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Duration of vancomycin treatment for coagulase-negative *Staphylococcus* sepsis in very low birth weight infants

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Coagulase negative *Staphylococcus* (CoNS) is the major causative pathogen of late-onset sepsis in very low birth weight (VLBW) infants.
- Nearly all VLBW infants with CoNS sepsis are treated with vancomycin.
- Vancomycin is associated with a risk of toxicity and resistance but there are no guidelines regarding the duration of its use in this setting.

WHAT THIS STUDY ADDS

- Treatment with vancomycin for 5 days after the last positive blood culture is associated with a satisfactory outcome when there is no evidence of endovascular thrombi or infective endocarditis.
- Prolonged treatment with vancomycin is not associated with adverse effects.
- Further well-controlled prospective studies are needed.

AIM

Vancomycin is widely used to treat late onset coagulase-negative *Staphylococcus* (CoNS) sepsis in very low birth weight (VLBW) infants. Although vancomycin is associated with a risk of toxicity and bacterial resistance, the appropriate duration of use has not been established. This study sought to investigate the association between the duration of vancomycin therapy and clinical outcome in VLBW infants with CoNS sepsis.

METHODS

The files of all VLBW infants treated for CoNS sepsis at a tertiary paediatric medical centre from 1995–2003 were reviewed for clinical data, laboratory variables and outcome. Only patients with two positive diagnostic blood cultures were included. The findings were analyzed by duration of vancomycin treatment after the last positive blood culture.

RESULTS

The study cohort included 126 infants, 48 treated for 5 days, 32 for 6–7 days, 31 for 8–10 days and 15 for >10 days. There were no differences among the groups in perinatal characteristics, central catheter dwell time, laboratory data including haematologic, renal and liver function tests, or rate of complications of prematurity. Five infants were diagnosed with infective endocarditis or aortic thrombi and were treated for >10 days. CoNS sepsis recurred in two infants (1.6%). No toxicity of vancomycin treatment was observed.

CONCLUSIONS

In VLBW infants with uncomplicated CoNS sepsis, treatment with vancomycin for 5 days after the last positive blood culture appears to be associated with a satisfactory outcome and no adverse effects. A well-controlled prospective multicentre study is needed to confirm these findings.

Introduction

Late-onset neonatal sepsis (LOS), in which symptoms are delayed beyond 72 h of age [1, 2], is a major cause of morbidity and mortality in very low birth weight (VLBW) infants [2, 3]. The rate of occurrence of LOS is inversely related to birth weight (BW) and gestational age (GA) and 43–51% of infants of less than 28 weeks' gestation are affected [1, 2, 4]. Coagulase-negative *Staphylococcus* (CoNS) is the predominant causative pathogen of LOS in VLBW infants. CoNS infection has been steadily increasing over the last three decades [5] and is currently responsible for 40–65% of cases of LOS [6–17].

Because CoNS is commonly resistant to oxacillin, nearly all episodes of CoNS sepsis in VLBW infants are currently treated with vancomycin. However, there is no consensus regarding the duration of treatment [13]. Given the risks of vancomycin-induced nephrotoxicity and ototoxicity and of enterococcal vancomycin resistance, it is of utmost importance that guidelines be established. The objective of the present study was to investigate the association of the duration of vancomycin therapy for CoNS sepsis with clinical outcome in VLBW infants.

Methods

Setting and patients

The present retrospective study was conducted in the Neonatal Intensive Care Unit (NICU) of Schneider Children's Medical Center of Israel, a tertiary university-affiliated hospital. The study was approved by the Institutional Research Ethics Board.

