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Positive Blood Cultures for Coagulase-Negative Staphylococci in Neonates: Does Highly Selective Vancomycin Usage Affect Outcome?

Summary: The implication of highly-selective vancomycin usage on the outcome for infants with positive blood cultures for coagulase-negative staphylococci (CONS) was assessed retrospectively. The analysis was performed on partly prospective collected data from infants under 3 months of age with a least one CONS-positive blood culture in the neonatal intensive care unit at the Soroka University Medical Center between 1990 and 1996. During the study period, 239 episodes of CONS-positive blood cultures were identified from among 64,226 live births (3.7 per 1,000). Vancomycin was administered in 22 (9%) episodes, in all cases only after identification of the bacteria. The remaining 217 episodes were managed either without antibiotics or with continuation or initiation of empiric antibiotic therapy (usually ceftazidime ± ampicillin) for suspected sepsis. Severity of the initial illness, subsequent morbidity and mortality were low regardless of the treatment administered. Only a single case of a blood-borne vancomycin resistant gram-positive organism was observed during the study period. The approach to CONS-positive blood cultures in neonates used here was associated with low morbidity and mortality. These findings support a policy of highly selective vancomycin usage in an era of emerging vancomycin resistance.

Introduction

In the past decade, coagulase-negative staphylococci (CONS), once thought to be non-pathogenic commensals, have emerged as important pathogens in the neonatal period and currently represent the most common cause (up to 31%) of late-onset nosocomial septicemia in neonatal intensive care unit (NICU) patients [1–5].

Factors which have contributed to the apparent increase in the incidence of CONS bacteremia include increased survival of very premature immunocompromised infants who spend long periods of time in the NICU, require many invasive procedures, and frequently receive intravenous alimentation and multiple courses of antibiotic therapy [6, 7]. All of the above have been shown to be risk factors for the development of this nosocomial infection [8]. The pathogenic features of infections with CONS are poorly understood [9]. Coagulase-negative staphylococcal infection is associated with low mortality, but significant morbidity [10].

As ubiquitous skin commensals, these organisms are also blood culture contaminants. Consequently, clinicians must determine whether a particular CONS isolate from blood represents a true infection or contamination [2, 4]. Clinical features alone are insufficient to distinguish CONS sepsis from contamination [11]. To date, no generally accepted criteria for the above dilemma have been formulated [12]. According to Centers for Disease Control (CDC) criteria, organisms that are commonly recovered from the skin, such as CONS, should be considered contaminants unless bacteremia is associated with clinical findings, positive cultures from other body sites, or at least two positive blood cultures with identical CONS organisms [13].

Vancomycin remains the mainstay of therapy for CONS infections because many strains are resistant to methicillin and all other β-lactam drugs [10, 14, 15]. Furthermore, even when susceptibility is reported for some β-lactam antibiotics, such as cephalosporins, a poor clinical response of CONS infections to these drugs has been observed [7, 16]. Therefore, although the effect of vancomycin therapy on morbidity and mortality rates is unknown, many neonatologists now routinely treat CONS bacteremia with vancomycin, sometimes as empirical antibiotic therapy for suspected sepsis, and even as prophylaxis in high-risk patients [7, 10]. A major problem with the strategy mentioned above is the recent emergence of resistance to vancomycin in gram-positive bacteria which is now recognized worldwide [17].

In view of the fear of emergence of vancomycin-resistant pathogens on the one hand and the difficulties of distinguishing between a contaminant and true pathogen in regard to CONS on the other, the policy of empirical antibiotic treatment for suspected sepsis adopted in our neonatal intensive care unit over a decade ago does not include vancomycin. Furthermore, vancomycin is only administered to infants in whom the diagnosis of a true CONS sepsis has been made, based on two consecutive positive blood cultures with identical antibiotic susceptibility pat-

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terns or a single positive blood culture associated with the presence of risk factors such as indewelling central venous catheter or ventriculo-peritoneal shunt.
The present study was conducted to assess retrospectively the implication of the above strategy on the outcome for neonates with CONS-positive blood cultures in our institution.

