Infections In Neonatal Intensive Care Prevalence, Prevention and Antibiotic use

Agnes van den Hoogen

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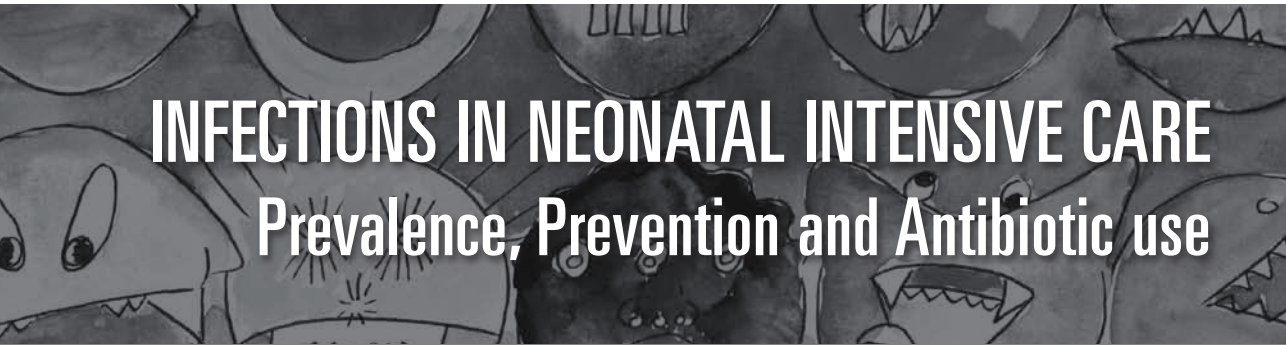

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Prevalence, Prevention and Antibiotic use

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Prevalence, Prevention and Antibiotic use

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Voor mijn vader en voor Frans

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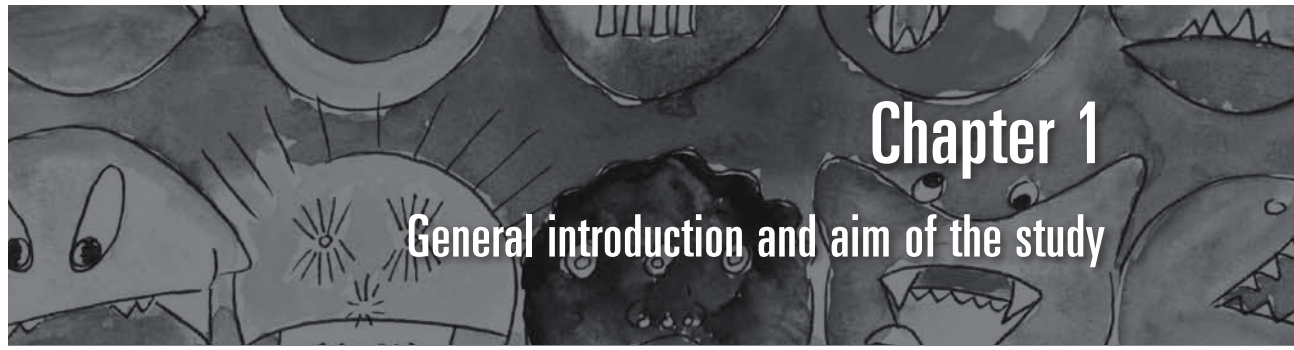

Chapter 1

General introduction and aim of the study

INTRODUCTION

Neonatal bacterial infections are an important cause of morbidity and mortality among infants admitted to neonatal intensive care units (NICUs).[1-4] Neonates may acquire infections in utero (transplacental and ascending), intrapartum, or postnatally. The incidence of neonatal bacterial sepsis varies from 1 to 4 cases per 1,000 live births in developed countries, with considerable fluctuation over time and with geographic location.[5]
Prematurity or very low birth weight (VLBW) is an important predisposing factor for neonatal infection. The incidence of neonatal infection is 3- to 10-fold higher in preterm infants than in full term normal birth weight infants. This may be explained by a higher frequency of intra-amniotic infection among mothers of infants with a short gestational age compared with full term infants. Moreover, maternal genital tract infection is considered to be an important cause of preterm labour and increased risk of infection of the fetus. In addition, preterm infants have a compromized immune system and they often require invasive procedures that provide a portal of entry.[5]

Microbial agents can be transmitted from the mother to the fetus or newborn infant either transplacentally, haematogenously, or ascending, via the birth canal. Microbial agents may penetrate the placental barrier and contaminate the fetus, often with devastating results.[6] However, normally a fetus is not exposed to potentially pathogenic microorganisms until the membranes rupture and ascending infection may occur. Finally, the fetus may be contaminated during passage through the birth canal, or later, by contact with the extra-uterine environment.[5] Instrumentation during pregnancy or delivery is an additional risk factor for contamination of the fetus.[7]

Focus

This thesis focuses on perinatally acquired and nosocomial bacterial infections among infants hospitalized in the neonatal intensive care unit, in particular infections of the bloodstream.

Neonatal bacterial infection

Neonatal infection comprises infection of the bloodstream, meninges and organs. The diagnosis of infection of the organs is usually difficult to establish. The diagnosis neonatal sepsis is confirmed when clinical signs of infection are present and the blood culture is positive. Neonatal bacterial sepsis is classified into two major categories based on the time of onset: early-onset sepsis and late-onset sepsis.

Early-onset sepsis

Early-onset sepsis is sepsis occurring during the first week of life, generally before 48-72 h of age.[8] Early-onset infections are acquired perinatally. The most important neonatal factor predisposing to infection is prematurity or (very) low birth weight.[6] Other factors which increase the risk of neonatal early-onset infections are maternal infection, prolonged rupture of membranes, virulence of the infecting organism and a compromized immune system and host response, and traumatic delivery.[5,9,10]

Group B streptococci (GBS) and *Escherichia coli (E. coli)* are the most predominant causative agents in early-onset neonatal sepsis. Epidemiological studies from Yale-New Haven have documented shifts in causative pathogens of early-onset sepsis from predominantly Gram-positive microorganisms (since 1928), in which group A streptococci featured prominently to predominantly Gram-negative microorganisms, mainly *E. coli* (during late 1940 and early 1950).[11] Since the late 1960's, Gram-positive microorganisms emerged as main causative agents.[12-14] The most important Gram-positive organisms causing early-onset sepsis are GBS, Group A streptococci, *Streptococcus viridans* and other streptococci. Gram-negative causative microorganisms are *E. coli, Enterobacter, Citrobacter, Acinetobacter, Klebsiella* and *Pseudomonas*. Infrequent causative microorganisms are *Staphylococcus aureus (S. aureus)*, coagulase-negative staphylococci (CoNS), *Listeria monocytogenes, Streptococcus pneumoniae, Haemophilus influenzae* and *Candida*.

GBS colonize the genital tract of 15 to 40% of pregnant women and half of all neonates born to women who are GBS-carriers become colonized, whereas 1-2% of these infants develop GBS disease. The risk of early-onset sepsis with GBS increases when the membranes are ruptured more than 18 h before delivery and in the case of onset of labour before 37 weeks of gestation.[5] The incidence of early-onset neonatal GBS sepsis declined after the introduction of intrapartum antibiotic use as a prophylaxis, offered to all women identified as GBS-carriers, to prevent perinatal transmission of GBS, from 1.7 cases per 1,000 live births in 1993 to 0.6 cases per 1,000 live births in 1998 in the USA.[15,16] In the Netherlands the incidence of early-onset neonatal GBS sepsis declined from 0.54 cases per 1,000 live births in 1997/98 to 0.36 cases per 1,000 live births in 1999/2001 after the introduction of selective intrapartum antibiotic administration (prolonged rupture of membranes, prematurity, previous infant with invasive GBS disease, heavy maternal GBS colonization or intrapartum maternal fever > 38.0 °C).[17]
E. coli are the most common Gram-negative bacteria causing neonatal early-onset sepsis, acquired by vertical transmission. The incidence of *E. coli* early-onset sepsis among very low births weight infants increased from 3.2 (in 1991 and1993) to 6.8 (during 1998 and 2000) per 1,000 live births.[2] Early-onset sepsis due to *E. coli* may be associated with meningitis. The incidence of *E. coli* meningitis in newborn infants is 0.2 to 0.4 cases per 1,000 cases of live births. [5]

Late-onset sepsis

Late-onset neonatal infection may be acquired through horizontal or vertical transmission. Nosocomial infections are infections acquired during hospitalization and are generally late-onset. Neonatal nosocomial infections usually present after 72 hours of age, and mostly during the second week of life. The Centres for Disease Control and Prevention (CDC) defines nosocomial infection as any infection occurring after

admission to the hospital which is not acquired transplacentally.[3,18] Rates of nosocomial infections in healthy term infants who are either rooming in with mothers or staying in the well baby nursery are low (<1%). The incidence of nosocomial infections is much higher among preterm infants <1500 g, admitted at NICUs (20-25%) and increases with decreasing gestational age and birth weight and has been reported to be 43% for infants of 401-750 g, 28% for infants 751-1000 g, 15% for infants 1001-1250 g and 7% for infants 1251-1500 g.[5] Multiple invasive procedures, indwelling vascular catheters, parenteral nutrition, endotracheal tubes, the use of broad-spectrum antibiotics and prolonged hospital stay are risk factors for nosocomial sepsis in these infants.[2,19,20] Transmission of causative microorganisms usually occurs by direct contact via the hands of Health Care Workers (HCWs), parents or visitors, or may be transmitted through breast milk or through contact with contaminated equipment.

The vast majority (70%) of late-onset sepsis is caused by Gram-positive microorganisms of which coagulase-negative staphylococci (CoNS) are the most frequent pathogens, causing 48% of all neonatal infections, and 68% of the Gram-positive infections in studies among VLBW infants.[3,21] Although CoNS are commensal organisms with little pathogenicity, preterm infants are particularly susceptible to invasive infection due to CoNS. Compromised immune responses and increased instrumentation in these infants play an important etiologic role.

Staphylococcus aureus (S. aureus) is reported to be the second most frequently diagnosed causative microorganism. Late-onset sepsis caused by *S. aureus* is less common (8% of all late-onset cases of sepsis), as reported in a multi-centre study by Stoll et al.[3,19] Although sepsis due to *S. aureus* usually is a mild disease in preterm infants, with a clinical course similar to CoNS sepsis, *S. aureus* may cause satellite infections, such as endocarditis, osteomyelitis or arthritis.[8]

Gram-negative pathogens are increasingly reported to cause neonatal nosocomial sepsis, among them *E. coli, Klebsiella, Pseudomonas, Enterobacter* and *Serratia*. Fungi and yeasts, in particular *Candida* species, are increasingly important causative microorganisms, especially among VLBW infants.[3,8,12,22] Prolonged use of antimicrobial agents, resulting in alterations of the normal skin and gastro-intestinal microbial flora, and instrumentation are recognised risk factors for invasive candidiasis.[8,23, 24]

Clinical symptoms of neonatal sepsis

Signs and symptoms of infection in neonates are subtle and non-specific.

The interpretation of clinical symptoms of sepsis in the newborn may be difficult during the first 48 hours after birth, since these symptoms may be caused by other clinical problems, such as birth asphyxia, respiratory distress syndrome, or metabolic diseases. To diagnose early-onset sepsis it is helpful to know the risk factors that predispose the neonate for sepsis such as maternal infection and prolonged rupture of membranes, and prematurity.[25]

Late-onset sepsis, however, is easier to recognize for health care workers because the infants present with a change in clinical appearance and symptoms. The most frequent clinical symptoms of bacterial sepsis are temperature instability (51%), jaundice (35%), respiratory distress (33%) feeding problems (28%), lethargy (25%), pallor and/or cyanose (24%), apneic attacks and/or bradycardias (22%), and distended abdomen (17%).[19,25,26] Laboratory parameters can be helpful in the diagnosis sepsis.