Included were all VLBW (<1500 g) infants born between January 1 1995 and January 31 2003 who had CoNS sepsis. For diagnosis of CoNS sepsis, The Vermont Oxford Network Database [18] requires positive microbial growth on one or more bloodstream cultures with accompanying clinical signs. In the present study, we used a more stringent definition of a minimum of two positive blood cultures for CoNS within 72 h with identical antibiotic susceptibilities. Exclusion criteria were only one positive blood culture, death during the disease course, initial treatment with an antibiotic other than vancomycin, presence of polymicrobial infection and change in treatment to oxacillin according to CoNS sensitivity. In infants with more than one episode of CoNS sepsis, we referred only to the first episode. Complicated CoNS sepsis was defined as organ involvement such as endovascular disease, endocarditis and osteomyelitis.

Work-up and treatment procedure

In patients with suspected CoNS infection, sepsis work-up consisted of cerebrospinal fluid culture, urine culture and blood cultures (at least 1 ml blood), one from a peripheral vein and one from the central venous catheter, if present. Venous blood was obtained aseptically and processed with the Bactec-450 system throughout the study period. Identification of microbial growth and determination of antimicrobial susceptibility by the disk diffusion technique were performed according to the criteria of the National Committee for Clinical Laboratory Standards, with the recommended media and standard control strains.

Empirical therapy for LOS changed during the study period. Before January 2001, ceftazidime and amikacin were administered and metronidazole was added in patients with abdominal involvement. All drugs were delivered by i.v. infusion using a syringe pump. Ceftazidime, 30 mg kg^{-1} per dose, was delivered over 30 min. For infants born at 29 weeks gestation or earlier, the dosing interval was 12 h during the first 28 days and 8 h thereafter, for infants born between 30 and 36 weeks, the interval was 12 h during the first 14 days and 8 h thereafter and for infants born after 37 weeks, the interval was 12 h in the first 7 days and 8 h thereafter. Amikacin was delivered over 30 min. For infants born at 29 weeks' gestation or earlier, amikacin 18 mg kg^{-1} was administered at 48 h intervals during the first 7 days, followed by 15 mg kg^{-1} administered at 36 h intervals on days 8 to 28 and thereafter at 24 h intervals, for infants born between 30–34 weeks, 18 mg kg^{-1} was administered at 36 h intervals for the first 7 days followed by 18 mg kg^{-1} administered at 24 h intervals and for infants born after 34 weeks, 15 mg kg^{-1} was administered at intervals of 24 h [19].

From February 2001 onward, amikacin and piperacillin-tazobactam were used for empirical treatment. Vancomycin was added in patients who had a central venous catheter (CVC) for more than 10 days or whenever the skin was the suspected source of infection. As soon as a positive CoNS culture was obtained, all other antibiotics were discontinued and the CVC was removed. Additional work-up for infants with three or more positive blood cultures for CoNS included echocardiography, brain and abdominal ultrasound, and echo-Doppler of the great vessels. Piperacillin-tazobactam, 100 mg kg^{-1} per dose, was administered as the piperacillin component by i.v. infusion over 30 min using a syringe pump. For infants born at 29 weeks or earlier, the dosing interval was 12 h during the first 28 days and 8 h thereafter, for infants born between 30 and 36 weeks, the interval was 12 h during the first 14 days and 8 h thereafter and for infants born after 37 weeks, the interval was 12 h during the first 7 days and 8 h thereafter. Vancomycin, 10 mg kg^{-1} per dose, was administered by i.v. infusion over 60 min using a syringe pump. For infants born at 29 weeks' gestation or earlier, the dosing interval was 18 h during the first 14 days and 12 h thereafter, for infants born between 30 and 36 weeks, the interval was 12 h during the first 14 days and 8 h thereafter and for infants born after 37 weeks, the interval was 12 h during the first 7 days and 8 h thereafter. Vancomycin blood concentrations were determined 1–2 days after initiating therapy, by fluorescent

polarization immune assay (FPIA), and the dosage was adjusted to achieve a therapeutic trough concentration of 10 μg ml^{-1} and a peak concentration of 30–40 μg ml^{-1}. The minimum duration of vancomycin therapy was 5 days after the last positive blood culture. In infants with positive cultures for 7 days or more, rifampicin was added, according to CoNS susceptibility. Rifampicin, 10 mg kg^{-1} per dose, was administered by i.v. infusion over 30 min using a syringe pump. The dosing interval was 12 h. Infants with endocarditis or endovascular thrombi were treated with vancomycin for a minimum of 1 month.