Patients and Methods

Background: The Soroka University Medical Center is the only general medical center of the southern region of Israel (the Negev) and provides full secondary and tertiary health services to the entire population of the area (450,000 inhabitants in 1996). Three-quarters are Jews and one quarter are Bedouin Arabs.
The average annual number of deliveries for the study period was 9,800, of whom 55% were Jews and 45% were Bedouins. The neonatal service consists of a 108-bed unit for healthy neonates, 32-bed special care unit, and 24-bed neonatal intensive care unit (NICU). The NICU and neonatal special care unit together admit 1,200 to 1,500 infants annually.
Study population and clinical methods: Data were collected prospectively during the period from 1 January 1990 through 30 April 1996 in the neonatal department. All CONS-positive blood cultures during that period were identified, the clinical features of the patients were immediately investigated, and the following data were recorded: admission date, postnatal age at time of positive blood culture, time to positive blood culture, antibiotic susceptibility patterns, clinical diagnosis, whether the CONS isolates were considered by the attending neonatologist to represent true sepsis and whether the infant died during the episode.
Inclusion criteria to the retrospective analysis were: age up to 3 months and hospitalization in the NICU or the special care unit at the time of CONS-positive blood culture. Two groups of infants were sampled. The first contained all infants in whom CONS isolates were considered by the attending neonatologist to represent true CONS sepsis, and all infants who died during the episode. The second group consisted of a 50% sample of infants in whom CONS isolates were considered by the attending neonatologist to represent contamination.
Medical charts of infants included in the study were reviewed retrospectively, and additional data were collected: ethnic origin, Apgar score, birth weight, gestational age, neonatal underlying disease, history of mechanical ventilation, presence of indewelling catheter (umbilical catheters, central venous line or ventriculo-peritoneal shunt), parenteral lipid administration, previous antibiotic therapy, surgical procedures, clinical and laboratory characteristics at start of episode, number of CONS-positive and negative blood cultures during the episode, the treatment that was adminstered, and the outcome during the 10 days from the first CONS-positive blood culture.