Laboratory diagnostics

Laboratory parameters such as peripheral white blood cell count and differential and C-reactive protein (CRP) have been evaluated for their discriminative power as an aid in the diagnosis. The predictive values of CRP and the ratio of immature to total neutrophilic leucocytes (I/T -ratio) was found to be low, 20-30% in early onset-sepsis and 50-60% in late-onset sepsis. In clinical practice however, CRP is generally used as a guideline for clinical improvement in the treatment of neonatal sepsis and is therefore used as an aid in the decision to discontinue antibiotic treatment.[27,28]

A number of the adjunctive tests, including measurements of serum interleukin-6 (IL-6), IL-8 and procalcitonin (PCT) levels have been studied for their ability to predict sepsis in neonates with clinical symptoms of infection. The positive predictive values of IL-6, IL-8, and PCT were higher than of CRP. These parameters were also found to be useful in the differentiation between viral and bacterial infection in infants.[29] However, in many hospitals determination of the latter parameters is not operational on a routine basis.

A positive blood culture is the golden standard for the diagnosis of sepsis. Especially in the diagnosis of sepsis due to CoNS there is discussion on the definition of true sepsis based on blood culture results, especially among infants with central venous lines. The required number of positive blood cultures, drawing blood cultures both from a peripheral vein and from a central venous- or arterial line and drawing repeat blood cultures are still subject to debate. Since the bacterial density, i.e. the number of colony forming units (CFUs) per ml blood, is related to the time to positive blood cultures, this so called 'time-to-positivity' is generally accepted in the discrimination between true and false positive blood culture, especially when the 'time-to-positivity' is < 48h.[30]

Risk factors

Many interventions that are common in NICUs have been identified as independent risk factors for infection, including (percutaneously inserted) central venous catheters, total parenteral nutrition and the administration of lipid emulsions, endotracheal tubes and nasogastric feeding tubes.[31]

Medications such as postnatal systemic steroids and H_2 -receptor antagonists are also important risk factors.[4,7, 32-34]

Furthermore, preterm infants have a compromised skin barrier; their stratum corneum is 3 cell layers thick at 26 weeks of age compared to 16 layers in full term infants. The thin keratin layer is easily damaged by handling, adhesives frequently applied to the skin and alcohol applications. In addition, to reduce insensible water loss the humidity in incubators is 80% during the first days of life of these preterm infants and bacteria and fungi rapidly multiply on moist or damaged skin.[8]

Neonatal immune response

Both term and preterm infants have a decreased function of neutrophils and other cells involved in the response to infection. Cellular deficiency of chemotaxis, phagocytosis and microbial killing further contribute to the vulnerability of preterm neonates to overwhelming infection.[8] Maternal-fetal transfer of IgG occurs in the third trimester of pregnancy. Therefore premature infants <32 gestational age (GA) have low levels of passively acquired antibody, in addition to a limited production of type-specific antibody in response to invading pathogens.

Treatment

Treatment of sepsis needs to be prompt and effective, as infants with systemic sepsis deteriorate very rapidly because of their poor host defences. Intravenous antibiotics must be started immediately when the diagnosis is suspected.

The most commonly used antimicrobials in NICUs are penicillins, aminoglycosides, in particular gentamicin, and vancomycin.[6] Generally, a combination of a penicillin and aminoglycoside is used for the treatment of early-onset neonatal sepsis to cover both Gram-positive (GBS) and Gram-negative *(E coli)* agents. In most protocols, ampicillin or amoxicillin is used to cover both GBS and *Listeria monocytogenes*, although the incidence of sepsis due to the latter is very low. Aminoglycosides cover most Gram-negative bacteria. However, when the blood culture yields a Gram-negative microorganism, therapy is changed into either a third generation cephalosporin (cefotaxim or ceftazidim) or a carbapenem (meronem).

Antibiotic treatment of nosocomial infections is based on the most frequent causative microorganisms, CoNS and *S. aureus* and usually includes (flu)cloxacillin and an aminoglycoside, or vancomycin.

In our institute the use of vancomycin for the treatment of CoNS sepsis is restricted to complicated cases that do not respond to the initial treatment, for which we use first generation cephalosporins (cephalotin or cefazolin).[35]

Although antibiotics are the mainstay of treatment, adjunctive therapy with intravenous immunoglobulin (IVIG), myeloid colony-stimulating factors (CSFs) including granulocyte colony-stimulating factor (G-CSF), probiotics, glutamine supplementation, recombinant human protein C and lactoferrin has been used in an attempt to improve host defences. These forms of adjunctive therapies for the prevention and treatment of neonatal sepsis holds promise. However, for most of these therapies tested to date, clinical trials have failed to demonstrate a positive effect on neonatal outcome and these therapies are not included in the protocols for treatment of neonatal sepsis.[36]

Overuse of antibiotics and resistance

Antibiotics are the most frequently prescribed medications in NICUs.[37, 38] Empiric antibiotic regimens, either narrow or broad spectrum in the range of pathogens that they target, are generally accepted as treatment of neonatal sepsis.[39]

Overuse of antibiotics among neonates is common because no set of universal signs/

symptoms or diagnostic tests has been found to be reliable for very early diagnosis of neonatal sepsis. For every newborn with a positive blood culture, as many as 20 newborns are treated with antibiotics.[40] Antibiotic overuse selects for bacterial resistance, which is an increasing problem in neonates. Therefore, the choice of the antibacterial drug should be reviewed when cultures and susceptibility tests become available. The majority of CoNS is resistant to methicillin, resulting in the use of vancomycin for adequate therapy. In our hospital however, we save vancomycin to complicated cases that do not respond to the initial treatment for which we use first generation cephalosporins, since 95% of CoNS blood isolates were found to be susceptible to cephalotin and cefazolin.

The CDC and others have recommended to avoid empiric vancomycin therapy in patients with suspected sepsis to prevent the emergence and spread of vancomycin resistant strains.[41,42]

Antibiotics should be used rationally, as for choice of drug (narrow spectrum when possible, broad spectrum in selected patients) and duration of therapy. It is recommended to discontinue antibiotic treatment after 2-3 days in patients whose blood culture or other systemic cultures are negative and when there are no clinical signs of infection.[3]

Prevention

Strategies to minimize the impact of identified risks can decrease neonatal infection rates. Prevention of preterm birth, intrapartum antibiotic prophylaxis for the prevention of neonatal GBS disease and minimizing obstetrical risk factors are important in the prevention of neonatal early-onset sepsis.[16, 43]

Principles for preventing nosocomial neonatal infections include the adherence to universal hygiene precautions during every patient contact, avoiding nursery crowding and increasing the nurse-to-patient ratio.

Numerous reports have shown that improved adherence to hand hygiene can reduce health-care-associated infection rates.[44-48] Despite the relatively simple procedure and the widespread knowledge that hand hygiene is one of the most effective measures in the prevention of nosocomial infections, the adherence to hand hygiene procedures remains low, often being less than 50%.[45-47] Multidisciplinary and multimodal interventions to promote hand hygiene practices appeared to have a positive impact.[49,50] Education and workshops on hand hygiene practices to improve the knowledge of guidelines and observation sessions with performance feedback for health care workers are factors that have been proven to have a positive effect on compliance rates. Hand hygiene practice requires continuous assessment of behaviour and interventions such as feedback and observation sessions. Preventing understaffing and overcrowding, both consistently linked with poor adherence to hand hygiene are important issues to influence the nosocomial infection rate.[51,52]

Increased attention to skin care, minimizing the risk of catheter contamination and decreasing the number and length of invasive procedures are other interventions in the prevention of nosocomial infections in neonates.[5]

Since central venous catheter use is a major risk factor for nosocomial infections among

infants admitted to a NICU, [3,4,53] special attention to strict asepsis during the insertion and care of the insertion site may reduce the incidence of such infections. Catheters should be removed as soon as possible.
The use of in-line filters in the intravenous administration sets, connected to the central venous catheters[54-56], antibiotic locks,[57] impregnation of catheters with antibiotics[58] and the continuous administration of vancomycin[59] have all been studied for their effect on the reduction of nosocomial infections. Although the use of vancomycin has shown to be effective, the continuous administration of antibiotics is not advocated in NICUs.

Infection disease teams

Active infection disease teams (IDTs) have shown to positively contribute to the accuracy of antibiotic therapy.[60-63] An IDT may include a paediatric infectious disease specialist, a medical microbiologist, and a neonatologist. They should be consulted frequently and regular meetings on infectious problems may add to the education on neonatal infectious diseases.[64]
Together with hospital hygiene specialists the epidemiology of neonatal infections and patterns of colonization are studied for the early detection of clustering of infants colonized with resistant microorganisms and to take adequate infection control measures.[65]

AIMS AND OUTLINE OF THIS THESIS

In this thesis a number of essential aspects of neonatal infections will be discussed, including epidemiology, therapy and prevention.

Epidemiology

To identify trends in the prevalence and the pathogens causing neonatal bacterial sepsis in an era of increased maternal antibiotic use as a policy to prevent preterm delivery and as a result of the introduction of a GBS-prevention protocol in the Netherlands, data were studied from a period of twenty-nine years, to cover a period before and after the increased maternal antibiotic use. In addition, the antibiotic susceptibility of the major causative agents was studied to evaluate the protocol for empiric antibiotic therapy for neonatal sepsis (Chapter 2).

Therapy

Antibiotic use is prescribed according to a defined protocol in the NICU of the Wilhelmina Children's Hospital (WCH). Infectious disease problems are discussed with the infection disease team (IDT), active since 1990, during weekly sessions and more frequently when necessary. A main purpose of the IDT is to restrict antibiotic use to cases of proven infection and to reduce the duration of therapy to what is strictly needed. Antibiotic use was studied over a period of 16 years (Chapter 3).

Prevention

A. Consolidation of correct adherence to protocols for hand hygiene is a major target of the IDTs. We studied the effect of a multimodal intervention program to improve the adherence to hand hygiene among all personnel of the NICU (Chapter 7)
B. Among several measures for the prevention of nosocomial sepsis in the NICU, for which central venous catheter (CVC) use and total parenteral nutrition are major risk factors, the use of in-line filters in CVCs was evaluated for its effect on the sepsis rate (Chapter 4)
C. Prevention of CVC-associated sepsis is a major goal in the reduction of neonatal nosocomial sepsis. We evaluated the incidence of CVC-associated sepsis and found that removal of a CVC was an additional risk factor for sepsis, caused by coagulase-negative staphylococci (CoNS). In a second prospective study, the administration of cefazolin 50 mg/kg 1h before and 12h after removal of a PCVC was evaluated for its effect on the incidence of CVC-removal associated CoNS sepsis (Chapters 5 & 6)

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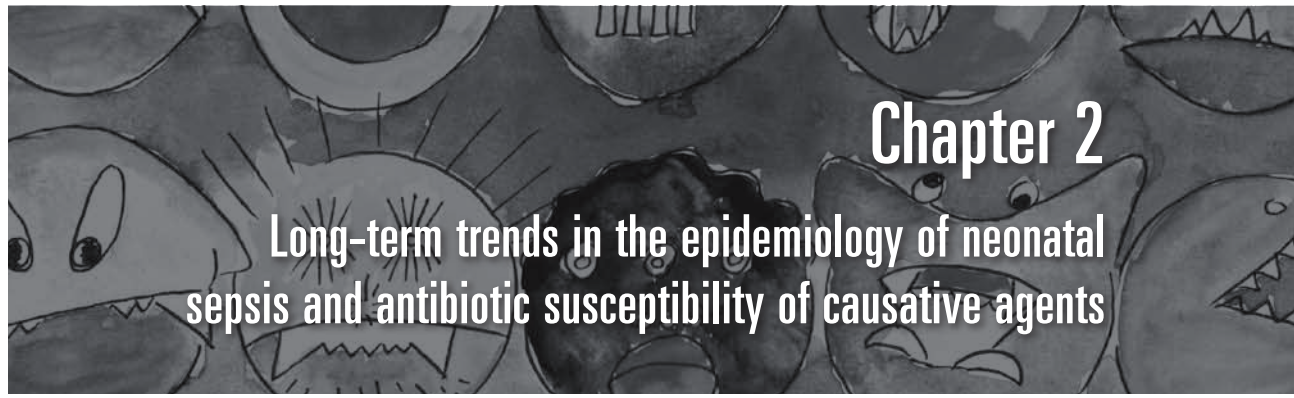

Chapter 2

Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents

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SUMMARY

Background:
In an era with increased maternal antibiotic use, patterns in early- and late-onset sepsis and antibiotic susceptibility may have changed.