Daily blood cultures were continued up to 72 h after a negative result was obtained.

Data collection

Data for the present study were collected from the NICU database, hospital medical records, and microbiology laboratory log, as follows:

Antenatal and delivery data Use of reproductive technology, multiple gestation, antenatal steroid treatment, duration of membrane rupture, chorioamnionitis, maternal antibiotic treatment prior to delivery, mode of delivery and Apgar scores wre recorded.

Post-natal data BW, GA, gender, respiratory distress and ventilatory support, severe intraventricular haemorrhage (grades 3–4), use of antibiotics, use of corticosteroids, dwell time of central catheters (umbilical artery, umbilical vein, peripherally inserted central catheter) before CoNS sepsis, duration of parenteral nutrition and predominant breastfeeding (breast milk constituting > 50% of total intake) were noted.

Sepsis data Age at onset and clinical signs, laboratory abnormalities, and culture data (blood, cerebrospinal fluid and urine) starting 2 days before sepsis, at onset of the septic episode on days 2, 7 and 14 after onset of sepsis and at discharge from the NICU were recorded.

Outcome data (at discharge or death) Weight, length, head circumference, neurological abnormalities, bronchopulmonary dysplasia (defined as need for oxygen at 36 weeks' corrected GA), severe retinopathy of prematurity (grades 3–4), brain stem auditory evoked responses, brain ultrasound data, medical treatment, recurrence of CoNS sepsis within 30 days of treatment and if relevant, age and cause of death. The clinical endpoints of adverse effects of vancomycin were neutropenia, fever, phlebitis, nephrotoxicity, ototoxicity, thrombocytopenia, skin disorders and the 'red man syndrome'. Findings were analyzed by duration of vancomycin treatment after the last positive blood culture, as follows: 5 days, 6–7 days, 8–10 days or >10 days.

Statistical analysis

All statistical analyses were performed with BMDP Statistical Software (1993, Chief Editor, W.J. Dixon, University of California Press, Los Angeles). Results for continuous variables are presented as mean (±SD). Univariate analysis was performed to identify significant differences in mean variables between study groups. Analysis of variance was used for continuous variables, and two-tailed Fisher's exact test or Pearson's chi-square test, for categorical variables. Statistical significance was defined as a P value of <0.05.

Results

Of the 1012 VLBW infants born at our centre during the study period, 253 (25.0%) had positive blood cultures for CoNS. We excluded 127 of these infants from the final analysis for the following reasons: only a single positive blood culture (55 infants), two blood cultures with different antibiotic susceptibility profiles (22 infants), polymicrobial growth (10 infants), incomplete data (23 infants), treatment with antibiotics other than vancomycin (14 infants) and death during CoNS sepsis (three infants). The excluded infants were equally spread across the time frame of the study. A comparison of the clinical characteristics of the excluded group with the study group in terms of gender, gestational age, birth weight, mode of delivery, ventilator support after delivery and age at the suspicion of sepsis showed no significant differences. Cultures were contaminated in 38 of the 55 infants with a single positive blood culture for CoNS. All these patients recovered within 2 days, and empiric antibiotics were stopped after 48 h. The remaining 17 infants recovered following 2–5 days of vancomycin.

The final study cohort included 126 VLBW infants who met our criteria for vancomycin-treated CoNS sepsis. CVCs were used prior to onset of sepsis in 120 infants (95.2%), of whom 76 (63.3%) still had a CVC at the time of diagnosis. Vancomycin was given either exclusively (111 infants) or in combination with rifampicin (15 infants). Forty-eight infants were treated for 5 days after the last positive blood culture (group 1), 32 were treated for 6–7 days (mean 6.2 ± 0.4 days, group 2), 31 for 8–10 days (mean 9.1 ± 0.8 days, group 3), and 15 for >10 days (mean 17.1 ± 7.3 days, group 4).