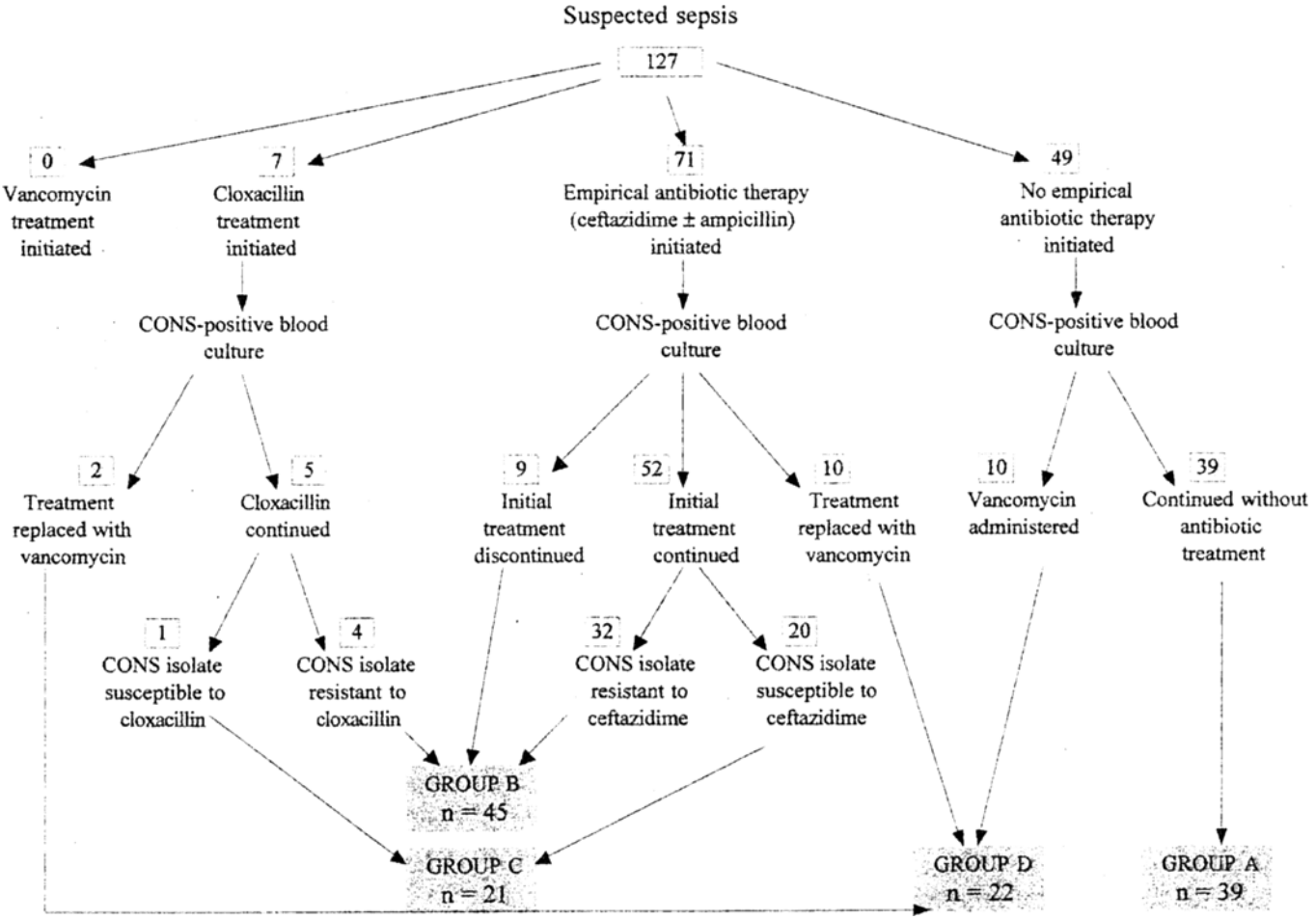

Figure 1: Management of 127 neonatal intensive care unit (NICU) patients with suspected sepsis in whom a blood culture was positive for coagulase-negative staphylococci (CONS).

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An episode was defined as all blood cultures that were drawn from a patient during 7 days from the first CONS-positive blood culture. CONS isolates that were recovered from a patient > 7 days apart were defined as being from independent episodes.

Abnormal hematological values were defined by one or more of the following: white blood cell count of > 20,000/mm^3 or < 5,000/mm^3; > 1,500 immature neutrophils (left shift); immature to total neutrophil ratio greater than 0.2; or platelet count of < 100,000/mm^3.

The policy of empirical antibiotic treatment for suspected sepsis adopted in the NICU consisted of ceftazidime alone during 1990–1991 and ceftazidime and ampicillin since 1992 for both early and late onset sepsis (a combination that usually does not give appropriate coverage against CONS isolates). In 1996, imipenem was administered for 6 months as empirical treatment due to a cluster of sepsis cases caused by multiresistant *Klebsiella*. Infants treated with imipenem during this period were excluded from the analysis.

The empirical antibiotic protocol was replaced by vancomycin when a neonatologist or pediatric infectious disease consultant decided that the CONS-positive blood cultures represented true sepsis. The diagnosis was based on two consecutive positive blood cultures with identical antibiotic susceptibility patterns or a single positive blood culture associated with the presence of risk factors such as indwelling central venous catheter or ventriculoperitoneal shunt. Four approaches were identified following the growth of CONS in a blood culture (Figure 1): Group A: patients who received no antibiotic treatment during the episode; Group B: patients who received inadequate antibiotic therapy (i. e., drugs to which the CONS isolate was found to be resistant or drugs to which the CONS isolate was found to be susceptible but the duration of treatment was ≤ 3 days); Group C: patients who received antibiotic treatment other than vancomycin to which the CONS isolate was found to be susceptible, and the duration of treatment was ≥ 4 days; Group D: patients who received vancomycin during the episode.

We assumed that vancomycin is the drug of choice against CONS isolates that are resistant to β-lactam antibiotics and thus, if a CONS-positive blood culture represented true sepsis, then groups A and B received inappropriate treatment. As for group C, although it has been reported that a routine test can show a strain to be susceptible to cephalosporin *in vitro*, it is in fact resistant *in vivo* [15]. However, we could not exclude that the outcome was affected, at least in part, by this treatment.