Objectives:
To identify longitudinal trends in causative microorganisms for neonatal sepsis and analyse antibiotic susceptibility of all blood isolates of infants with sepsis.

Methods:
Early- and late-onset sepsis cases from 29 years (1978–2006) were studied retrospectively, in five clusters of 5 years (period I-V) and one cluster of 4 years (period VI), including antibiotic susceptibility profiles of blood isolates during the years 1999-2006.

Results:
The incidence of early-onset sepsis decreased ($p<0.01$) from 4% during period I (1978-1982), to 1.2 % during Period VI (2003-2006). 78% of the infants with Group B Streptococcal GBS sepsis was premature during period I, compared to 47% during period VI ($p<0.05$).
The incidence of early-onset Gram-negative infections remained low during all periods. The incidence of late-onset sepsis, predominantly caused by coagulase-negative staphylococci (CoNS) and *S. aureus,* increased since period III from 7.1% to 13.9% in period VI ($p<0.01$). Infections due to fungi or yeasts were rare (incidence < 0.3%). The majority of CoNS blood isolates were oxacillin-resistant, but vancomycin-susceptible. Ninety-five percent of CoNS blood isolates were susceptible for first generation cephalosporins. Amoxicillin/clavulanic acid-resistant *E. coli* were infrequent causes of infection.

Conclusions:
The incidence of early-onset sepsis mainly caused by GBS decreased. In contrast, the incidence of late-onset sepsis, predominantly caused by CoNS, increased significantly. The incidence of fungal and yeast infections remained low. The majority of CoNS blood isolates were susceptible for first generation cephalosporins.

INTRODUCTION

Neonatal sepsis remains an important cause of morbidity in neonatal intensive care units.[1-6] Several epidemiological studies on neonatal sepsis document a substantial shift from early-onset sepsis to late-onset sepsis, as well as a change in the pattern of bacterial blood culture isolates. In an early review of all cases of neonatal sepsis in Yale-New Haven from 1928 to 1978 a shift was reported from Gram-positive microorganisms, in which group A streptococci featured prominently in the earlier years, to Gram-negative microorganisms, mainly *E. coli*, during the late 1940s and early 1950s.[7] Since the late 1960s group B streptococci emerged as major perinatal pathogens. In the same period other Gram-positive cocci, such as enterococci, were also recognised as important pathogenic microorganisms. Nosocomial infections, caused by *Staphylococcus aureus* became clinically important in the 1970s.[7] Since the 1980s coagulase-negative staphylococci (CoNS), S. aureus and Candida species were widely recognised as nosocomial pathogens.[8,9] During the present years CoNS are the major causative microorganisms in late-onset sepsis, accounting for 48% of all cases of late-onset sepsis.[3,4]
The mortality due to sepsis has decreased substantially over the years due to important improvements in neonatal intensive care.[1]
The present study was conducted to identify longitudinal trends in causative microorganisms for neonatal sepsis in an era of increased maternal antibiotic use, since the introduction of guidelines for prevention of GBS disease in 1999 in The Netherlands and as a result of the policy to prolong the latency time in women with preterm rupture of the membranes and as adjuvant treatment in preterm labor.[10,11] For the same reasons antibiotic susceptibility of all blood isolates of the infants with sepsis were analysed.

METHODS

Data of all infants admitted to the neonatal intensive care unit (NICU) of the Wilhelmina Children's Hospital, University Medical Centre, Utrecht, the Netherlands, during January 1, 1978 – December 31, 2006 were studied retrospectively. Data were reported for 5 periods of 5 years (period I: 1978-1982, II: 1983-1987, III: 1988-1992, IV: 1993-1997, V: 1998-2002) and a period of 4 years (period VI: 2003-2006). Our NICU was an 11-bed level III unit during period I and expanded to a 28-bed unit with 550 annual admissions, covering 30.000 live births. Since the start of our NICU in 1973, important clinical patient data have been collected prospectively in a patient register. Since 1992 these data are also added to the Perinatal Registry of the Netherlands, a registration system of all Dutch NICUs.
The diagnosis sepsis was based on clinical symptoms of sepsis and a positive blood culture in addition to positive laboratory parameters. Early-onset sepsis was defined as clinical signs of infection during the first 48h of life and a positive blood culture.[12] Late-onset sepsis was defined as clinical signs of infection and a positive blood culture obtained after 48h of life.[13] Blood cultures were performed when clinically indicated and standard

procedures were applied. A blood culture yielding coagulase-negative staphylococci was considered positive when the blood culture was positive within 24-48 hours.[14]
Empiric antibiotic therapy was initiated according to the protocol used in our NICU. The protocol for antibiotics was based on the current susceptibility profile of the most important causative microorganisms and only changed after major and sustained alterations in susceptibility profiles. For suspected early-onset sepsis the combination of a penicillin-derivative (penicillin, amoxicillin or amoxicillin-clavulanic acid) and an aminoglycoside (amikacin or gentamicin) was used. For suspected late-onset sepsis a combination of a first generation cephalosporin (cephalotin or cefazolin), mainly active against Gram-positive microorganisms and an aminoglycoside was used. In case of resistance to first generation cephalosporins a combination of vancomycin and ceftazidim was used. Dosages used were in accordance with the actual recommendations in the literature.[15]
Antibiotic susceptibility, studied for blood isolates during 1988-2006, was determined using Kirby-Bauer disk diffusion until 1993 and by a Vitek automated determination and susceptibility testing system (bioMerieux SA, Marcy-l'Etoile, France) since 1993.
The maternal antibiotic policy changed since the introduction of the guidelines for prevention of GBS disease in The Netherlands during 1999, based on risk factors.[11] In addition, since that period women with preterm labour at gestational age <32 weeks and preterm rupture of the membranes were treated with antibiotics to prolong pregnancy.

Statistics
Differences between the groups for all variables were tested by Student t-test and Chi Square where appropriate. Statistical analyses were performed using SPSS® for Windows, version 12.1 (SPSS Inc., Chicago, IL, USA).
Statistical significance was assumed for $p < 0.05$.

RESULTS

Figure 1 shows both the incidence of early- and of late-onset sepsis over a period of 29 years. The figure clearly shows a low and further decreasing incidence of early-onset sepsis and an increase in incidence of late-onset sepsis since 1993-1997 (period IV).
Tables 1A and 1B show the main causative microorganisms in early- and late-onset sepsis, respectively, and both the number of infants with sepsis and the incidence of early- and late-onset sepsis, in the periods I-VI. In addition to what is displayed graphically in figure 1, tables 1A and 1B show a significant decrease in the incidence of early-onset sepsis from 4% in period I to 1.2% in period VI ($p < 0.05$). In contrast, the incidence of late-onset sepsis increased from 7.1% in period III to 17.4% and 13.9%, during periods V and VI, respectively.

Early-onset sepsis
Figure 2 shows a gradual change in the distribution of Gram-positive and Gram-negative

Figure 1 Incidence of early- and late-onset sepsis during 1978-2006, shown as 5 periods of 5 years (period I-V) and 1 period of 4 years (period VI).

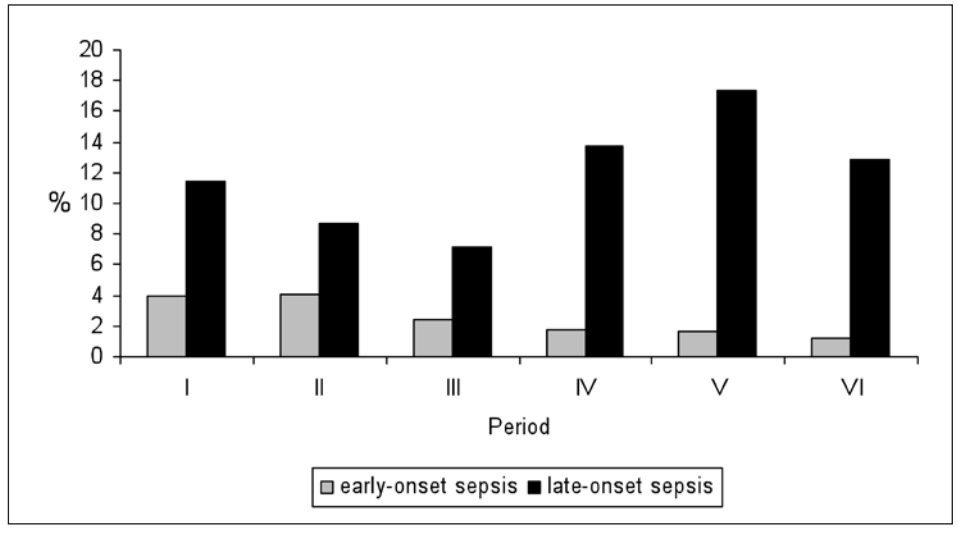
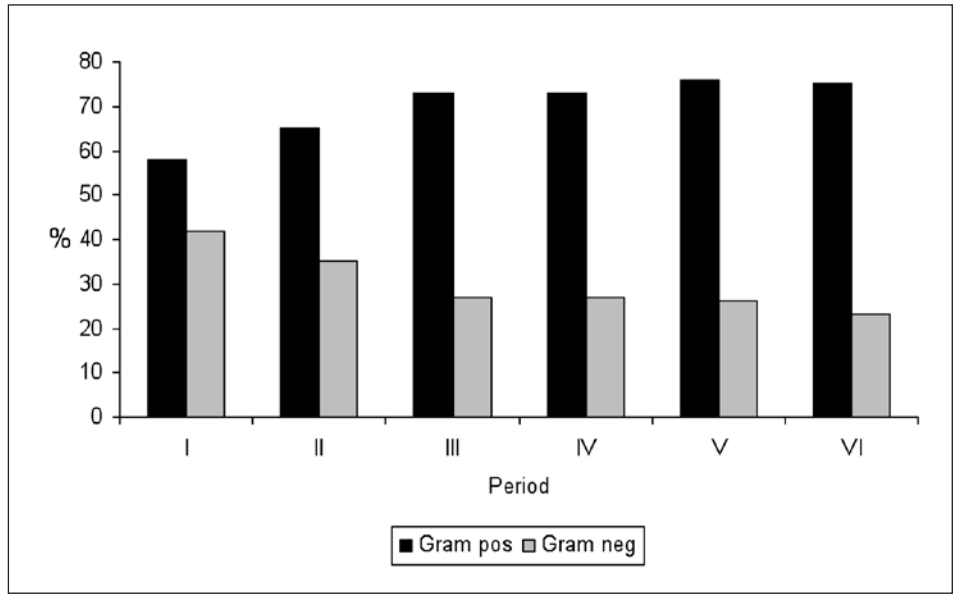