There were no significant differences among the four groups in clinical characteristics (Table 1) or abnormal laboratory parameters during treatment (Table 2). Additionally, no differences among the study groups were noted in rates of respiratory distress syndrome, pneumothorax, patent ductus arteriosus and necrotizing enterocolitis, or in the use of surfactant, intubation or re-intubation, inotrope support, indomethacin or ibuprofen. Growth parameters and age at discharge were similar in all groups.

CoNS sepsis recurred in two infants (1.6%) within 14 days of treatment. One was treated for 9 days after the last positive culture. The second CoNS isolate differed from the first in terms of rifampicin resistance. The other infant had cardiac vegetations and was treated for 1 month with

Table 1

Clinicalcharacteristics of very low birth weight infants with coagulase negative *Staphylococcus* sepsis by duration of treatment*

	Group 1 5 days (*n* = 48)	Group 2 6–7 days (*n* = 32)	Group 3 8–10 days (*n* = 31)	Group 4 > 10 days (*n* = 15)	Total (*n* = 126)
Male gender, *n* (%)	25 (52%)	17 (53%)	16 (52%)	3 (20%)	61 (48%)
Gestational age (weeks), mean (SD)	27.5 (2.6)	28.3 (2.5)	28.2 (2.0)	27.1 (2.4)	27.9 (2.4)
Birth weight (g), mean (SD)	1001 (269)	1065 (248)	1026 (211)	918 (280)	1000 (253)
Age at sepsis onset (days), mean (SD)	14.3 (11.4)	19.1 (16.4)	12.8 (11.4)	17.2 (10.8)	15.8 (12.5)
Ventilated after birth, *n* (%)	39 (89%)	31 (97%)	30 (97%)	12 (86%)	112 (93%)
Caesarean delivery, *n* (%)	34 (71%)	27 (84%)	28 (90%)	10 (67%)	99 (79%)

*None of the between group differences was statistically significant.

Table 2

Abnormallaboratory results in very low birth weight infants with coagulase negative *Staphylococcus* sepsis by duration of treatment*

	Group 1 5 days (*n* = 48)	Group 2 6–7 days	Group 3 8–10 days (*n* = 31)	Group 4 > 10 days (*n* = 15)	Total (*n* = 126)
Platelet count < 100 000/mm^3, *n* (%)	14 (29%)	6 (19%)	5 (16%)	1 (7%)	26 (20%)
AST > 100 IU l^{-1}, *n* (%)	4 (8%)	1 (3%)	1 (3%)	2 (13%)	8 (6%)
Creatinine > 1.2 mg%, *n* (%)	5 (10%)	13(%)	1 (3%)	1 (7%)	8 (6%)

*Data included at least one abnormal value at any time during treatment. None of the between group differences was statistically significant. AST, aspartate aminotransferase.

Table 3

Outcomeof surviving very low birth weight infants with coagulase negative *Staphylococcus* sepsis by treatment duration*

