

Clinical Outcome of Cephalothin Versus Vancomycin Therapy in the Treatment of Coagulase-negative Staphylococcal Septicemia in Neonates: Relation to Methicillin Resistance and *mec A* Gene Carriage of Blood Isolates

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ABSTRACT. *Objective.* Coagulase-negative staphylococci (CONS) are the most common causative agents in neonatal nosocomial septicemia. Because of widespread methicillin resistance among CONS, empiric therapy with vancomycin is recommended as the primary antibiotic regimen for these infections. In our unit, empiric treatment of nosocomially acquired septicemia consists of cephalothin and gentamicin, which are adjusted subsequently according to the determined bacterial susceptibility profile. Vancomycin is initiated only when the patient has been treated recently with cephalothin or when intravascular lines or endotracheal tube are colonized with oxacillin/cephalothin-resistant CONS strains. The aim of the present study was to evaluate the efficacy of our antibiotic regimen for CONS septicemia, in relation to methicillin-resistance and the carriage of *mec A* gene, encoding methicillin resistance, among CONS blood isolates from our unit.

Methods. Clinical symptoms of septicemia, clinical outcome, and laboratory parameters of septicemia (C-reactive protein) were studied retrospectively in 66 patients with CONS septicemia. The diagnosis of septicemia was made by the attending neonatologist and was defined by clinical symptoms of septicemia in the presence of a positive finding of a blood culture test, which was performed using a defined protocol. All CONS blood isolates were included to determine *mec A* gene carriage.

Results. In the 66 patients, three treatment categories were distinguished: treatment with cephalothin (25 patients, 38%); with vancomycin (15 patients, 23%); and primary treatment with cephalothin, switched subsequently to vancomycin (26 patients, 39%). It was found that 92% of all CONS blood isolates (61/66) were *mec A*-positive. Concordance of *mec A* gene carriage with methicillin/oxacillin resistance was found in 56 of 66 isolates (85%); 10 of 61 (16%) isolates that were *mec A*-positive were determined as oxacillin-susceptible. Although 22 of the 25 blood isolates of the cephalothin-treated patients were *mec A*-positive, clinical recovery was uneventful. In the 26 patients in whom antibiotic therapy was switched from cephalothin to vancomycin, two strains were cephalothin-susceptible and 8 patients

already had recovered clinically before the switch, which was based solely on susceptibility test results.

Conclusions. Cephalothin was found to be clinically efficacious in the treatment of neonatal CONS septicemia, despite a steadily increasing *mec A* gene carriage of CONS blood isolates in our neonatal intensive care unit and a corresponding high methicillin/oxacillin resistance. Hence, cephalothin remained the antibiotic of first choice in the treatment of CONS septicemia in our unit, with vancomycin selected exclusively for cases not responding to initial cephalothin treatment, or for patients developing CONS septicemia during or after recent cephalothin treatment. By applying this approach in our unit, we were able to reduce vancomycin use from 62% in 1994 to 1995 to 21% in 1997. This shows that such a policy may result in an important reduction of vancomycin use, which may aid in postponing the threatening emergence of vancomycin resistance among Gram-positive cocci. *Pediatrics* 1999;103(3). URL: <http://www.pediatrics.org/cgi/content/full/103/3/e29>; *neonatal septicemia, nosocomial septicemia, coagulase-negative staphylococcus, cephalothin, vancomycin, methicillin-resistance, mec A gene.*

ABBREVIATIONS. CONS, coagulase-negative staphylococci; NICU, neonatal intensive care unit; CVC, central venous catheter; NCCLS, National Committee for Clinical Laboratory Standards; CRP, C-reactive protein.

During the last 2 decades, coagulase-negative staphylococci (CONS) have evolved as the most common causative agents of nosocomial septicemia in neonatal intensive care units (NICUs).¹⁻⁴ According to the National Nosocomial Infections Surveillance System of the National Center for Infectious Diseases, 58% of neonatal nosocomial bacteremia cases are caused by CONS. Similarly, the National Institute of Child Health and Human Development Neonatal Research Network reported CONS as the causative agents in 55% of all cases of nosocomial bacteremia, with the rate of nosocomial bacteremia ranging from 11.5% to 32.4%. In our NICU, >70% of all nosocomial infections are caused by CONS. Furthermore, the incidence of CONS septicemias has increased from 2.5% in 1988 to 15% at present. This increase is most likely attributable to more aggressive, invasive therapeutic measures used in NICUs, such as central venous catheters (CVCs), arterial lines, artificial ventilation, and total parenteral nutrition for prolonged periods.⁴⁻⁶ Although vancomycin is recommended as the primary antibi-