Figure 2 Distribution of Gram-positive and Gram-negative microorganisms causing early-onset sepsis during 1978-2006, shown as 6 periods.



microorganisms in early-onset sepsis over the years. The figure shows an increasing predominance of Gram-positive agents in early onset sepsis (from 58% in period I to 75% in period VI). Group B streptococci (GBS) and *E. coli* were the two most important

Table 1 Number of infants with early-onset sepsis (1A) and late-onset sepsis (1B), major causative agents and incidence during 1978-2006, shown as 5 periods of 5 years (periods I-V) and 1 period of 4 years (period VI)

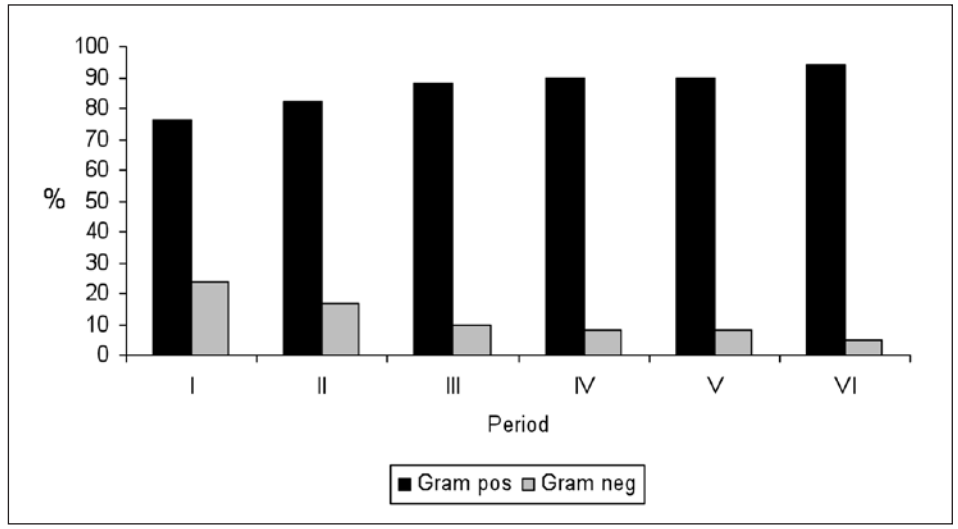
A. Early-onset sepsis.

Years Period	1978-1982 I	1983-1987 II	1988-1992 III	1993-1997 IV	1998-2002 V	2003-2006 VI
Admitted infants (n)	1276	1523	1909	2034	2382	2278
Sepsis (n,%)	52 (4)	63 (4.1)	45 (2.4)	37 (1.8)	37 (1.6)	28 (1.2)
Gram-positive agents						
Total (n,%)	30 (58)	41 (65)	33 (73)	27(73)	28 (76)	21 (75)
GBS (n,%)	23 (1.8)	28 (1.8)	22 (1.2)	21 (1.0)	16 (0.7)	15 (0.7)
Other Gram-positive agents (n,%)	7 (0.5)	13 (0.9)	11 (0.6)	6 (0.5)	12 (0.5)	6 (0.3)
Gram-negative agents						
Total (n,%)	22 (42)	22 (35)	12 (27)	10 (27)	9 (24)	7 (25)
E. coli (n,%)	13 (1)	18 (1.2)	10 (0.5)	6 (0.3)	8 (0.3)	5 (0.2)
Other Gram-negative agents (n,%)	9 (0.7)	4 (0.3)	2 (0.1)	4 (0.2)	1 (0.04)	2 (0.09)

B. Late-onset sepsis

Years Period	1978-1982 I	1983-1987 II	1988-1992 III	1993-1997 IV	1998-2002 V	2003-2006 VI
Admitted infants (n)	1276	1523	1909	2034	2382	2278
Sepsis (n,%)	146 (11.4)	133 (8.7)	137 (7.1)	279 (13.7)	415 (17.4)	318 (13.9)
Gram-positive agents						
Total (n,%)	111 (76)	109 (82)	120 (88)	252 (90)	375 (90)	298 (94)
CoNS (n,%)	89 (7)	83 (5.4)	77 (4)	205 (10)	329 (13.8)	248 (10.9)
S.aureus (n,%)	14 (1)	17 (1.1)	34 (1.8)	30 (1.5)	42 (1.8)	39 (1.7)
Other Gram-positive agents (n,%)	8 (0.6)	9 (0.6)	9 (0.5)	17 (0.8)	4 (0.2)	11 (0.5)
Gram-negative agents						
Total (n,%)	35 (24)	23 (17)	14 (10)	22 (8)	34 (8)	16 (5)
E. coli (n,%)	20 (1.6)	12 (0.8)	6 (0.3)	9 (0.4)	13 (0.5)	7 (0.3)
Enterobacter (n,%)	2 (0.2)	8 (0.5)	4 (0.2)	5 (0.2)	8 (0.3)	5 (0.2)
Klebsiella (n,%)	9 (0.7)	1 (0.06)	3 (0.15)	3 0.14)	10 (0.4)	3 (0.13)
Other Gram-negative agents (n,%)	4 (0.3)	2 (0.13)	1 (0.05)	5 (0.2)	3 (0.12)	1 (0.04)
Yeasts						
Candida (n,%)	0 (0)	1 (0.1)	3 (0.2)	5 (0.2)	6 (0.3)	4 (0.1)

Figure 3 Distribution of Gram-positive and Gram-negative microorganisms causing late-onset sepsis during 1978-2006, shown as 6 periods.



causative microorganisms in early-onset sepsis (Table 1A). The incidence of early-onset GBS sepsis decreased from 1.8% during period I to 1% in period IV, just prior to 1998, during which year the program for GBS prevention was implemented in The Netherlands, which is based on risk factors, such as prematurity, prolonged rupture of membranes, signs of maternal infection during delivery and an earlier infant with GBS disease. However, since 1998 the incidence decreased further to 0.7% during periods V and VI. Table 1A also shows a gradual and significant decrease in incidence of early-onset *E.coli* sepsis from 1% during period I to 0.2% in period VI ($p<0.05$). Early-onset sepsis due to all other microorganisms, including Gram-negatives occurred sporadically.

Because the GBS prevention program is based on risk factors such as prematurity, we studied the gestational age of all infants with GBS sepsis and found that before the GBS prevention program, GBS disease occurred more frequently among premature infants: 78% of all infants with GBS disease during period I was preterm, as compared with period VI, when 47% of all infants with GBS disease was preterm ($p< 0.05$).

Late-onset sepsis

Figure 3 shows a gradual change in the distribution of Gram-positive and Gram-negative microorganisms in late-onset sepsis over the years. Table 1B shows an increasing predominance of CoNS and *S. aureus*, which were the most frequent causative agents in late-onset sepsis, together accounting for 90% (80% CoNS and 10% *S. aureus*) of all cases of late-onset sepsis in period VI. Most cases of late-onset sepsis were due to CoNS. During the earlier years (periods I-III) the incidence of CoNS sepsis was relatively low (4-7.1%). However, since period IV the incidence increased significantly, to 10.9% during period VI (p=0.001). *S. aureus* was the second most frequent causative agent of late-onset sepsis,

but the incidence (1-1.8%) was low during all periods. Gram-negative microorganisms were infrequent causative microorganisms in late-onset sepsis in our unit, even showing a decreasing trend over the years. Late-onset sepsis due to *Candida* species occurred sporadically, with a low incidence among the total NICU population (<0.3%). Since Gram-negative sepsis and sepsis due to *Candida* species affects the group of very low birth weight infants, we determined the incidence of these sepsis cases among infants with birth weight less than 1500 g and found, even in this selected group, a very low incidence of sepsis due to Gram-negative microorganisms (2.6% in period V and 1.1% in period VI) and sepsis due to *Candida* species (0.6% in period V and 0.2% in period VI).

Antibiotic susceptibility

GBS blood isolates remained fully susceptible for penicillins and other beta-lactam antibiotics. Before 1988 *E. coli* blood isolates were fully susceptible to ampicillin and amoxicillin (data not shown). In 1988 ampicillin- and amoxicillin-resistant *E. coli* isolates were found among blood isolates and colonising strains, which was reason to change the antibiotic regimen to amoxicillin/clavulanic acid that year. During 1993-1997 (data not shown) and incidentally in 2003 a temporary increase was noted in resistance to amoxicillin/clavulanic acid among *E. coli* blood isolates (1 out of 4 isolates was resistant in 2003). However, in 2005 and 2006 *E. coli* blood isolates were fully susceptible for amoxicillin/clavulanic acid (3/3 and 4/4, respectively). Except for 2003, when 1 out of 4 isolates was resistant for aminoglycosides, *E. coli* were fully susceptible for aminoglycosides and third generation cephalosporins (cefotaxime, ceftazidime), the latter used in the treatment of *E. coli* sepsis and meningitis in our NICU. Methicillin-resistant *S. aureus* blood isolates were not found, despite the presence of isolated cases of infants colonised with MRSA in our unit. *S. aureus* isolates remained fully susceptible to oxacillin, vancomycin and first generation cephalosporins. Table 2 shows the susceptibility patterns of CoNS sepsis during a period between 1999 and 2007. CoNS blood isolates showed increasing oxacillin resistance over the years, but were fully susceptible to vancomycin. Infants with late-onset sepsis are treated with first generation cephalosporins in our unit and CoNS blood isolates are tested for cephalotin and cefazolin susceptibility; 95% of the CoNS blood isolates in 2006 appeared to be susceptible for these antibiotics.

Table 2 Susceptibility of CoNS in neonatal sepsis.

	1999	2001	2003	2005	2006
CoNS isolates (n)	57	54	81	81	79
Oxacillin	9/56 (16%)	4/54 (7%)	15/80 (19%)	13/78 (17%)	4/79 (5%)
Clindamycin	52/56 (93%)	48/52 (92%)	75/80 (94%)	64/78 (82%)	63/74 (85%)
Vancomycin	56/56(100%)	54/54(100%)	80/80(100%)	78/78(100%)	78/78(100%)
Cefazolin/Cephalotin	49/50 (98%)	45/54 (83%)	68/81 (84%)	66/78 (85%)	76/79 (95%)
Rifampicin	55/57 (96%)	50/52 (96%)	76/79 (96%)	78/80 (98%)	78/78(100%)
Gentamicin	17/55 (31%)	11/52 (21%)	51/79 (65%)	37/78 (47%)	12/79 (15%)

CoNS: coagulase-negative staphylococci

DISCUSSION

The low incidence of early-onset sepsis and high incidence of late-onset sepsis in our NICU is in concordance with what is found in large multi-centre studies among preterm infants.[4,16] A recent update on the epidemiology of early-onset neonatal sepsis of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network revealed that the increasing use of intrapartum antibiotics over the last decade did not influence the overall rates of infection.[16] Since the introduction of guidelines for the prevention of neonatal GBS disease a shift is reported from Gram-positive microorganisms as causative pathogens (mainly GBS) to Gram-negative microorganisms, with a prominent role for *E. coli*.[10,16-18] In contrast to the NICHD Neonatal Research Network Study, our study found a gradual preponderance of Gram-positive infections.[16] In addition, we noticed a steady decrease in the rate of GBS sepsis, occurring even before the introduction of the GBS prevention program in 1998, which was probably related to the increased maternal antibiotic use to prevent preterm delivery. Although a decrease in cases of GBS sepsis is found, GBS still are the most important causative agents in early-onset sepsis in our neonatal unit, which is similar to the nationwide situation in The Netherlands.[11,19] A second interesting finding in our study was the significant trend toward more affected term infants among the infants with early-onset GBS sepsis, which may be explained by the increased maternal antibiotic use in an effort to prolong pregnancy and by the fact that in The Netherlands the GBS prevention program is based on risk factors and not on screening results.[19] We did not find an increased incidence in early-onset sepsis caused by other organisms than GBS, especially *E. coli*, as was observed in other studies and for which the increased maternal ampicillin use was considered responsible.[16-18]

