2008 and January 1st 2009 in NICU of Şişli Etfal Education and Research Hospital. The files of all patients hospitalized in our hospital during this one year period were extracted and examined. The patients who had inadequate medical and microbiological data and who had congenital and community-acquired infections were excluded from the study.

Collection of the data

Data of the patients [prenatal history of the mother, demographic properties (gestational age, diagnoses, gender, birth weight, mode of delivery), interventional procedures (mechanical ventilation and number of days of mechanical ventilation, cathether and number of days with cathether), species of the isolated microorganisms, antibiotic sensitivity] were recorded by two investigators on a worksheet prepared previously. Demographic properties, infectious agents and risks and mortality rates of preterm and term babies with infection were compared.

Definitions and tests used

Subjects who had no infection and/or were not in the incubation period at presentation and who developed infection 72 hours after hospitalization were considered to have nasocomial infection. The diagnosis of nasocomial bloodstream infection was made by clinical findings, laboratory findings and hemoculture. Clinical fiindings including hypothermia-hyperthermia, apnea, bradycardia, circulatory disorder, lethargy, hypotonia, feeding difficulty and laboratory findings including leucocytosis, leucopenia, thrombocytopenia, a rate of immature/mature leucocytes >0.2 and a C-reactive protein (CRP) value of >1 mg/dL were considered to be significant. Bloodstream infection rate related to nasocomial infection (number of nasocomial infection/number of hospitalized patients x 100), ventilator associated pneumonia rate (number of ventilator associated pneumonia/ventilator days x 1000) and cathether related bloodstream infection (number of cathether related bacteremia/cathether days x 1000) were calculated.

In our unit, hemoculture is taken according to previously determined standard rules. Hemoculture is taken under sterile conditions using sterile gloves and cloths from two different veins with an interval of 30 minutes. Iodine is applied to venipuncture site skin on the peripheral vein from which hemoculture will be taken and iodine is let to dry for at least one minute and at least 0.5-1 ml blood is taken by closed system and cultured in the culture bottle. After the blood is cultured in hemoculture vehicle (BactAlert, Biomerieux, France), the results are evaluated. When Bacillus, Coryneobacterium and coagulase negative staphylococcus (CNS) are cultured without clinical findings, contamination is considered to be present. Antibiotic sensitivity is evaluated by disc diffusion method determined by NCCLS (National Committee for Clinical Laboratory Standards). In our clinic, penicillin and aminoglycosides are started ampirically when infection is suspected. According to the clinical and risk state of the patient approval from the pediatric infectious diseases specialist is taken for third generation cephalosporins, glycopeptides, carbapenem and antifungal treatments. Wide-spectrum antibiotics are not used, if possible.

Statistical analysis of data

Statistical Package for Social Sciences (SPSS) for Windows 15 program was used for statistical analysis of the results obtained in the study. Demographic properties in the study were assessed by “descriptive” statistical analysis. “Unpaired” t test was used for comparision of groups, chi-square test or Fisher’s “exact” test were used for categorical variables. “Univariate” and “multivariate” logistic regression analysis were done for efficiency of risk factors in terms of nasocomial infection. Since our study was retrospective, risk analysis between variables Odd Ratio (OR) and 95% confidence interval were calculated. A p value of <0.05 or OR 95% CI>1 was considered to be statistically significant.

Results

During the one year period, 955 babies were hospitalized in NICU. 126 of the patients were excluded from the study, since they were discharged in the first 72 hours or died. 807 babies who were under risk in terms of nasocomial infection were evaluated. 363 of the babies were preterm (45%) and 444 were term (55%). Hemoculture was taken from 243 of the patients because of suspicious nasocomial bloodstream infection. 115 of these cultures were found to be positive (43%). 18 were

excluded from the study because of contamination and inadequate microbiological evidence. Results of 97 positive hemocultures were evaluated. 42 patients with a positive hemoculture (65.6%) were preterm and 22 were term (34.4%). Nasocomial infection rate was found to be 12.1%.

The most common reason for hospitalization was preterm delivery in patients with nasocomial infection. The other reasons for hospitalization included meconium aspiration syndrome, transient tachypnea of the newborn, asphyxia, congenital cardiac disease, genetic and chromosomal anomalies and congenital metabolic diseases.

In 47% of the patients who had a positive culture, there was no problem in antenatal history, but in 53%, preeclampsia, eclampsia, abortus imminens, hypothyroidism and cardiac problems were present in antenatal history. While positive pressure ventilation was applied in 47% of preterm babies and entubation was performed in 6%, the same rates were found to be 27% and 2% in term babies, respectively.