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otic for nosocomial infections with CONS,^{1,3,7} in our unit the combination of a first-generation cephalosporin, cephalothin, and gentamicin is used. Cephalothin was chosen based on resistance patterns of the most common causative microorganisms, CONS, and *Staphylococcus aureus*. Gentamicin is added to this antibiotic regimen to cover Gram-negative organisms, because they cannot be excluded as causative agents at the moment of initiation of therapy. During the last few years, a fivefold increase in use of vancomycin has been noted in our unit. This is attributable to the increased reporting of methicillin resistance of CONS blood isolates from our neonatal unit as a result of the introduction of methods of antibiotic susceptibility testing based on guidelines from the National Committee for Clinical Laboratory Standards (NCCLS).⁸

One aim of the present study was to define more exactly the incidence of β -lactam, in particular methicillin, resistance. To accomplish this, we conducted a molecular epidemiologic study of *mec A* gene carriage of the CONS blood isolates from the years 1994 and 1995. The *mec A* gene encodes penicillin-binding protein 2a that determines methicillin resistance.⁹ The second aim of the study was to evaluate the efficacy of our antibiotic regimen for CONS septicemia. This regimen featured prominently a first-generation cephalosporin, cephalothin, apparently without ill consequences. For this reason, we studied the clinical outcome of cephalothin versus vancomycin therapy of CONS neonatal septicemia in relation to susceptibility to methicillin and cephalothin and *mec A* gene carriage of the CONS blood isolates.

PATIENTS AND METHODS

All patients with CONS septicemia during 1994 and 1995 were included in the study. Septicemia was defined by the concurrence of clinical symptoms of septicemia (apneic attacks, bradycardias, respiratory distress, tachycardia, hypotension, diminished peripheral circulation, poor skin color, lethargy, irritability, feeding problems, abdominal distension, fever, temperature instability) and a positive blood culture result. Either the first occurrence or a definite change in the symptoms noted above was considered as a clinical sign of septicemia.¹⁰ The diagnosis of septicemia was made by the attending neonatologist. Clinical symptoms of septicemia, laboratory values (C-reactive protein [CRP]), antibiotic regimen, and clinical outcome were studied retrospectively. Patients were considered clinically recovered when a clear clinical improvement was observed, including active behavior, pink skin color, disappearance of apneic attacks and bradycardias, discontinuation of ventilatory support, normal blood pressure without medication, absence of abdominal distention and gastric fluid retention, and normal regulation of body temperature. All patients were followed clinically until discharge. CRP was measured by the particle-enhanced immunoturbidimetric method (ACA, DuPont, Wilmington, DE); a value of >7 mg/L was defined as increased.^{11,12} One sample of blood (1 to 2 mL) for culture was drawn from a peripheral vein using a defined protocol. Samples were inoculated into two pediatric blood culture bottles (Bactec, Beckton-Dickinson, United Kingdom), which were incubated at 37°C in an automated blood culture incubator (Bactec NR 730). Blood culture isolates of CONS were considered significant if results of both blood culture bottles were positive within 24 to 48 hours.¹³ CONS blood isolates were subcultured on blood agar plates. Bacterial colonies were identified as CONS by virtue of Gram stain, production of catalase, and absence of a coagulase gene. All CONS blood isolates were included to determine *mec A* gene carriage. The coagulase and *mec A* gene were detected using a multiplex polymerase chain reaction protocol as described by Schmitz and colleagues.¹⁴ Bacterial typing and susceptibility testing were con-

ducted by a Vitek automated determination and susceptibility testing system (bioMérieux SA, Marcy-l'Étoile, France).