In contrast to previous reports we only found a few cases of early-onset sepsis caused by coagulase-negative staphylococci.[16] These microorganisms, however, are the main causative agents in neonatal late-onset sepsis, which is confirmed in many other studies.[6,8,9,16,20,21]

We found a marked increase in incidence of late-onset sepsis due to CoNS, especially since period IV, which was probably associated with the strong increase in the use of percutaneously inserted central venous catheters since their introduction in period III, which are recognised risk factors for neonatal sepsis.[4,22,23]

The interpretation of CoNS as true pathogens is still under debate.[24-26] However, it is accepted to consider CoNS as true pathogens in an infant with clinical symptoms of sepsis, when the blood culture is positive within 24-48 hours.[14,27]

The second most frequent causative agent for late-onset sepsis was *S. aureus,* which usually presents with comparable clinical symptoms as in sepsis due to CoNS. Despite the world-wide increased circulation of methicillin-resistant *S. aureus* isolates, we did not have a single case of sepsis due to MRSA in our neonatal unit, which may be associated with the Dutch policy to strictly isolate patients colonised with MRSA strains. Our study did not confirm the internationally reported increase in late-onset sepsis due to Gram-negative rods, such as *E. coli*.[10,18] An additional difference between our study and other reports is the very low incidence in our study of late-onset sepsis due to *Candida* species,

even among very low birth weight infants.[28]. Interestingly the incidence of neonatal *Candida* sepsis is low in the Netherlands in general [29]. Prolonged use of antimicrobial agents, resulting in alterations of the normal skin and gastro-intestinal microbial flora, are recognised risk factors for invasive candidiasis, as are host risk factors, especially in very preterm infants with gestational age below 28 weeks. A factor which may be associated with the lower rate of Gram-negative and *Candida* infections in our unit is the use of a strict protocol for antibiotic treatment, which restricts the use of vancomycin and third generation cephalosporins and suggests the discontinuation of antibiotics after 48 hours when the blood culture is negative and clinical signs of infection are absent.[30]

Analysis of the susceptibility of the major pathogens in neonatal sepsis to the antibiotics used in our NICU showed increasing resistance among *E. coli* blood isolates to ampicillin, which is in agreement with other studies.[23] The susceptibility of *E. coli* blood isolates to amoxicillin-clavulanic acid and gentamicin was high, except for a short period during 2003. The empiric treatment for suspected early-onset sepsis due to *E. coli* in our unit is amoxicillin-clavulanic acid in combination with gentamicin. However, when the diagnosis *E. coli* sepsis is confirmed, the antibiotic therapy is switched to third generation cephalosporins (ceftazidime), for which all *E. coli* blood isolates were 100% susceptible throughout the years.

CoNS generally are resistant to oxacillin and for this reason the empiric therapy for suspected CoNS sepsis is vancomycin in most neonatal units.[15] Indeed, CoNS blood isolates from infants admitted at our NICU have become increasingly resistant to oxacillin, which was shown by a steady increase in *mecA* gene carriage in an earlier study.[31] Another study from our NICU reported the successful treatment of infants with CoNS sepsis with first generation cephalosporins instead of vancomycin even in cases of oxacillin resistance.[32] The policy in our unit is to use vancomycin only in cases of treatment failures with first generation cephalosporins. As a result of this policy, vancomycin use is still limited in our NICU. Karlowicz et al confirmed the successful treatment of CoNS sepsis with oxacillin, avoiding the use of vancomycin, and suggested that this is possible because CoNS sepsis usually is a mild disease.[33]

In summary, our epidemiological study confirmed the generally reported increased incidence of neonatal late-onset sepsis, predominantly caused by CoNS, and a decrease in incidence of early-onset sepsis caused by GBS. However, in contrast to other studies we do not experience an increase in Gram-negative infections, neither in early-onset sepsis, nor in late-onset sepsis. We found a gradually increasing preponderance of Gram-positive infections in early-onset sepsis, with a shift towards term infants with early-onset GBS sepsis, probably associated with the increased maternal antibiotic use before preterm delivery. The incidence of sepsis due to *Candida* species is very low. Moreover, in contrast to the widely implemented protocol for treatment of infants with CoNS sepsis with vancomycin, these infants may successfully be treated with first generation cephalosporins, saving the use of vancomycin for selected cases.

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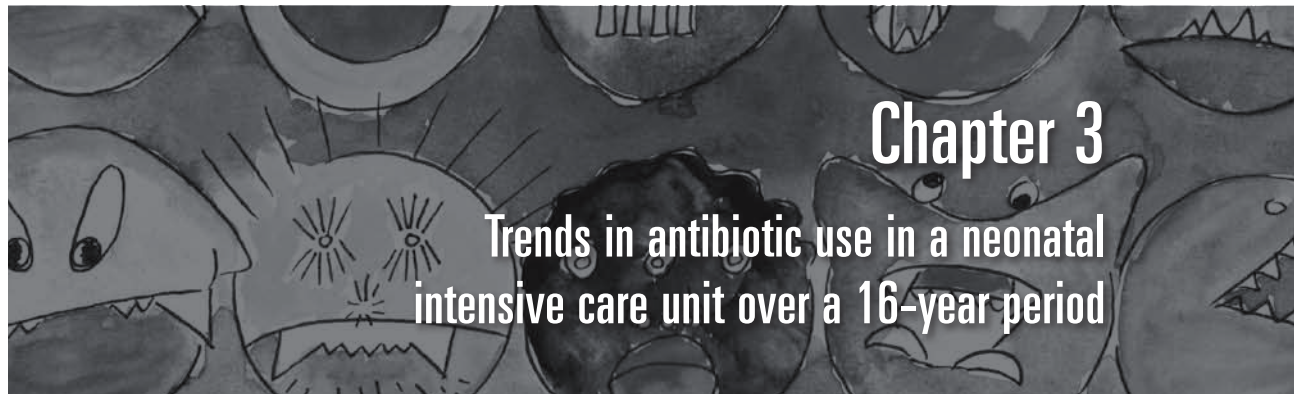

Chapter 3

Trends in antibiotic use in a neonatal intensive care unit over a 16-year period

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Submitted

ABSTRACT

Background:
Infectious disease teams (IDT) contribute to the accurate prescription of antibiotic therapy in hospitals. Reducing antibiotic pressure is important to prevent the emergence of antimicrobial resistant microorganisms, especially in (neonatal) intensive care units (NICUs). Therefore, monitoring antibiotic use is essential. Antibiotic use was studied in the NICU over a period of 16 years, from 1990 onwards, when the IDT started its activity.

Methods:
Antibiotic use was retrospectively studied of all infants admitted to the NICU during 2-year intervals (1990-2006) and shown for three periods of 3 years. Antibiotic use was compared over time by linear regression analysis.

Results:
Length of hospitalization (20 days in period I, 16 days in period III, p=0.029) and mortality (17% in period I, 10% in period III, p=0.031) decreased, whereas the incidence of sepsis was unchanged (14.1% and 15.6% during periods I and III, respectively). Eighty-five to 90% of infants received antibiotics, relative to the much lower incidence of sepsis. A significant decrease in length of use was noted for amoxicillin-clavulanic acid (p=0.011), aminoglycosides (p=0.003) and cephalotin/cefazolin (p=0.002).

Conclusions:
The percentage of infants treated with antibiotics remained high, whereas the duration of treatment with amoxicillin-clavulanic acid, aminoglycosides and cephalotin/cefazolin decreased significantly over time, without increase in incidence of sepsis or mortality. Guidelines for antibiotic therapy for neonatal sepsis were unchanged during 16 years. The IDT may have played a key role. Correct identification of infants with sepsis remains a major challenge in attempts to further reduce antibiotic use and postpone the emergence of antibiotic resistant microorganisms.

INTRODUCTION

Antibiotics are among the most frequently used drugs in neonatal intensive care units (NICUs).[1-5] The extensive use of antibiotics in NICUs is the result of specific risk factors for infection, such as compromised immunological defenses, especially in preterm infants, and multiple invasive procedures, in particular the insertion of central venous catheters, the administration of parenteral nutrition and mechanical ventilation.[6] Finally, clinical symptoms of infection are non-specific and difficult to distinguish from symptoms occurring in other neonatal diseases. Therefore the vast majority of infants are treated with antibiotics at some time during their NICU stay. Another important issue in the high rate of antibiotic use is the prolonged duration of antibiotic treatment, even when cultures are negative. Equal to the difficulty to accurately identify a neonate with infection, is the exclusion of infection, especially in very preterm infants with increased risk factors for infection.[7]

It is well recognized that extensive and inappropriate antimicrobial use, further adding to the antibiotic pressure, contributes to the emergence and spreading of antibiotic resistant microorganisms among hospitalized patients, which has a major impact on patient morbidity and mortality, and healthcare costs.[8-10] Therefore, restricted and appropriate antibiotic use is essential to prevent the emergence of multidrug resistant microorganisms.[11] Multidisciplinary infectious disease teams (IDTs) have shown to positively contribute to the accuracy of antibiotic therapy.[12-16]

Since 1990 an IDT has been active in the NICU of the Wilhelmina Children's Hospital, University Medical Center Utrecht. All cases of infection and antibiotic treatment are discussed with the IDT. Recently, this IDT studied trends in antibiotic susceptibility of the major blood isolates from infants with neonatal early- and late-onset sepsis from the NICU over a period of 29 years. The study showed no major changes in susceptibility patterns among the four most frequently isolated causative microorganisms (Group B streptococci, *E. coli*, *S. aureus* and coagulase-negative staphylococci).[17] However, since increasing antibiotic resistance is reported, especially among Gram-negative microorganisms, it is essential to monitor antibiotic susceptibility patterns of causative microorganisms and antibiotic use, to determine the optimal antibiotic therapy for the treatment of neonatal sepsis. Therefore, the aim of this study is to identify trends in antibiotic use in our NICU over a period of 16 years from 1990 onwards, with a special focus on neonatal sepsis.

METHODS

Setting

The Wilhelmina Children's Hospital is a 200 bed referral center for a population of approximately 2 million inhabitants (12% of the Dutch population) and part of the University Medical Center Utrecht, located in the central part of the Netherlands. From 1990-1999 the NICU was a 21-bed level III unit, which expanded, after moving

to a new location, to a 28-bed unit with 550 annual admissions, covering an area with 30,000 annual live births (15% of the total annual birth rate in the Netherlands). The NICU is one of eight universities and one of a total of ten neonatal referral centers. The indications for admission at the NICU are in agreement with guidelines implemented by the Dutch Society of Neonatology. Since 1990 an IDT was functional, including a pediatric infectious disease specialist, a medical microbiologist specialized in the field of pediatric infectious diseases and a neonatologist with special interest in neonatal infectious diseases. All cases of infection are discussed during weekly meetings and more often if required. Although the indications and the antibiotic regimen for neonatal infections are described in a protocol, the IDT is frequently consulted before initiation or discontinuation of antibiotic treatment.

Study population and clinical data

Demographic data (gender, birth weight [BW], gestational age [GA], length of hospitalization and mortality) and clinical characteristics (proven early-, or late-onset sepsis, presence of a central venous catheter [CVC], administration of total parenteral nutrition [TPN], and mechanical ventilation) were obtained from all infants admitted to the NICU during each second year (1990 through 2006) and reported for three clusters of three years (period I: 1990, 1992, 1994; period II: 1996, 1998, 2000; period III: 2002, 2004, 2006).