The most common clinical findings of bloodstream infection were found to be apnea and bradycardia (37%). Temperature disregulation (hypo-hyperthermia) was found in 23%, circulatory disorder was found in 13% and feeding intolerance was found in 12%. Laboratory findings included leucocytosis (60%), leucopenia (25%), thrombocytopenia (40%), an immature/mature leucocyte rate of >0.2 (43%) and increased CRP (70%).

One bacterial sepsis episode was observed in 25 of the preterm babies (59.3%), two bacterial sepsis episodes were observed in 13 (31%) and four or more bacterial sepsis episodes were observed in 4 (9.5%). Although two bacterial sepsis episodes were observed more frequently in preterm babies, the difference was not statistically significant. Positive hemoculture was accompanied by meningitidis (12.3%), urinary infection (5%) and pneumonia (24.7%). 12.5% of the patients with a positive hemoculture were lost and mortality rate was specifically higher in preterm babies. Clinical and demographic properties of the patients are shown in Table 1.

During the one year period, time of hospitalization was found to be 16297 days. Number of days of bloodstream infection was found to be 5.9:1000 days. In 24 of the babies with a positive hemoculture pneumonia was present. Number of ventilator days was found to be 1729. Ventilator associated pneumonia rate was found to be 13,8:1000 days. During the one year period, 165 patients were applied cathether for 4155 days and cathether related bloodstream infection was observed in 39 patients. Cathether related bloodstream infection rate was found to be 9.6:1000 days.

72 of microorganisms (74.2%) obtained by hemoculture were gram-positive and 25 (25.8%) were gram-negative. Candida was isolated in two of our patients. The first patient was a baby weighing less than 1000 g who received total parenteral nutrition (TPN) for a longtime and was catheterized; on the 21st day after delivery Candida was isolated by hemoculture. The second patient was a baby weighing 1350 g who was followed up with a diagnosis of respiratory distress syndrome and necrotizing enterocolitis and who could not be fed enterally for a long time; on the 30th day after delivery Candida was isolated by hemoculture. Since Candida typing and sensitivity could not be performed, this patient was excluded from the study.

In term and preterm babies, coagulase negative Staphylococcus was the most commonly isolated gram-positive microorganism. 36 of coagulase negative staphylococci and 2 of Staphylococcus aureus were found to be meticillin-resistant. The most common gram-negative miroorganism isolated was K.pneumonia. 3 of K. Pneumonias were ESBL (expanded spectrum beta lactamase) positive. Acinetobacter spp. were isolated only in one preterm baby and this patient was lost because of multiple organ failure. In patients with pneumonia with a positive hemoculture, the most commonly isolated microorganisms were K. Pneumonia and CNS. Distribution of microorganism is shown in Table 2.

Coagulase negative staphylococci were found to be sensitive to vancomycine, linesolide and teicoplanine with a rate of 100% and resistant to ampicillin and penicilin. S. aureus was found to be sensitive to amikacin, vancomycin, teicoplanin and linesolid with the highest degree and to oxacillin with the lowest degree. K.pneumonia was found to be

Table 1. Demographic and clinical properties of preterm and term babies with a positive hemoculture

	Term	Preterm	p
Gestational age[a], weeks	38.9±0.9	31.5±3.3	0.001
Gender (male) (n; %)	13 (59.1)	27 (64.3)	0.5
Birth weight[a], g	3228±410	1539±567	0.001
Delivery (caesarean section) (n,%)	11(50)	36 (85.7)	0.006
Number of patients experiencing bacterial episode, n %			
One bacterial episode	14 (63.6)	25 (59.3)	
Two bacterial episodes	6 (27.3)	13 (31)	0.8
Three or more bacterial episodes	2 (9.1)	4 (9.5)	
Death n, %	2 (9.1)	6 (14.3)	0.54

[a]Values: Given as Mean and StandardDeviation

sensitive to imipenem and meropenem with the highest degree. Aminoglycosides were found to be as efficient as third generation cephalosporins. All Enterobacter spp. bacteriae were found to be sensitive to piperacillin-tazobactam, sulperazon, imipenem, meropenem, amikacin and ciprofloxacin with a rate of 100%. They were found to be sensitive to aminoglycosides with a rate of 60%. Acinetobacter spp. which were isolated only from one hemoculture were found to be resistant to penicilin, aminoglycosides and all cephalosporins. Pseudomonas spp. were found to be sensitive to ciprofloxacin, imipenem, meropenem, sulperazon and piperacillin-tazobactam with the highest degree and resistant to ampicillin, gentamycin, tobramycin, netylmycin, cefotaxim and ceftriaxone. Antibiotic sensitivities of microorganisms are shown in Table 3 and 4.