RESULTS

During the study period, CONS septicemia was diagnosed in 70 patients. A CVC was in situ in all patients. This CVC was either an umbilical vein catheter or a percutaneous silicone or polyurethane catheter. The umbilical vein catheter was replaced by a percutaneous catheter within 7 days after birth. The policy in our NICU is that the CVC is not removed when clinical signs of septicemia occur, but after antibiotic therapy is initiated and these clinical signs persist. The data of 4 patients, 2 of whom were treated with cephalothin and 2 with vancomycin, could not be evaluated because in these patients, the CVC was removed concurrent with initiation of antibiotic therapy. Therefore, data of 66 patients with CONS septicemia, treated only with antibiotics, were evaluated. Patient demographics, clinical signs of septicemia, time to recovery, and CRP values are shown in Table 1. Three treatment categories were distinguished: patients treated with cephalothin; patients treated with vancomycin; and patients treated initially with cephalothin, which subsequently was switched to vancomycin. The reason for primary treatment with vancomycin instead of cephalothin according to the regimen used in our NICU was either recent treatment with cephalothin or colonization with oxacillin/cephalothin resistant-CONS of intravascular lines or endotracheal tube. Reasons for switching from cephalothin to vancomycin were oxacillin/cephalothin resistance, as determined by the susceptibility test results; a negative clinical response to treatment with cephalothin, determined by a lack of clinical improvement; or a rise in CRP not explained by the physiologic delay in response to the infection. Gentamicin, which was added to the antibiotic regimen according to the treatment protocol, was discontinued as soon as the blood culture yielded Gram-positive cocci, which was after 24 hours in 44 (67%) of the 66 cases and after 48 hours in the remaining 22 cases (33%). Of the 66 CONS blood isolates, 55 (83%) were gentamicin-resistant, thus only 11 (17%) were gentamicin-susceptible.

Of the 66 CONS blood isolates, 61 (92%) were *mec A* gene-positive (Table 2). All 5 *mec A* gene-negative isolates were oxacillin/methicillin-susceptible. Concordance with susceptibility to oxacillin was found in 56 (85%) of the 66 isolates. A discordant result was found in 10 (16%) of the 61 *mec A* gene-positive CONS blood isolates, which were oxacillin-susceptible.

In Table 3, the distribution of susceptibility to cephalothin and gentamicin among the three treatment categories is shown, as well as the *mec A* gene carriage. A high discrepancy between *mec A* gene carriage and oxacillin/cephalothin-susceptibility was found in the patients treated with cephalothin: 3 of 25 blood isolates were *mec A* gene-negative, whereas 11 isolates were susceptible to oxacillin/cephalothin. Thus, in 8 of 25 isolates, a discrepancy existed between *mec A* gene carriage and oxacillin/cephalothin-susceptibility. In the vancomycin-treated patients, 2 of 15 isolates were oxacillin/

TABLE 1. Patient Demographics, Clinical Signs of Septicemia, and Outcome of CONS Septicemia

Patient Demographics	Treatment category		
	Cephalothin	Vancomycin	Ceph → vancomycin
No. of patients (%)	25 (38%)	15 (23%)	26 (39%)
Gestational age median (range) (wk)	31.2 (26½–42½)	30 (27½–42)	30.1 (26½–40)
Birth weight median (range) (g)	1325 (610–4000)	1055 (650–4670)	1150 (780–4900)
Age at onset septicemia median (range) (d)	14 (8–39)	15 (11–48)	14 (7–41)
Clinical Signs of Septicemia (No. of Patients, %)			
Apnea/bradycardias	17 (68%)	8 (53%)	13 (50%)
Poor skin color/diminished peripheral circulation	11 (44%)	6 (40%)	12 (46%)
Tachycardia	9 (36%)	3 (20%)	7 (27%)
Lethargy	3 (12%)	4 (27%)	10 (38%)
Respiratory distress/increased ventilator settings	5 (20%)	1 (7%)	5 (19%)
Fever/temperature instability	6 (24%)	6 (40%)	6 (23%)
Distended abdomen/feeding problems	4 (16%)	4 (27%)	3 (12%)
Outcome of CONS			
CRP (maximum, mg/L) median (range)	48 (20–197)	55 (11–137)	58 (10–190)
Days to normal CRP median (range)	5 (3–10)	6 (1–14)	6 (1–19)
Artificial ventilation median (range) (d)	2 (1–3)	1	2 (1–7)
Days to clinical recovery median (range)	1	1 (1–3)	1 (1–3)
Follow-up (d) median (range)	16 (2–58)	20 (7–86)	14 (6–50)

TABLE 2. Concordance Between *mec A* Gene PCR and Oxacillin Susceptibility Determination (Vitek) for CONS Blood Isolates (*n* = 66)