Four different outcomes were observed during the 10 days of follow-up: 1) total recovery, 2) clinical and bacteriological recovery together with development of another medical problem during the follow-up period, 3) persistent clinical problems, i. e., continuation of symptoms that were present at the time the clinical signs of sepsis appeared, 4) death during the follow-up period.

Microbiologic methods: Blood samples for cultures were obtained using standard aseptic techniques with inoculation into sterile vacuum bottles. All samples underwent a routine blood culture using the BACTEC system (Becton Dickinson, Cockeysville, MD, USA), model 460, until 1991 and model 660 NR thereafter. Positive blood culture bottles were Gram stained and subcultured onto trypticase-soy agar with 5% added sheep blood and chocolate agar media. They were then characterized as coagulase-pos-

Table 1: Characteristics of infants with coagulase-negative staphylococci-positive blood cultures: comparison between vancomycin treatment group and all other groups combined.

	Vancomycin treatment (n = 22)	Treatment other than vancomycin (n = 105)	P
Baseline characteristics (mean ± SEM)			
Birth weight (g)	1,294 ± 134	1,505 ± 79	0.255
Gestational age (wk)	30 ± 0.69	31 ± 0.43	0.13
Apgar 1 min/5 min	6 ± 0.4/8.8 ± 0.2	6 ± 0.2/8.8 ± 0.1	0.9/0.8
Hospitalization before episode (days)	28 ± 5	20 ± 1.6	0.084
Risk factors			
History of catheters (%)	18/21 (86%)	73/105 (69%)	0.13
Catheters at time of episode (%)	4/18 (22%)	18/104 (17%)	0.73
Duration of catheter use (days/mean ± SEM)	10 ± 4.8	4.8 ± 0.7	0.26
History of parenteral lipids (%)	20/20 (100%)	73/104 (70%)	0.0048
Parenteral lipids at time of episode (%)	20/20 (100%)	66/104 (63%)	0.001
Duration of parenteral lipids (days/mean ± SEM)	26 ± 4.9	14 ± 1.4	0.003
History of antibiotic treatment (%)	18/20 (90%)	67/103 (65%)	0.027
Antibiotic treatment at time of episode (%)	1/20 (5%)	3/103 (3%)	0.51
Duration of antibiotic treatment (days/mean ± SEM)	9.7 ± 1.8	6.1 ± 0.7	0.038
History of ventilation (%)	17/22 (77%)	69/105 (66%)	0.29
Ventilation at time of episode (%)	2/22 (9%)	13/105 (12%)	0.49
Duration of ventilation (days/mean ± SEM)	6.2 ± 1.3	3.9 ± 0.7	0.18
Microbiologic characteristics			
Number of positive blood cultures (mean ± SEM)	2.4 ± 0.3	1.2 ± 0.04	0.001
Time to positive culture ≤ 2 days (%)	19/21 (90%)	63/102 (62%)	0.022
Methicillin-resistant CONS (%)	21/22 (95%)	66/102 (65%)	0.004
Multiresistant CONS (%)	20/22 (91%)	51/102 (50%)	0.0004

CONS = coagulase-negative staphylococci.

Table 2: Clinical and laboratory characteristics of infants with coagulase-negative staphylococci-positive blood cultures: comparison between vancomycin treatment group and all other groups combined.

	Vancomycin treatment (n = 22)	Treatment other than vancomycin (n = 105)	OR (CI)
Clinical characteristics			
Hyperthermia	5/21 (24%)	16/105 (15%)	1.74 (0.48–6.06)
Hypothermia	0/21 (0%)	1/105 (1%)	–
Apnea/bradycardia	14/21 (67%)	49/105 (47%)	2.29 (0.78–6.78)
Convulsion	0/21 (0%)	0/105 (0%)	–
Irritability	2/21 (10%)	6/105 (6%)	1.74 (0.22–10.73)
Lethargy	5/21 (24%)	29/105 (28%)	0.82 (0.24–2.68)
Abdominal distension	3/21 (14%)	23/105 (22%)	0.59 (0.13–2.41)
Hypotension	0/21 (0%)	1/105 (1%)	–
Suspected focal infection	3/21 (14%)	12/105 (11%)	1.29 (0.26–5.68)
Laboratory characteristics			
Abnormal white blood cell count	6/20 (30%)	26/100 (26%)	1.22 (0.37–3.88)
Shift to the left	7/17 (41%)	31/100 (31%)	1.56 (0.48–5)
Abnormal immature neutrophil/ total neutrophil ratio	7/17 (41%)	45/100 (45%)	0.88 (0.27–2.70)
Thrombocytopenia	2/20 (10%)	8/101 (8%)	1.29 (0.18–7.49)