				Group 4 (>10 days) (*n* = 15)		
	Group 1 (5 days) (*n* = 44)	Group 2 (6–7 days) (*n* = 31)	Group 3 (8–10 days) (*n* = 31)	Uncomplicated sepsis (*n* = 10)	Complicated sepsis (*n* = 5)	Total (*n* = 120)
Bacteremia duration (days), mean (SD)	3.5 (3.1)	3.2 (3.1)	3.3 (3.2)	4.4 (3.2)	7.3 (4.0)	3.4 (3.2)
Vancomycin duration (days), mean (SD)	7.7 (2.1)	9.2 (2.0)	12.5 (2.5)	15.6 (5.9)	34.3 (1.9)	10.7 (5.0)
Mechanical ventilation duration (days), mean (SD)	10.5 (13.1)	7.4 (10.0)	6.1 (13.7)	9.9 (13.9)	13.5 (11.4)	9.4 (13.7)
Retinopathy of prematurity grade 3–4, *n* (%)	4 (9%)	4 (13%)	3 (10%)	1 (11%)	1 (20%)	13 (11%)
Intraventricular haemorrhage grade 3–4, *n* (%)	3 (7%)	3 (10%)	0 (0%)	1 (10%)	1 (20%)	8 (7%)
Abnormal brainstem evoked potential, *n* (%)	4 (9%)	3 (10%)	2 (7%)	2 (20%)	0 (0%)	11 (9%)
Periventricular leukomalacia, *n* (%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (20%)	2 (2%)
Post-haemorrhagic hydrocephalus, *n* (%)	1 (2%)	0 (0%)	1 (3%)	0 (0%)	1 (20%)	3 (3%)
Bronchopulmonary dysplasia, *n* (%)	1 (2%)	2 (7%)	3 (10%)	2 (20%)	3 (60%)	11 (9%)
Hospital length of stay (days), mean (SD)	69.2 (28.1)	68.2 (26.7)	69.3 (28.3)	68.5 (28.0)	83.5 (7.9)	76.7 (25.2)
CoNS sepsis recurrence, *n*	0	0	1	0	1	2

*All between group differences were non-significant except for the complicated sepsis subgroup which had a significantly longer duration of bacteremia, longer respiratory support, more bronchopulmonary dysplasia and longer hospitalization than the other groups ($P < 0.02$ for all four parameters).

vancomycin combined with rifampicin. However, 6 days after treatment was completed, re-infection with the same microorganism was noted.

Six patients died less than 10 days after completion of vancomycin treatment for reasons unrelated to the CoNS sepsis. These infants had a significantly lower mean GA and BW than the survivors (GA 25.5 ± 2.6 weeks *vs*. 27.9 ± 24.0 weeks, $P < 0.003$; BW 701 ± 193 g *vs*. 1000 ± 253 g, $P < 0.003$). The outcome data for the surviving infants are shown in Table 3. No differences were found among the groups in incidence of severe retinopathy of prematurity, severe intraventricular haemorrhage, abnormal brain stem evoked responses, periventricular leukomalacia, post-haemorrhagic hydrocephalus or bronchopulmonary dysplasia. The length of hospital stay was similar in all groups.

All infants in group 4 (>10 days' treatment) received vancomycin combined with rifampicin. Five of them had complicated CoNS sepsis: cardiac vegetations in four (three mitral valve, one tricuspid valve) and evidence of aortic

thrombus on sonography of the great vessels in one. The infants with complicated sepsis were treated with vancomycin for 30 days or more following the last positive culture. Compared with the other infants, they required longer respiratory support and had a higher incidence of bronchopulmonary dysplasia and longer hospitalization (Table 3). None of our patients had other infections, such as CNS involvement, ventriculoperitoneal shunt infection or pneumonia related to CoNS.

Discussion

The present study investigated the association between duration of vancomycin therapy and clinical outcome in VLBW infants with CoNS sepsis. The results showed that when the disease course was uncomplicated, treatment with vancomycin for a period of 5 days from the last positive blood culture was not associated with a worse outcome than longer treatment and was not associated with recurrence of CoNS bacteremia. CoNS pathogens were isolated in 25% of our cohort. The immediate mortality rate associated with CoNS sepsis was 2.4%, although it is possible that some of the later deaths were also associated with CoNS sepsis, particularly in cases of persistent CoNS bacteremia.

To ensure the quality of the study, we excluded a relatively high number of patients. As CoNS is found on normal skin, a single positive culture may represent external contamination rather than a trough infection.