Regarding data on antibiotic use, a sample of all infants admitted to the NICU during the first three months of each two-year time window was included in the study. For each included infant, data on antibiotic use were obtained: specific antimicrobial agent and total duration, expressed as mean number of days, of treatment with each individual antimicrobial agent. Antibiotics are prescribed according to a protocol in use since before 1990, which includes indications, choice of antibiotics and the recommended duration of therapy. The standard dose is prescribed in the local formulary.[18] In general, a penicillin-derivative combined with an aminoglycoside is recommended for suspected early-onset sepsis and in infants at risk for early-onset sepsis, and a first generation cephalosporin in combination with an aminoglycoside for suspected late-onset sepsis. For meningitis, necrotizing enterocolitis and local infections specific antibiotic combinations are recommended, as well as for the treatment of infections due to antibiotic resistant microorganisms.

Data analysis

Antimicrobial drug use was compared over time by linear regression analysis. *P*-values < 0.05 were considered statistically significant. Descriptive analyses were performed to assess the distribution and frequency of the dependent and independent variables. Statistical analyses were performed by SPSS for Windows, version 15.0 (SPSS Inc., Chicago, Il, USA).

RESULTS

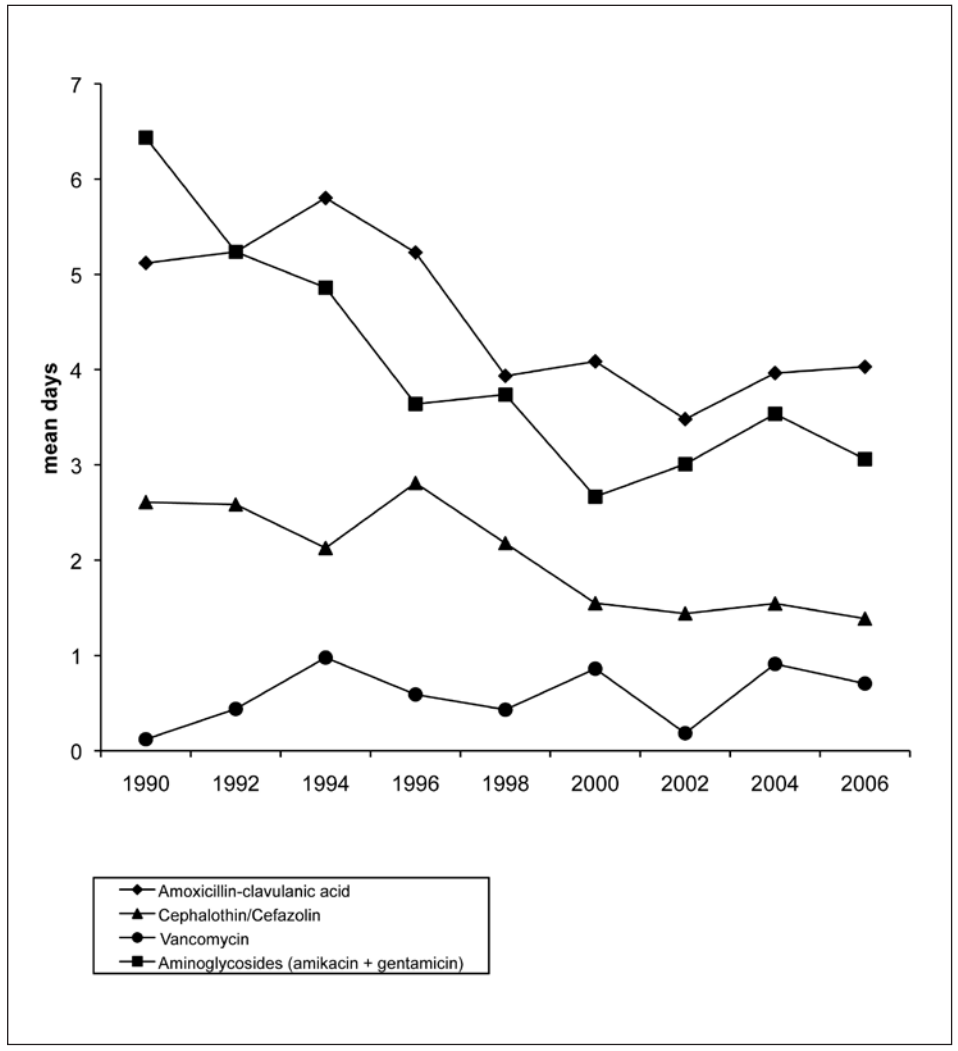
The clinical and demographic characteristics of all included infants did not show significant differences between the three periods, with exception of a decreased length of hospitalization (20 days in period I and 16 days in period III, p=0.029) and decreased mortality (17% in period I and 10% in period III, p=0.031). The incidence of sepsis did not change significantly during all periods (Table 1). A steady and high percentage (range 85-90%) of all admitted infants received antibiotic treatment during any time of their stay, which was in contrast to the proportion of infants with proven early-, or late-onset sepsis (range 1.2-2.4% and 7.1-14%, respectively).

Although the proportion of infants treated with antibiotics remained more or less constant during the study period, a significant decrease was observed in the duration of antibiotic treatment for the three most frequently used antimicrobial agents for neonatal sepsis, i.e. amoxicillin-clavulanic acid, the first generation cephalosporins (cefazolin and cephalotin) and the aminoglycosides (gentamicin and amikacin), (Figure 1). The decrease in duration was significant for all three antimicrobial agent groups and

Table 1 Clinical and demographic characteristics of all infants admitted to the NICU of each two-year time interval (1990–2006)

		Period I	Period II	Period III	
Years		1990, 1992, 1994 (n=1207)	1996, 1998, 2000 (n=1368)	2002, 2004, 2006 (n=1656)	*p*-value
Gender	Male, n (%)	674 (55.8)	762 (55.7)	965 (58.3)	*ns*
Birth weight (grams)	< 1500, n (%)	473 (39.2)	486 (35.6)	568 (34.3)	*ns*
	≥ 1500, n (%)	734 (60.8)	881 (64.4)	1088 (65.7)	*ns*
Gestational age (weeks, mean)	< 32, n (%)	520 (43.1)	522 (38.2)	664 (40.1)	*ns*
	≥ 32, n (%)	687 (56.9)	845 (61.8)	992 (59.9)	*ns*
Length of stay (days, mean ± SD)		20.1 ± 24.1	18.1 ± 21.7	16.4 ± 20.1	*0.029*
Mortality, n (%)		203 (16.8)	178 (13.0)	163 (9.8)	*0.031*
Presence of mechanical ventilation, n (%)		833 (69.0)	992 (72.5)	1205 (72.8)	*ns*
Presence of central venous catheter, n (%)		963 (79.8)	1069 (78.1)	1284 (77.5)	*ns*
Administration of Total Parenteral Nutrition, n (%)		788 (65.3)	1139 (83.3)	1349 (81.5)	*ns*
Proven neonatal sepsis, n (%)		170 (14.1)	227 (16.6)	259 (15.6)	*ns*

Figure 1 **Duration of treatment with the most frequently used antimicrobial agents in the NICU, expressed as mean number of days of treatment for all infants, based on data of a sample of infants admitted to the NICU during the first three months of each two-year time interval (1990-2006)**



most strongly both for amoxicillin-clavulanic acid, B = -0.117; 95% CI -0.197; -0.036; p=0.011 and aminoglycosides, B = -0.194; 95% CI -0.297; -0.09; p=0.003 and to a lesser extent for cephalotin/cefazolin, B = -0.089; 95% CI -0.134; -0.043; p=0.002. The use of vancomycin was limited (mean number of days of treatment per admission varied between 0.1 and 1) and did not show a decreasing or increasing trend. Likewise, the use of other antimicrobial agents, particularly extended spectrum beta-lactam antibiotics, e.g. meropenem, or ceftazidim, remained limited during all 16 years (data not shown).

DISCUSSION

In a 16-year period we observed a steady and high percentage of infants treated with antibiotics, whereas the length of use of amoxicillin-clavulanic acid, cephalotin/cefazolin and aminoglycosides (amikacin and gentamicin) decreased. The disproportion between the number of infants treated with antibiotics and infants with proven sepsis is more prominent during the first days of life than later during hospitalization. During the latter period a change in appearance of an infant and in symptoms is more easily attributed to infection than during the period directly after birth, when symptoms are not specific and may be attributed to other neonatal diseases. Since the interpretation of clinical symptoms of sepsis during the first days of life is difficult, antibiotic therapy is easily initiated in these situations. Moreover, according to the general guidelines, antibiotics are initiated in infants with increased risk factors for infection, such as in infants born prematurely with prolonged rupture of membranes. However, when blood cultures remain negative and the clinical situation has improved, the IDT decides to discontinue antibiotic treatment after 2 or 3 days. It is very likely that this regimen is the basis of the more prominent decrease in duration of therapy with amoxicillin-clavulanic acid and aminoglycosides, which combination is the empiric regimen for early-onset sepsis, as compared with the more modest decrease in duration of therapy with first generation cephalosporins, which are first choice in late-onset sepsis. Nevertheless, the duration of treatment with first generation cephalosporins in infants with sepsis caused by coagulase-negative staphylococci (CoNS) did also decrease over the years, since the IDT ever more frequently decides to early discontinue the administration of anti-CoNS therapy in infants who quickly recovered, who did not have an indwelling central venous catheter and in whom laboratory parameters, such as C-reactive protein normalized. Although sepsis due to CoNS may well be treated without removal of the central venous catheter, it is recommended to remove the catheter whenever possible.

This study showed that the use of vancomycin was limited over the years. Vancomycin is used selectively in infants with sepsis due to CoNS who fail to recover after treatment with first generation cephalosporins, even when a central venous catheter has been removed. Based on susceptibility patterns of CoNS the treatment protocol for CoNS sepsis did not have to be changed in our NICU. Remarkably, the protocol for antibiotic treatment of neonatal sepsis was unchanged during the entire period of 16 years. In this way, antimicrobial agents such as third generation cephalosporins and carbapenems, in addition to vancomycin, were used infrequently and did not play an important role in the antibiotic pressure in the NICU. Moreover, a previous study from our NICU did not reveal increasing antibiotic resistance among the four most frequently isolated microorganisms from the bloodstream .[17] Although increasing antibiotic resistance is observed among Gram-negative microorganisms that colonize the infants during hospitalization, sepsis due to these microorganisms did not occur during the study period. Because of increasing antibiotic resistance, continuous adherence to the prudent use of antibiotics is warranted. Finally, the use of a restricted number of antimicrobial agents during the period of 16 years did not have negative effects on the incidence of sepsis nor on

mortality. On the contrary, our study showed that mortality decreased.

There are scarce data on antibiotic use in NICU patients.[19-22] Similar patterns in antibiotic use in the neonatal period were reported: the most frequently used classes of antibiotics are penicillins, cephalosporins, aminoglycosides and glycopeptides.[23] However, none of these studies have investigated antibiotic use over a long time period, hence comparisons are difficult to make.

In conclusion, we have shown that there was a decrease in the length of use of the three most important antibiotic regimens in our NICU, amoxicillin-clavulanic acid, cephalotin/cefazolin and aminoglycosides without an increase in incidence of sepsis and mortality. The treatment protocol for neonatal sepsis was unaltered over the 16 year period. An active IDT, as was introduced in our NICU in 1990, may have played a key role. However, since no reduction was found in the total percentage of infants treated with antibiotics, the correct identification of infants with infections remains a major challenge in the attempts to further reduce antibiotic use and postponing the emergence of antibiotic resistant microorganisms.