OR = odds ratio; CI = confidence interval.

itive or negative by the DNAse test and confirmed by the Staphy-Tec plus kit (Oxoid Diagnostic Reagents, Hampshire, England). If two CONS isolates had the same antibiotic susceptibility patterns, their biochemical profile was determined by the Appi-Strip system (BioMérieux, Marcy L'Etoile, France). All isolates which were considered to represent true CONS sepsis were stored on stock agar for a few months.

Susceptibility to antimicrobial agents was determined by disk diffusion method. Each isolate was tested against: oxacillin, cefuroxime, ceftriaxone, tetracycline, gentamicin, erythromycin, clindamycin, vancomycin, ciprofloxacin, and fusidic acid. For the purpose of this report, multiple antibiotic resistance was defined as resistance to methicillin and two antibiotics other than a β-lactam drug.

Susceptibility patterns of all gram-positive blood isolates obtained from NICU patients during the study period were recorded in order to determine the occurrence of vancomycin resistance among them.

Data analysis: Proportions of non-continuous variables were compared by Pearson Chi-square analysis or the Fisher's exact test, as needed. Continuous variables were compared by independent-sample Student's t-test. In those cases where Levene's test for equality of variances showed the variables to be not normally distributed ($P < 0.05$) the comparison was made using the t-tests for unequal variances. Stepwise logistic regression analysis was performed to identify variables discriminating between the vancomycin treatment and the non-vancomycin treatment groups. Exact P values are provided in the tables, with $P \leq 0.05$ considered statistically significant. Two-tailed tests were used throughout.

Results

During the study period (6 years and 4 months), 64,226 live births were recorded. Coagulase-negative staphylococci were isolated from 286 blood cultures obtained from 214 infants under 3 months of age hospitalized in the NICU, representing 239 different episodes of CONS-positive blood cultures. The above figures correspond to an incidence of 3.7 episodes per 1,000 live births.

Medical charts of 104 (47.5%) infants who represented 127 (53%) episodes with a total of 183 CONS-positive blood cultures were reviewed retrospectively. Those episodes included all 22/239 (9%) episodes in which CONS isolates were considered by the attending neonatologist to represent true sepsis and a sample of 105/207 (51%) episodes in which CONS isolates were considered by the neonatologists to represent contamination. A total of 10 (4%) episodes in which the CONS isolates were considered to represent contamination were excluded since the infants received imipenem as empirical treatment. Medical records for all 4 (1.7%) cases of death during the study period were available for review. Fifteen (14%) patients had two different episodes and four (4%) patients had three different episodes during their hospitalization. Fifty-six (54%) of all patients were male.

Of 127 episodes, 71 (56%) received initial empirical antibiotic treatment including ceftazidime with or without ampicillin, six received clindamycin in addition for suspected necrotizing enterocolitis (NEC), 49 (39%) did not receive initial empirical antibiotic treatment, seven (5%) received treatment with cloxacillin due to suspected focal infection, and none received vancomycin as empirical treatment. After culture results, therapy was adjusted as shown in Figure 1. Thirty-nine infants received no treatment during the episodes (Group A); 45 infants received inadequate antibiotic therapy (Group B); 21 infants received antibiotic treatment to which the CONS isolate was found to be susceptible and the duration of treatment was ≥ 4 days (Group C), and 22 infants received vancomycin during the entire episode (Group D).

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Table 3: Outcome for infants with coagulase-negative staphylococci-positive blood cultures: comparison between vancomycin treatment group and other groups.