The duration of antibiotic therapy for sepsis depends on the specific indication for treatment, patient characteristics and duration of bacteremia. As positive cultures may persist due to endocarditis or infected vascular venous thrombus, we believe it is more appropriate to time vancomycin therapy according to the culture results, rather than defining a set time for treatment discontinuation after CVC withdrawal. The criteria for the administration of longer treatment include prolonged bacteremia, endovascular focus of infection, and presence of neutropenia. In these cases, the optimal duration of vancomycin treatment of CoNS sepsis in VLBW infants remains unclear. One survey reported a wide variability in neonatologists' prescription patterns in the absence of, or following, removal of an intravascular catheter in VLBW infants with CoNS sepsis: 5% treated for 5 days after the last positive blood culture, 59% treated for 7 days, 31% for 10 days and 5% for 14 days or more [13]. However, none of these practices was based on prospectively collected data.

CoNS sepsis usually requires treatment with vancomycin. It is important to shorten the treatment duration in order to prevent bacterial resistance, minimize side effects and contain costs. Several studies have reported substantial inappropriate use of vancomycin in the paediatric population [1, 20], including a survey on adherence to the Centers for Disease Control recommendations for prevention of antimicrobial resistance [21]. In the present study, VLBW infants with CoNS sepsis were treated with vancomycin for 5 to 30 days following the last positive blood culture. In infants with uncomplicated infections, treatment for 5 days after the last positive blood culture appears to be associated with a satisfactory outcome. CoNS infection recurred in only two infants, one of whom had endocarditis following 30 days of treatment. It can be argued that the time during which vancomycin concentrations were maintained within the target range may serve as a better predictor of clinical outcome than total duration of vancomycin therapy. However, the retrospective nature of the present study made it impossible to measure this factor. For example, data on the precise time at which vancomycin concentrations were achieved were often missing, concentrations were determined 1–2 days after initiating therapy and received a few hours later, and so on.

In the paediatric population, the reported adverse effects of vancomycin include neutropenia, fever, phlebitis, nephrotoxicity, ototoxicity, thrombocytopenia, skin disorders and the 'red man syndrome' [22–26]. Some studies reported that the risk may well exceed 60% [22] whereas others concluded that the risk was low, even for overdoses of vancomycin [26]. In the present cohort, thrombocytopenia was common. However, given the lack of association of the thrombocytopenic episodes with treatment duration, we presume they were most likely related to the sepsis itself or consumption of an intravascular thrombus rather than the vancomycin. In all affected patients, the thrombocytopenia was mild and reversible. We did not observe any of the other described adverse effects, including the rare haematopoietic side effects of neutropenia and pancytopenia [27–29], even in the prolonged treatment group. The absence of long term abnormalities of renal function agrees with the report of Bhatt-Mehta *et al*. [30] but not with that of Craft *et al*. [25]. There was also no statistically significant difference among the study groups in abnormal results on the brain stem evoked potential test.

Fifteen infants received prolonged concomitant treatment with vancomycin and rifampicin. Unlike Shama *et al*. [31], we found that the addition of rifampicin did not lead to prompt resolution of the bacteremia. The patients treated with rifampicin did not have liver function abnormalities or decreased platelet counts.

Our study assessed a relatively large cohort of VLBW infants with CoNS sepsis in a single tertiary care NICU. We used a strict definition of CoNS sepsis, so that cases of contamination were excluded. During the study period, there were no changes in the NICU evaluation and treatment practices for CoNS sepsis. However, the study had some limitations. First, the data were collected retrospectively. Second, we did not predefine the duration of vancomycin treatment after the last positive blood culture. Hence, it may have been influenced by the clinical severity of the septic episode or the preference of the attending

neonatologist. Third, we did not perform echocardiography for all infants with non-persistent bacteremia, so the actual incidence of endocarditis could not be ascertained.

In conclusion, in VLBW infants with CoNS sepsis, treatment with vancomycin for 5 days after the last positive blood culture is not associated with a worse outcome than longer treatment, except in the presence of complications such as thrombi or cardiac vegetations. Prolonged treatment with vancomycin is not associated with adverse effects. A well-controlled prospective multicentre study is warranted which might allow future reduction of vancomycin use in the NICU.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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