Table 2: Distribution of microorganisms isolated from hemoculture of term and preterm babies

	Term	Preterm
Number of nasocomial infection episode, n	34	63
Gram positive bacteria	28	44
CNS (n, %)	26 (76.5)	38 (60.3)
Staphylococcus aureus (n, %)	2 (5.9)	6 (9.5))
Gram negative bacteria (n, %)	6	19
K. pneumonia (n, %)	3 (8.8)	13 (20.6)
Enterobacter spp. (n, %)	1(2.9)	4 (6.4)
P. aeruginosa (n, %)	2 (5.9)	1(1.6)
Acinetobacter spp. (n, %)	[a]	1(1.6)

[a] Hemoculture was negative in term babies

CNS: Coagulase negative staphylococcus

In the univariate analysis of term and preterm babies, period of hospitalization, mechanical ventilation and presence of cathether were found to be significant risk

Table 3 Antibiotic sensitivity of gram positive microorganisms isolated in hemoculture:

	Staphylococcus aureus (n:8) sensitivity (n, %)	CNS (n:64) sensitivity (n, %)
Beta-lactams		
Penicillin	0	0
Ampicillin	0	0
Oxacillin	3 (37.5)	12 (18.8)
Amoxycillin- clavulanic acid	7 (87.5)	32 (50)
Ceftazidime	4 (50)	23 (35.9)
Ceftriaxone	5 (62.5)	38 (59.4)
Imipenem	5 (62.5)	54 (84.4)
Meropenem	7 (87.5	61(95.3)
Non- Beta-lactam		
Amikacin	8 (100)	52 (81,3)
Gentamycin	3 (37.5)	36 (56.3)
Netilmicin	5 (62.5)	38 (59.4)
Ciprofloxacin	4 (50)	34 (53.1)
Clindamycin	4 (50)	40 (62.5)
Erythromycin	4 (50)	19 (29.7)
Trimethoprim sulphametoxasole	7 (87.5)	38 (59.4)
Vancomycin	8 (100)	64 (100)
Teicoplanin	8 (100)	64 (100)
Linezolid	8 (100)	64 (100)

CNS: Coagulase negative staphylococcus

Table 4: Antibiotic sensitivities of gram negative microorganisms

	Klebsiella pneumonia (n:16) sensitivity (n,%)	Enterobacter spp. (n:5) sensitivity (n,%)	Acinetobacter spp. (n: 1) sensitivity (n,%)	Pseudomonas aeruginosa (n:3) sensitivity (n,%)
Beta-lactams				
Ampicillin	3(18.8)	0	0	0
Piperacillin-tazobactam	11(68.8)	5 (100)	1(100)	3 (100)
Sulperazone	10 (62.5)	5 (100)	1(100)	3 (100)
Cefataxim	11(68.8)	4 (80)	0	0
Ceftazidime	10 (62.5)	4 (80)	0	2 (66.7)
Ceftriaxone	13 (81.3)	3 (60)	0	0
Imipenem	16 (100)	5 (100)	1(100)	3 (100)
Meropenem	16 (100)	5 (100)	1(100)	3 (100)
Non-Beta-lactam				
Amikacin	11(68.8)	5 (100)	0	3(100)
Gentamycin	11(68.8)	3 (60)	0	0
Netilmicin	13 (81.3)	3 (60)	0	0
Tobramycin	12 (75)	3 (60)	0	0
Ciprofloxacin	12 (75)	5 (100)	1(100)	3 (100)

factors. In addition, presence of TPN in preterm babies was also found to be a significant risk factor (Table 5). In the multivariate analysis of these risks, OR was found to be 25.2; %95 CI (7.5-84.1) for hospitalization period, 14.2; %95 CI (4.8-42.4) for mechanical ventilation and 2.46; %95 CI (1.19-4.14) for presence of cathether in term babies and these values were found to be significant. In preterm babies, OR was found to be 3.34; %95 CI (1.4-8.0) for hospitalization period, 5.9; %95 CI (2.1-16.4) for mechanical ventilation and 3,1; %95 CI (1.2-4.2) for presence of cathether and these values were found to be significant.