Outcome	No treatment* (n = 84)	Treatment other than vancomycin (n = 21)	Vancomycin treatment (n = 22)
Cure	67 (80%)	19 (90%)	17 (77%)
Persistent medical problems not related to CONS	13 (16%)	2 (10%)	4 (18%)
Persistent medical problems where relation to CONS could not be ruled out	1 (1%)	0	0
Death not related to CONS	1 (1%)	0	1 (5%)
Death where relation to CONS could not be ruled out	2 (2%)	0	0

CONS = coagulase-negative staphylococci; * = group A and B, patients who received no antibiotic treatment or inadequate treatment against CONS during the episode.

The characteristics of the vancomycin-treated group (Group D) versus those of the groups who did not receive vancomycin (Groups A to C) are shown in Table 1. By univariate analysis, it can be seen that the vancomycin-treated group was notable for more infants receiving parenteral nutrition with lipids either before or during the episode, longer duration of exposure to parenteral nutrition with lipids, more infants receiving antibiotic treatment before the episode, longer prior exposure to antibiotics, more positive blood cultures, shorter time to positive blood culture, and for the presence of methicillin-resistant and multiresistant CONS isolates. Multiple logistic regression analyses showed the number of positive blood cultures ($P < 0.001$) and the multiresistance of CONS isolate ($P < 0.05$) to be highly significant independent variables for administration of vancomycin treatment.

No differences were found between the groups in birth weight, gestational age, Apgar score, duration of hospitalization before the episode, exposure to intravascular catheters, ventilator use, time to positive culture, and the time from the presence of one of the risk factors (indwelling catheters, parenteral nutrition, antibiotic course, and ventilator use) to the episode.

The clinical and laboratory characteristics including temperature instability, apnea/bradycardia, irritability, lethargy, abdominal distention, focal infection, and hematological data of the infants from whom CONS were isolated were examined; no single clinical sign or laboratory finding was found to be significantly associated with the decision to use vancomycin (Table 2).

During the 10 days of follow-up from the first CONS-positive blood culture, no difference was found between the groups in terms of morbidity and mortality (Table 3). Of 84 episodes in groups A and B combined, 67 (80%) totally recovered. In 14 (17%) infants, cure was not observed during the follow-up period, but in 13 of them the cause was definitely not CONS-related, and one infant developed cellulitis of the arm 4 days after start of the episode, and relation to CONS could not be ruled out. Of these 14 episodes, seven (50%) totally recovered both clinically and bacteriologically, but during the follow-up period developed another medical problem. The other seven recovered bacteriologically, but continued to be ill due to an underlying disease or to sepsis from another microorganism (Table 4).

Of the infants not treated with vancomycin, three died during the follow-up period. The first was a premature infant (32 weeks of gestation, birth weight 2,660 g) with nesidioblastosis (diffuse pancreatic islet cell hyperplasia) and recurrent hypoglycemic attacks which required high glucose intake via a central line and had to undergo pancreatectomy. On day 18 of life, the infant developed fever with two CONS-positive blood cultures with the same antibiotic-susceptibility pattern. Although according to the NICU policy, this infant should have received vancomycin at that point, the inital empirical antibiotic treatment (including ceftazidime and cloxacillin) was not replaced, and the infant died the next day. No explanation was found in the infant's medical chart as to why vancomycin was not administered. The second infant was a premature infant (29 weeks of gestation, birth weight 800 g) who on day 30 of life developed a clinical appearance of NEC with a single CONS-positive blood culture and in whom empirical antibiotic treatment (including ceftazidime, ampicillin, and clindamycin) was not replaced by vancomycin. Two days later the infant died. In both cases, no additional blood cultures were taken and post mortem examination was not performed, so relation to CONS could not be ruled out. The third was a severely premature infant (28 weeks of gestation, birth weight 808 g) with congenital hydrocephalus, apnea of prematurity, and severe respiratory distress syndrome who on day 30 of life had clinical evidence of respiratory failure with a single CONS-positive blood culture for which no treatment was administered. The infant died on the same day, post mortem examination was not performed, but relation to CONS could

Table 4: Clinical manifestations of infants with CONS-positive blood cultures who had persistent medical problems during the follow-up period.