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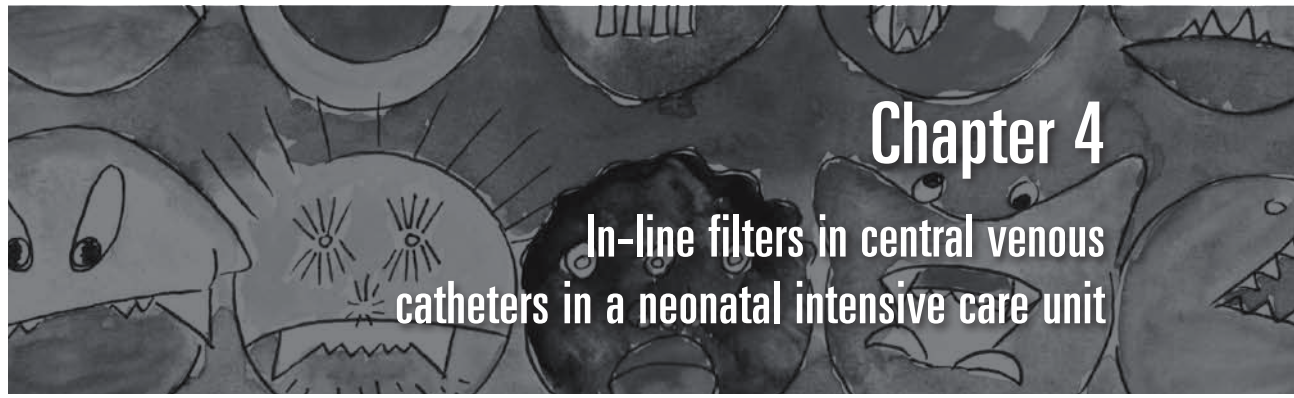

Chapter 4

In-line filters in central venous catheters in a neonatal intensive care unit

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ABSTRACT

Nosocomial sepsis remains an important cause of morbidity in neonatal intensive care units. Central venous catheters (CVCs) and parenteral nutrition (TPN) are major risk factors. In-line filters in the intravenous (IV) administration sets prevent the infusion of particles, which may reduce infectious complications. We randomized infants to in-line filter (for clear fluids and lipid emulsions) or no filter placement. Sepsis, nursing time and costs were assessed. IV-sets without filters were changed every 24h, IV-sets with filters every 96h. Of 442 infants with a CVC 228 were randomized to filter placement, 214 to no filter. No differences were found in clinical characteristics, CVC-use and catheter days. Nosocomial sepsis occurred in 37 (16.2%) infants with filters, in 35 (16.3 %) in the group without filter (N.S.). Nursing time to change the IV-administration sets was 4 minutes shorter in the filter-group ($p< 0.05$). Costs of materials used were comparable.

In conclusion, the incidence of sepsis when using filters was not reduced but the nursing time for changing the intravenous administration systems was reduced without a difference in costs.

INTRODUCTION

Nosocomial infections are a major cause of morbidity in neonatal intensive care units (NICUs).[1] The majority of these infections are blood stream infections associated with prematurity and invasive diagnostic and therapeutic procedures.[1, 2] Almost all low birth weight infants receive total parenteral nutrition (TPN) administered through a central venous catheter (CVC). TPN, including lipid emulsions, and the use of CVCs are the most important risk factors for nosocomial sepsis in these infants. Coagulase-negative staphylococci are the most frequent causative microorganisms of neonatal nosocomial sepsis.[1-5]

The incidence of nosocomial sepsis remains high, despite adherence to strict hygienic measures.[1] In-line filters placed in all intravenous (IV) systems may prevent the accidental infusion of particles, air bubbles, microbes and endotoxins [6-9] Therefore, using in-line intravenous filters may be effective in the reduction of CVC-associated complications.[10] Although recommendations for the use of in-line intravenous filters have been published, there is no consensus on their use.[11, 12] Because of the potential reduction in infectious complications, the reduction in time necessary for handling the IV systems, diminished interruption of the administration of intravenous medication and TPN and possible reduction in costs for disposable materials[10], we intended to implement the use of in-line filters in our NICU. Before we decided to use in-line intravenous filters we evaluated their effect on the incidence of nosocomial sepsis, nursing time, and costs for disposable materials in a large group of infants in need for a CVC for TPN and medication.

PATIENTS AND METHODS

The study was approved by the local ethical committee. After thorough introduction of the use of in-line intravenous filters, all infants consecutively admitted to the NICU who needed a CVC were randomized, strictly by order of admittance, to in-line filter placement in all IV-administration catheters, or no filter placement. In almost all patients an umbilical vein catheter (UVC) was inserted, accepted only when the tip was in correct central position. Otherwise, the UVC was withdrawn and a peripherally inserted central venous catheter (PICC) was inserted. According to the protocol use in our NICU, UVCs are replaced by PICCs after the first week of life. For clear fluid filtration we used Posidyne Neo filters (Pall ®) with a diameter of 0.2 micron, positioned at the distal end of the IV-administration catheter after a series of stopcocks and 75 cm before the last stopcock at the proximal end of the indwelling CVC. This construction guaranteed that all clear fluids, such as glucose-, amino acid solutions and IV-medication were administered via the filter. Posidyne Neo filters were changed every 96 h as recommended by the manufacturer. For lipid emulsions we used Lipipor TNA filters with a diameter of 1.2 micron (Pall ®), positioned at the distal end of the IV-administration catheter for the lipid solution (Intralipid 20%). This catheter was placed distally to the Posidyne Neo filter and connected to the CVC with a stopcock. Because 1.2 micron filters are not

able to retain endotoxin, Lipipor filters were changed every 24 h as recommended by the manufacturer. In the group without filters the IV-administration sets were changed every 24 h as recommended in the guidelines issued by the Hospital Infection Control Practices Advisory Committee.[12]
Clinical characteristics, CVC insertion site, number of catheter days, the occurrence of sepsis or phlebitis, costs of disposable materials and the nursing time necessary for changing the IV-administration sets were compared between the two groups. Sepsis was defined as occurrence of clinical signs of infection and a positive blood culture. Phlebitis was defined as signs of local infection and a positive culture from the infected site.

Differences between the groups for all variables were tested by Students t-test. Statistical analyses were performed using SPSS® for Windows, version 10.1 (SSPS Inc., Chicago, IL, USA). Statistical significance was assumed for $p < 0.05$.

RESULTS

From November 5, 2001 to November 6, 2002 five hundred and seven neonates were admitted to the NICU. A CVC was inserted in 442/507 (87%) infants, of which 228 were included in the in-line filter group, 214 in the non-filter group. Data of 65 neonates (26 in the in-line filter group, 39 in the non-filter group) were excluded, either because the patient was discharged soon after birth, died within a few days, or because of incomplete data.
The clinical characteristics are shown in Table 1. Gestational age, birth weight, gender, and Apgar score were not different between the two groups, neither were the number of infants with assisted ventilation and the number of ventilation days, the number of hospital days, or mortality. The groups were comparable in the number of infants with a UVC, PICC, or catheter inserted in the subclavian or femoral vein (CVC) (Table 2). Moreover, the number of catheter days was not different between the groups (Table 2).

Table 1 Clinical characteristics

Groups	Filter (n = 228)	No Filter (n = 214)
Gestational age (wks) [median, range]	32 (25-42)	34 (26-43)
Birth weight (g) [median, range]	1653 (610-4410)	2003 (600-4640)
Male/Female	126/102	124/90
Apgar 5 min (median, range)	8 (0-10)	9 (1-10)
Assisted ventilation (number) (%)	137 (60)	131 (61)
Assisted ventilation (days) [median, range]	2 (1-37)	2 (1-26)
Hospital days (median, range)	8 (2-77)	8 (2-51)
Mortality (number) (%)	24 (11)	22 (10)

Table 2 Number of patients with various central venous catheters and catheter days

Groups	Filter (number = 228)	No filter (number = 214)
UVC (number) (%)	144 (63)	124 (58)
UVC (days) [median, range]	4 (1-14)	6 (1-18)
PICC (number) (%)	101 (44)	84 (39)
PICC (days) [median, range]	8 (1-26)	7 (1-40)
CVC (number) (%)	20 (9)	14 (7)
CVC (days) [median, range]	8 (2-21)	6 (2-27)

UVC: umbilical vein catheter
PICC: peripherally inserted central venous catheter
CVC: central venous catheter inserted in subclavian or femoral vein

Table 3 Costs of disposable materials per patient per four days in the groups with and without in-line intravenous filter

Materials	In-line filter	No filter
IV administration set	€ 60.44	€ 241.76
Clear fluid filters	€ 47.27	---
Lipid emulsion filters	€ 130.90	---
Total	€ 238.63	€ 241.76

Sepsis occurred in 37/228 (16.2%) of the infants with filters and in 35/214 (16.3 %) of the infants without filters (p=0.654). When sepsis was expressed as sepsis per 1000 catheter days, the analysis did not reveal differences between the groups: in the total group of patients (filter and no filter use) sepsis occurred in 24/1000 catheter days, whereas in the filter group 22/1000 catheter days and in the group without filter 28/1000 catheter days (p>0.05). The number of catheter days until the occurrence of sepsis was equal in both groups (11 days in the filter group, 10 days in the non-filter group). The most frequent causative microorganisms were coagulase-negative staphylococci, both in the filter and non-filter group (26/37 [70%] and 28/35 [80%], respectively) and *S. aureus* (4/37 [11%] and 2/35 [6%], respectively). Phlebitis did not occur during the study period. In one patient of the filter group the clear fluid filter became blocked, probably due to the administration of very high glucose concentrations (glucose 50%).
The time necessary for changing the IV-administration sets was significantly longer in the non-filter group: the mean nursing time was 14 min ± 7 min in the non-filter group, compared to 10 min ± 5 min in the filter group (p=0.000). The costs associated with placement of filters and changing the IV administration sets once every 96h (but Lipipor filter every day) were in balance with the costs for the daily change of all IV administration sets in the group without filters (Table 3).

DISCUSSION

The use of in-line filters in intravenous administration systems did not result in a reduction of nosocomial sepsis in our study. This finding is remarkable since several experimental studies have confirmed that 1.2 and 0.2 micron filters are able to retain microbes and particles and the latter endotoxins as well.[6-9] The trend towards a decrease in the number of sepsis with the use of in-line filters found in Van Lingen's study could not be confirmed in our study of a five-fold larger number of infants.[10] However, we compared in-line filters with changing the IV systems once every 96h with the conventional used method of daily changing administration sets without filters, as described in the guidelines.[12] Moreover, we also used filters for fat emulsions that had to be changed daily. These two conditions might influence the risk for infection. Our study clearly shows that intravenous administration sets with filters can be safely used for 96h. The important advantage of leaving the administration sets unchanged is that the flow of TPN and medication does not have to be interrupted during 96h. Although we did not substantiate this, it was observed that the clinical situation of infants treated with cardio-inotropics for unstable blood pressure was more stable when the IV administration sets did not have to be changed. An additional advantage of the use of filters is the reduction in total nursing time to handle the intravenous administration sets. This reduction in nursing time is confirmed in other studies.[10, 13] How the nursing time was spent was not an objective in our study. Hospital pharmacy time was found to be reduced as well in hospitals where TPN and continuous IV medication are prepared by the hospital pharmacy with build up of the complete IV-administration systems.[13] We did not evaluate the impact in time and costs for the pharmacy in our hospital, but it is expected to be substantial. The analysis of costs for disposable materials revealed no difference between filter use and no filter use. The extra costs associated with the implementation of in-line filters are compensated by the reduced consumption of IV-administration sets as found in our study. However, when nursing time and hospital pharmacy time are included in the financial balance, in-line filter usage may result in a significant reduction in costs.