Discussion

Improvement in technical background of neonatal intensive care units, hair-rasing innovations in treatment and practices and increase in experienced labour have led to an increase in chance of survival for small for gestational age babies. However, we face with infections as an important health problem as a result of long hospitalization periods of these babies. The fact that the immune system of preterm and small for gestational age babies is immature cause these infections to have a more severe course and sometimes lead to mass baby deaths. These infections are usually caused by microorganisms resistant to antimicrobial agents. Therefore, hemoculture results and "surveillance" studies are very important in antibiotic selection and planning (6,7).

Different methods are used in "surveillance" studies related to nasocomial bloodstream infection. In many studies, surveillance for nasocomial infection is performed considering the clinical findings and culture results determined by Centers for Disease Control and Prevention for the diagnosis of nasocomial infection (8-10). The most commonly observed nasocomial infections in neonatal intensive care units are bloodstream infections. In some countries, nasocomial bloodstream infections are observed in approximately half of the hospitalized patients and the mortality rate is increased up to 52% (11). The rate of nasocomial infection is reported to be 7% in Europe, 11.4% in USA and 16.7% in Spain (12-14). In the prospective 6-year study performed by Yapıcıoğlu et al. (15), the rate of infection was reported to range between 14% and 29% by years. In our study, the rate of bloodstream infection was found to be 12.1% and it was noted that this rate was lower than the rates reported in the literature. We believe this is caused by the fact that the patients who had negative culture results and who received antibiotics more than 72 hours were excluded from the study. If the patients with suspicious sepsis were included, this rate would be higher than the rates observed in developed countries.

Since patients hospitalized in neonatal intensive care units are mostly preterm babies or small for gestational age babies, interventions, procedures, intubation and mechanical ventilation aiming to continue their vital functions are performed frequently (16). Babazono et al.(17) reported that gestational age, cathether use and mechanical ventilation were related to nasocomial infection in an infection survaillence study which included seven centers. In the prospective study performed by Yapıcıoğlu et al.(18), use of total parenteral nutrition, cathether, ventilator and chest tube were found to be risk factors. In our study, we found that hospitalization period, use of intubation, use of mechanical ventilation and use of cathether were significant risk factors in term and preterm babies who developed nasocomial infection. In contrast to the literature, we found that TPN was not related to nasocomial infection in term babies.

In neonatal intensive care units, nasocomial bloodstream infections are frequently associated with use of cathether (12). In the NNIS (National Nasocomial Infections Surveillance in USA) study, the rate of bloodtream infection caused by use of cathether was found to be 3.5-9.1: 1000 days (19). In the prospective studies performed by Perlman et al. (20) in two NICU's,

Table 5. "Univariate" analysis of risk factors in terms of nasocomial infection in term and preterm babies

	NI present	NI absent	OR (%95 CI)	P
Term babies				
Hospitalization period[a], days	12-42	5-9	1.14 (1.09-1.2)	0.001
Mechanical ventilation[a], days	10-40	1-3	1.07 (1.01-1.1)	0.001
Cathether[a], days	9-19	5-9	1.35 (1.23-1.4)	0.01
TPN[a]	3-5	2-5	0.82 (0.54-1.2)	0.4
Preterm babies				
Hospitalization period[a], days	24-56	13-25	1.09 (1.06-1.12)	0.001
Mechanical ventilation[a], days	8-15	2-7	1.37 (1.26-1.49)	0.001
Cathether[a], days	19-29	7-10	1.32 (1.26-1.49)	0.001
TPN[a], days	33-53	7-14	1.33 (1.22-1.46)	0.001

NI: Nasocomial infection, TPN: Total parenteral nutrition

[a]Median vaues between the 25th and 75th percentile

the rate of cathether related bloodstream infection was found to be 18.5:1000 days in one unit and 13:1000 days in the other unit. Yapıcıoğlu et al.(18) reported the rate of cathether related bloodstream infection to be 14.3: 1000 days. In the USA National Hospital study, the rate of cathether related bloodstream infection was reported to be 7.4-16.1: 1000 days in newborns between 1000 and 2500g for 90th percentile (18). In our study, the rate of cathether related bloodstream infection was found to be 9,6:1000 days. It was noted that this rate was lower than the rate found in the study performed in our country by Yapıcıoğlu et al.(18). It was found that nasocomial infection was observed 2,46 fold more frequently when cathether was used in term babies and 3,1 fold more frequently when cathether was used in preterm babies.