Treatment group	Episode number	Time after start of episode (days)	Clinical problem	Microorganism isolated
Group A	19	7 days	Suspected sepsis	None
	20	7 days	Suspected NEC	None
	21	5 days	Suspected NEC	None
	33	3 days	Suspected NEC	None
	43	5 days	Urinary tract infection	*Escherichia coli* (urine)
	53	Entire F/U period	Apnea of prematurity	None
	54	Entire F/U period	Apnea of prematurity	None
	59	Entire F/U period	VSD and PDA	None
	96	Entire F/U period	VSD and PDA	None
	88	Entire F/U period	Surgery for transposition of great arteries	None
Group B	106	4 days	Cellulitis of left arm	None
	50	Entire F/U period	Jejunal atresia	None
	17	5 days	NEC	*Escherichia coli* (blood)
	89	Entire F/U period	NEC	*Klebsiella* and *Enterobacter* (peritoneal fluid)
Group C	113	Entire F/U period	Suspected sepsis	*Klebsiella* (blood)
	12	Entire F/U period	Respiratory failure	Measles virus (throat)
Group D	98	3 days	Urinary tract infection	*Klebsiella* (urine)
	56	Entire F/U period	Heart failure (persistent fetal circulation)	None
	117	Entire F/U period	Apnea of prematurity	None
	125	Entire F/U period	Heart failure (fetofetal transfusion)	None

NEC = necrotizing enterocolitis; VSD = ventricular septal defect; PDA = patent ductus arteriosus; F/U = follow-up.

be ruled out due to the presence of severe underlying disease and lack of clinical and laboratory signs of sepsis.

Of 21 episodes in group C, 19 (90%) totally recovered, two (10%) were not cured during the follow-up period, but the cause was definitely not CONS-related (Table 4). Of 22 episodes from group D, 17 (77%) totally recovered, four (18%) were not cured during the follow-up period, but the cause was definitely not CONS-related (Table 4). One infant in this group died during the follow-up period, a premature infant (30 weeks of gestation, birth weight 948 g) who on day 34 of life developed clinical appearance of NEC with a single CONS-positive blood culture and in whom empirical antibiotic treatment was replaced by vancomycin. In this case, post mortem examination was performed and revealed no evidence of DIC or NEC, and the cause of death was determined as respiratory failure. Relation to CONS could be ruled out.

The total case fatality rate in this study was 4/239 (1.7%). However, when excluding the non-CONS-related cases, the fatality rate was 2/239 (0.8%).

During the study period, a total of 532 blood cultures obtained from NICU patients yielded a gram-positive isolate. Of those, 56 (11%) were enterococci and only one isolate (detected in 1993) was vancomycin resistant (0.2%). All non-enterococcal isolates were vancomycin susceptible.

Discussion

The policy of highly-selective vancomycin usage in infants with CONS-positive blood cultures adopted in our NICU was associated with low morbidity and mortality.

Potential limitations of the current study include the relatively small size of the vancomycin treatment group and the partially retrospective study design. Nevertheless, we believe that since ethical limitations will never permit a similar prospective randomized study, ours is important because it describes an approach which enables us to selectively treat patients with CONS-positive blood cultures without compromising outcome. However, since this selection relies heavily on the clinician's judgement, we could not develop a firm algorithm recommending a strict approach to such infants. We believe that despite this limitation, in view of the emerging vancomycin resistance among gram-positive organisms in intensive care units, more NICUs should adopt our approach weighing the low potential risk of missing a case of true CONS sepsis against the risk of increasing vancomycin resistance.

Our data are in the range found by other investigators who reported that only 4.1–26% of patients whose blood cultures were positive for CONS met criteria for septicemia [1, 18–20]. In the current study, the clinicians decided in 22/239 (9%) episodes that CONS-positive blood cultures represented true septicemia, and in these cases vancomy-

cin was administered. The decision to give vancomycin was found to be based mainly on microbiological characteristics and presence of risk factors for CONS sepsis rather than on the basis of clinical or laboratory manifestations.