	Oxacillin Resistant (%)	Oxacillin Susceptible (%)
<i>mec A</i> gene-positive (<i>n</i> = 61, 92%)	51 (84)	10 (16)
<i>mec A</i> gene-negative (<i>n</i> = 5, 8%)	0 (0)	5 (100)

cephalothin-susceptible, whereas all 15 isolates were *mec A* gene-positive. As to the clinical outcome, a striking finding was that although the *mec A* gene was detected in 22 of the 25 blood isolates of patients treated with cephalothin, all 25 patients recovered uneventfully. All patients were treated with gentamicin for 24 to 48 hours. As presented in Table 3, gentamicin resistance among the CONS blood isolates was high (55 of 66, 83%). Twelve of the 14 cephalothin-resistant CONS blood isolates of patients treated with cephalothin also were gentamicin-resistant, making it highly unlikely that those patients recovered by virtue of gentamicin therapy. Therefore, no relation could be established between clinical recovery or CRP normalization, treatment with cephalothin, and susceptibility to cephalothin in these 25 patients. CRP normalized after a median of 4 days (range, 3 to 6 days) in the cephalothin-susceptible and after a median of 6 days (range, 1 to 10 days) in the cephalothin-resistant CONS blood isolate group. In addition, clinical recovery occurred within 1 day in both groups of patients. Furthermore, no significant difference in clinical recovery and normalization of CRP levels was found between the cephalothin and vancomycin treatment categories. In both groups, recovery occurred within a median of 1 day (range, 1 to 3 days) after initiation of antibiotic therapy, and CRP was normal after a median of 5 days (range, 3 to 10 days) in the cephalothin-treated group and after a median of 6 days (range, 1 to 14 days) in the vancomycin-

treated group. In the 26 patients in whom the antibiotic therapy was switched from cephalothin to vancomycin, 24 of the 26 blood isolates were *mec A* gene-positive. In 12 of these 26 patients, the therapy was switched on the second or third day, immediately after the availability of susceptibility test results. However, 8 of these 12 patients already had recovered clinically before the switch was made. In these patients, the switch in therapy was based solely on the susceptibility test results. In 2 of the other 14 patients, the blood isolate was found to be susceptible to cephalothin. In retrospect, in these 2 patients the decision to change the antibiotic therapy was not justified. All patients included in the study were followed until discharge. There have been no cases of recurrent CONS septicemia during follow-up.

DISCUSSION

Because of widespread methicillin resistance among CONS, the most frequent causative microorganism in neonatal late-onset septicemia, empiric treatment of this infection with vancomycin is advocated strongly in many NICUs.^{1,3,7} Because of a strong association between CONS septicemia and invasive procedures such as central venous catheterization and total parenteral nutrition,^{4–6} the prophylactic use of vancomycin in these patients has been studied.^{15–18} However, because of the emergence of Gram-positive organisms with reduced susceptibility to vancomycin—notably enterococci,¹⁹ *Staphylococcus hemolyticus*,²⁰ and recently *S aureus*²¹—there is growing concern about the increasing use of vancomycin.²⁰ Moreover, although vancomycin is effective in the prevention of neonatal CONS septicemia, the consensus is that such use should be discouraged to reduce the threat of an additional increase of vancomycin resistance.¹⁶

In our unit, a strict protocol is enforced for the treatment of early-onset septicemia, as well as for nosocomially acquired septicemia: primary treatment with amoxicillin-clavulanate and gentamicin

TABLE 3. *Mec A* Gene Carriage, Cephalothin, and Gentamicin Susceptibility (Vitek) of CONS Blood Isolates From Various Treatment Categories

Number of	Treatment Category		
	Cephalothin	Vancomycin	Cephalothin → Vancomycin
Blood isolates (total 66)	25	15	26
Cephalothin-susceptible*, <i>mec A</i> gene-negative (gentamicin-resistant, No., %)	3 (2, 67%)	0	2 (1, 50%)
Cephalothin-susceptible, <i>mec A</i> gene-positive (gentamicin-resistant, No., %)	8 (4, 50%)	2 (1, 50%)	0
Cephalothin-resistant, <i>mec A</i> gene-positive (gentamicin-resistant, No., %)	14 (12, 86%)	13 (11, 85%)	24 (24, 100%)