Ventilator related pneumonia (VRP) is commonly observed in NICU's and is even the most commonly observed nasocomial infection in some NICU's. It is one of the most important complications leading to mortality and morbidity in intubated patients and in patients hospitalized for long periods. Limited information about the frequency of VRP, risk factors and outcomes is available. Preterm delivery, repeated intubation and intubation for long periods, genetic diseases and transportation outside the hospital with intubation were reported to be risk factors (21). In the NNIS (National Nasocomial Infections Surveillance in USA) study, the rate of VRP for 2002-2004 was reported to be 1.4-3.5:1000 days (19). Yapıcıoğlu et al. (18) reported the rate of VRP to be 28.1:1000 days in 2008. According to the surveillance report the rate of VRP was reported to be 3.2-8.5:1000 days for the 90th percentile (19). In our study, the rate of VRP was found to be 13.8:1000 days. The rate found in our study was noted to be higher than the 90th percentile which was considered to be the highest value. In another study performed in our country by Yapıcıoğlu et al.(18), a more higher value was found. We believe this is related to the fact that our unit has a high patient load and nurse-patient ratio is low. However, we think that more accurate conclusions can be drawn as a result of large studies aiming to decrease VRP in NICU's.

Microorganisms causing bloodstream infection in neonatal intensive care units vary in time and from unit to unit. Currently, gram-negative agents are usually found in developing countries and coagulase negative staphyloccocci are reported to be more frequently found in developed countries (22-24). Efird et al. (10) reported that CNS was the most commonly isolated microorganism and K. Pneumonia was the second most commonly isolated microorganism in eight NICU's in USA. Couto et al. (25) reported that K.pneumonia was the leading causative agent (26.6%) and CNS was the second most commonly isolated microorganism (20.8%) in their 10 years prospective cohort study including six neonatal units. Macharashvili et al. (23) reported that gram negative bacteriae were isolated with a rate of 78% (most commonly K.pneumonia) and gram positive bacteriae were isolated with a rate of 22% (most commonly Staphylococcus aureus) in two NICU's in Georgia during a period of one year. In the study performed by the Turkish Neonatology Association including 22 centers 19 of which were university centers, nasocomial infections were reported to be caused by gram positive bacteriae with a rate of 45.5% and gram negative bacteriae with a rate of 42.9% (26). Yalaz et al. (27) reported that coagulase negative staphylococci were isolated with a rate of 31.3%, Staphylococcus aureus was isolated with a rate of 13% and K. Pneumonia was isolated with a rate of 10.5% from hemoculture in patients with a diagnosis of nasocomial infection in NICU's. In our study, the most commonly isolated agent was coagulase negative staphylococcus and the second most commonly isolated agent was K.pneumonia in preterm and term babies with a positive hemoculture, as observed in developed countries.

Recently, increases in the rates of gram positive and gram negative bacilli have been noted. The resistance of gram positive bacteriae against vancomycin and meticillin and the resistance of gram negative bacteriae against third generation cephalosporins have led to significant concern in terms of antibiotic selection. Resistance against third generation cephalosporins develops more rapidly in the presence of combination of penicilin and an aminoglycoside (24, 28). Aurangzeb et al. (29) reported that gram negative microorganisms in NICU's were resistant to ceftazidime with a rate of 19.4% and resistant to cephotaxim with a rate of 44.8%. In our study, enterococci resistant to vancomycin were not isolated. Staphylococcus aureus and coagulase negative staphylococcus were found to be sensitive against vancomycin, teicoplanin and amikacin with a rate of 100%. Pseudomonas aeruginosa and Acinetobacter spp. had the highest resistance against the third generation cephalosporins and K.pneumonia and Enterobacter spp. had a lower resistance aginst the third generation cephalosporins. We believe that the lower antibiotic resistance in our unit compared to the rates reported in the literature is caused by limited use of glycopeptide and third generation cephalosporins in our unit.

Conclusion

It was found that there was no difference between preterm and term babies in terms of distribution of microorganisms and mortality, coagulase negative staphylococci were the most commonly isolated agent for bloodstream infection in our unit and gram positive cocci did not develop resistance against glycopeptide. While hospitalization period, mechanical ventilation and cathether use were significant risk factors for term and preterm babies, TPN was not found to be a risk factor in term babies.

Conflict of interest: None declared.

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