Nataro et al. have previously demonstrated that no single clinical sign was associated with CONS infection and that hematologic data were generally not helpful in distinguishing between infection and contamination [9]. Other studies reported the usefulness of complete blood cell count, differential count, and platelet count in the identification of infants with CONS infection [21, 22]. In the present study, no differences were found between the groups in clinical presentation, severity of initial illness, and hematological data.

Appropriate and early antibiotic treatment was reported to reduce mortality associated with neonatal bacteremia [23]. Thus, it has been suggested that management of patients suspected of bacteremia and at high risk for staphylococcal infections should include an anti-staphylococcal drug. *St. Geme* et al. have recommended initial empiric therapy with vancomycin for hospitalized infants at risk for CONS-infections [7]. In the present study, vancomycin was administered only after identification of CONS and not as empirical therapy for suspected sepsis. This allowed us to assess our approach retrospectively, having a large comparison group of infants who received inadequate treatment against CONS whose baseline characteristics (such as birth weight, gestational age, Apgar score, etc.) were similar to those who received vancomycin.

We found that morbidity and mortality were low regardless of the treatment that was administered. During the study period, the incidence of CONS-positive blood cultures among NICU patients was 3.7 per 1,000 live births and case fatality rate was 0.8% or less. By comparison, the incidence of neonatal sepsis from all other pathogens in our institution during approximately the same period was 3.2 per 1,000 live births, and the case fatality rate was 14% in general and 26% for very low birth weight infants [24]. The same trend was found when mortality in sepsis in general and in CONS sepsis in particular was compared, in published series both in the United States and in Europe [25–28]. The difference in mortality rate between cases of proven sepsis with other pathogens and our CONS-positive cases may either indicate that most of the cases from whom CONS were isolated did not represent true sepsis (in other words: they could represent transient bacteremia or contamination) or that CONS sepsis is associated with low mortality, even when inadequately treated.

As for morbidity, in contrast to our findings other investigators reported that CONS was associated with significant morbidity and often resulted in prolonged hospitalization [10, 27, 28]. This difference probably reflects the difficulty in diagnosis of CONS-sepsis resulting in the lack of homogenicity between study populations. Furthermore, in premature infants with multiple underlying diseases who sometimes go from one medical condition to another and from infection with one microorganism to the other, relation of morbidity and mortality to one specific cause is often difficult to assess.

An increasing rate of vancomycin resistance among gram-positive organisms was recently noticed in many intensive care units [29, 30]. This was especially prominent in enterococci which are well established albeit infrequent pathogens in neonates. These organisms are increasingly found to be resistant to vancomycin: a 20-fold increase in the incidence of such resistance in the United States from 1989 (0.4%) to 1995 (10%) was recently reported by the CDC [29]. Transfer of vancomycin resistance genes from enterococci to other organisms, especially to staphylococci, has been demonstrated *in vitro* [10, 31]. It is currently not uncommon to see CONS strains in the neonatal intensive care unit that are susceptible only to vancomycin and the possible emergence of vancomycin-resistant strains represents a frightening scenario [10]. The recently reported first isolate of *Staphylococcus aureus* with reduced susceptibility to vancomycin further increased the above-described fear [32]. During the study period, only a single case of a blood-borne vancomycin-resistant gram-positive organism (*Enterococcus* detected in 1993) has been observed in our NICU (0.2%). By comparison, from yet unpublished data, overall incidence of vancomycin-resistant enterococci in other departments within our institution reached 24% in 1996.

Excessive usage of vancomycin and cephalosporins is considered to be a potential risk factor for the emergence of vancomycin-resistant enterococci. Consequently, widespread and prolonged therapy with these antibiotics should be avoided when possible in order to minimize the spread of vancomycin resistance [29, 30, 33]. Thus the policy of highly selective vancomycin usage for infants with CONS-positive blood cultures adopted in our NICU has probably contributed to the very low incidence of vancomycin-resistance in gram-positive organisms to date.

We believe that the decision to administer vancomycin cannot rely solely on a single blood culture. Strict adherence to diagnostic criteria for CONS sepsis and highly selective vancomycin usage are justified in view of the low morbidity and mortality and low rate of vancomycin resistance in gram-positive organisms associated with such a policy in our NICU.

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