* According to the NCCLS guidelines, *S* susceptibility of CONS to all β -lactam antibiotics is determined by oxacillin susceptibility testing. Therefore, cephalothin susceptibility, as presented in the Table, was assessed by testing oxacillin susceptibility.

for early onset and primary treatment with cephalothin and gentamicin for late-onset septicemia. When the causative microorganism is identified, the treatment is adjusted according to the susceptibility profile. However, although we found a high incidence of resistance to methicillin/oxacillin in nosocomial CONS blood isolates (77%) since the introduction of the Vitek system in our microbiologic laboratory in 1993 and an even higher *mec A* gene carriage of 92% among these isolates, the present study shows that even in those patients in whom the blood isolate was cephalothin-resistant according to NCCLS criteria, ie, oxacillin-resistant, clinical recovery was similar to that in patients infected with a cephalothin-sensitive isolate. In addition, in the majority of patients (8 of 12) who were switched from cephalothin to vancomycin (based on susceptibility results), recovery already had occurred before the switch was made. As such, we did not find a difference in clinical outcome of treatment with cephalothin, regardless of whether the isolate was classified as cephalothin-susceptible or cephalothin-resistant, according to NCCLS criteria, as incorporated in the Vitek system. Moreover, our data show that despite the high incidence of *mec A* gene carriage of 92%, treatment with cephalothin still is clinically efficacious. Maybe the *in vivo* expression of the *mec A* gene in CONS is low as opposed to the high *in vitro* expression in standardized susceptibility testing, which is designed to maximally facilitate expression of the *mec A* gene.²² The 85% concordance between Vitek oxacillin susceptibility results and *mec A* gene carriage is in agreement with the 80% concordance found in a recently published French study.²³ Thus, one could argue that possibly *in vitro* testing is not relevant for the clinical situation in which transcription of the *mec A* gene may be suppressed or switched off, for example by phase variation, as described by Mempel and associates.²⁴ Alternatively, even when *mec A* is expressed *in vivo*, it is not unlikely that this expression is strongly heterogeneous,^{9,22} and cephalothin treatment possibly still will result in substantial growth inhibition or even killing of the staphylococcal cells not expressing oxacillin resistance. Subsequently, the patient's host defenses, although immature, may be capable of clearing the relatively small subpopulation of bacteria that fully expresses *mec A* and thus oxacillin and cephalothin resistance, and that therefore escapes antibiotic-induced killing.

In our unit, in all patients with nosocomial infections gentamicin is added to cover Gram-negative nosocomial pathogens, but synergistic interaction of gentamicin and cephalothin against CONS cannot be excluded. However, although *in vitro* synergism between β -lactams and gentamicin against staphylococci has been demonstrated, the clinical significance of this is doubtful, even in staphylococcal endocarditis.²⁵ Thus, the addition of gentamicin to β -lactam therapy remains controversial. Moreover, only 17% of our CONS blood isolates is susceptible to gentamicin and, according to a recent review by Archer and Climo,²⁶ gentamicin resistance of CONS limits the use of combination regimens markedly.

It should be emphasized that in the present study, the CVC was not removed when clinical signs of septicemia occurred. Considering the rapid and uneventful recovery of the majority of patients, one may wonder whether antibiotics are at all necessary and whether removal of the CVC without antibiotic treatment would be just as efficacious. It would be of considerable interest to study the effect of CVC removal as a single therapeutic measure in suspected CONS septicemia and to compare this approach prospectively with treatment with antibiotics.

In conclusion, the present study clearly demonstrates that cephalothin still is clinically efficacious in the treatment of nosocomial septicemia attributable to CONS in neonates, despite a high prevalence of *mec A* gene carriage of CONS blood isolates in our NICU and a correspondingly high methicillin/oxacillin resistance. Therefore, we think it is justified to conclude that cephalothin is the antibiotic of first choice in the treatment of CONS septicemia in neonates. With this approach, vancomycin can be selected exclusively for those rare cases either not responding to initial cephalothin treatment or developing CONS septicemia during or after recent cephalothin treatment. This will reduce vancomycin use and possibly aid in postponing the threatening emergence of vancomycin resistance among Gram-positive cocci. Indeed, by applying this approach in our NICU since 1997, we were able to reduce vancomycin use from 62% in 1994 and 1995 to 21% in 1997. These data clearly show the benefits of this policy for curtailing vancomycin use.

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