Generally, there is still controversy on the use of in-line intravenous filters.[7, 14] A survey in the United Kingdom found that 43% of the medical centres used filters. Of the centres that used filters, 85% filtered amino-acid/glucose solutions, 27% filtered all-in-one solutions and 22% lipid solutions.[11] However, at present, with the increased awareness for patient safety, the use of in-line intravenous filters is advocated, aiming at the retention of particles and air bubbles.[11, 13, 14] The British Pharmaceutical Nutrition Group Working Party has issued recommendations for filter usage during the administration of parenteral nutrition.[11] We have implemented the use of in-line filters in our NICU. Strikingly, the use of in-line filters had a positive effect on the awareness of medical personnel for aseptic procedures, rather than allowing for a more careless approach and trusting the filter as a safety device. In-line filters do not replace the need for wise and sensible handling of intravenous administration sets and central venous catheters.

In conclusion, the use of in-line filters in CVCs did not result in a significant decrease in nosocomial sepsis. The increased costs for in-line filters were compensated by the four times longer usage of intravenous administration sets. The nursing time for changing the intravenous administration systems was significantly reduced with the use of in-line filters. Since the time for handling of the intravenous administration systems is reduced and more continuous administration of intravenous medication and parenteral nutrition is guaranteed, the use of in-line filters in all intravenous administration systems may be recommended in neonatal intensive care units.

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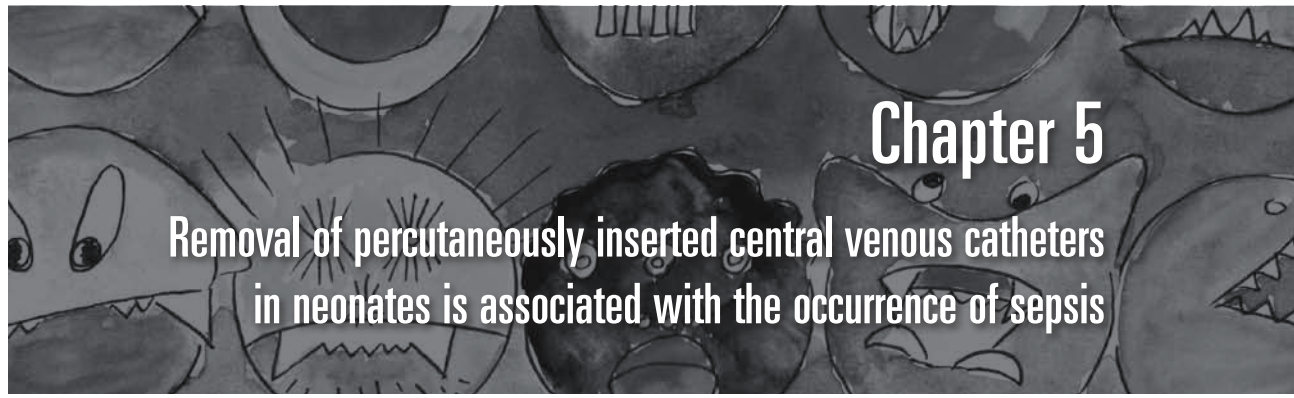

Chapter 5

Removal of percutaneously inserted central venous catheters in neonates is associated with the occurrence of sepsis

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ABSTRACT

Background:
Clinical signs of sepsis are frequently observed after removal of a percutaneously inserted central venous catheter (PCVC) in neonates admitted at our Neonatal Intensive Care Unit (NICU). To substantiate this finding and to evaluate the effect of antibiotics administered at removal of a PCVC we conducted a retrospective study among all infants with a PCVC, admitted at our NICU during 2002 and 2005.

Methods:
Clinical data, infectious complications and antibiotic use were studied retrospectively.

Results:
A PCVC was inserted in 345 infants. Sepsis occurred in 90/345 (26%) infants, in 50/90 (56%) during indwelling PCVC and in 40/90 (44%) after removal of the PCVC. Of the latter 40 sepsis episodes, 24 sepsis episodes (60%) occurred within 5 days after removal of a PCVC, with a clustering of 21 cases of sepsis within 72 hour after removal. The remaining 16 episodes occurred after 7 days. Administration of antibiotics during removal of the PCVC significantly reduced the incidence of sepsis: 22/213 (10.3%) cases of sepsis occurred when no antibiotics were administered versus 2/132 (1.5%) cases of sepsis when antibiotics were administered (p=0.002).

Conclusions:
Our study suggests that peripherally inserted central venous catheters are associated with sepsis, not only during the indwelling period of the catheter, but also after removal. Administration of antibiotics targeted at the time of removal of the catheter significantly reduced the incidence of sepsis. Future prospective studies are warranted to confirm this observation.

INTRODUCTION

Central venous catheters (CVCs) are associated with blood stream infections and account for the major part of the incidence rate of sepsis (11.5 -32.4 %) in neonatal intensive care units (NICUs).[1-3] The risk of sepsis increases with longer duration of an indwelling CVC. [2] Percutaneously inserted central venous catheters (PCVCs) are used in NICUs for long-term venous access to deliver total parenteral nutrition (TPN) and medication, especially in very low birth weight infants.[4] In these infants the risk for CVC-associated sepsis is high.[2] Prophylactic administration of antibiotics during catheterization has been shown to be effective to prevent sepsis.[5-7] However, the long-term use of antibiotics is not advocated in NICUs, because of the danger for emerging multi-resistant microorganisms.[8,9] In addition to the frequently occurring sepsis episodes during the period of indwelling PCVC, we regularly observed that infants developed clinical signs of sepsis within 24-72h after removal of a PCVC. These infants had elevated plasma C-reactive protein (CRP) levels and a positive blood culture. To further substantiate this finding, we studied all infants with a PCVC for the occurrence of sepsis after its removal in relation to antibiotic usage at the moment of removal of the PCVC.

METHODS

We studied all infants with a PCVC admitted at the NICU of the Wilhelmina Children's Hospital, University Medical Centre Utrecht, the Netherlands, during the years 2002 and 2005. Clinical characteristics, sepsis incidence and the use of antibiotics at the time of removal of the PCVC were studied retrospectively.
We used single-lumen, silastic or polyurethane PCVCs (Vygon®), inserted aseptically (including the use of sterile gowns, caps and masks) as a bedside procedure. Insertion sites were covered with a transparent adhesive dressing (Tegaderm®). The preferred position of the catheter tip was in the vena cava superior or vena cava inferior. PCVCs were placed when intravenous access for more than 1 week was considered likely. PCVCs were removed electively when TPN-fluids were less than 50% of the total required intake or no longer necessary. When clinical signs of infection occurred during the indwelling PCVC it was our policy to leave the PCVC inserted and initiate antibiotic therapy. The PCVC was removed when the antibiotic treatment failed, or when *S. aureus,* Gram-negative rods, or yeasts were cultured.
The diagnosis sepsis was based on clinical signs of infection and a positive blood culture. Blood cultures yielding coagulase-negative staphylococci (CoNS) were considered significant when the time to positivity was less than 48h.[10]
In our NICU the combination of first generation cephalosporins (cefazolin) and gentamicin is used for suspected late-onset sepsis. Gentamicin is discontinued when the blood culture yields Gram-positive cocci. Removal of a PCVC in an infant with antibiotic use until 48h prior to the removal was considered as removal without the use of antibiotic. However, it is the policy to continue antibiotic treatment when removal of a PCVC is

expected soon. Of the infants with more than one inserted PCVC, only the first PCVC was included in the analyses.

Statistics

Descriptives were calculated for all important clinical characteristics separately, for infants with and without sepsis after removal of a PCVC, and for infants with and without antibiotic use during removal of the PCVC. Kaplan Meier Survival Curves were performed to show the time until occurrence of sepsis after removal of the PCVC, in the group with and without antibiotics at the moment of removal and differences were analysed with the log-rank test. The remaining analyses were performed by Student t-test and chi square, where appropriate. Statistical analyses were performed using SPSS® for Windows, version 12.1 (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed for $p< 0.05$.

RESULTS

During the study period 1058 infants were admitted at our NICU. In 345/1058 (33%) infants a PCVC was inserted. Sepsis occurred in 90/345 (26%) of these infants, in 50/90 (56%) during indwelling PCVC (incidence 18.1/1000 catheter days) and in 40/90 (44%) after removal of the PCVC, of which 24 cases (60%) occurred within a period of 5 days, with a clustering of cases within 72 h after removal of the PCVC. The remaining 16 episodes occurred beyond 7 days and were apparently not associated with the PCVC removal. Sepsis was due to CoNS in 75% of the cases, *S. aureus* in 6% and Gram-negative rods (*Enterobacter*, *Klebsiella*, *E. coli*) in 19% of the cases. All CoNS and *S. aureus* isolates were susceptible to cefazolin and all Gram-negative rods for gentamicin.

Table 1 shows that gestational age and birth weight were significantly lower in the infants who developed sepsis after removal of a PCVC compared with infants without

Table 1 Clinical characteristics of infants with and without sepsis within 6 days after removal of the PCVC

PCVC (n=345)	Sepsis after removal of PCVC (n=24)	No-sepsis after removal of PCVC (n=321)	Statistics p-value
PCVC duration, d (mean, SD)	9.5 ± 5.1	7.8 ± 4.9	0.096
Gestational age, week (mean, SD)	29 ± 1.8	32 ± 4.4	0.001
Birth weight, g (mean, SD)	1045 ± 228	1754 ± 965	0.000
Ventilation, d (mean, SD)	11.9 ± 7.6	8.3 ± 7.6	0.081

Table 2 Clinical characteristics of infants with sepsis occurring after removal of a PCVC and association with antibiotic use.

PCVC (n=345)	Antibiotic use at removal of PCVC (n=132)	No antibiotic use at removal of PCVC (n=213)	Statistics p-value
Sepsis after removal (n)	2	22	0.002
PCVC duration, d (mean, SD)	7.1 ± 4.9	7.7 ± 4.3	0.773
Gestational age, week (mean, SD)	32 ± 4.8	31.7 ± 4	0.389
Birth weight, g (mean, SD)	1822 ± 1044	1632 ± 880	0.072
Ventilation, d (mean, SD)	8.9 ± 7.4	8.2 ± 7.8	0.470

sepsis during this period. The duration of indwelling PCVC and mechanical ventilation did not differ between the groups.

In all, 132 infants received antibiotics at the time of removal of the PCVC. In 50/132 infants, antibiotics were administered because they developed sepsis during indwelling PCVC. In these infants the antibiotics were continued for at least 24 h after removal of the PCVC. The used antibiotics were cefazolin and gentamicin. In 82/132 infants antibiotics were administered because of suspected but unproven infection or prophylaxis in severe granulopenia, but in all of these cases the blood culture, drawn before the start of antibiotics, remained negative. Administration of antibiotics at the time of removal of the PCVC significantly reduced the incidence of sepsis occurring after removal: two cases of proven sepsis occurred on the second day after removal in the group of 132 infants treated with antibiotics versus 22 cases of sepsis in the group of 213 infants who did not receive antibiotics at the time of removal of the PCVC (p =0.002).

Figure 1 shows the difference in incidence of sepsis and time until the occurrence of sepsis among the infants with and without the use of antibiotic during removal of the PCVC. Both groups, with and without antibiotics at the moment of removal of the PCVC, were similar for gestational age, birth weight, catheter duration and duration of mechanical ventilation (Table 2).

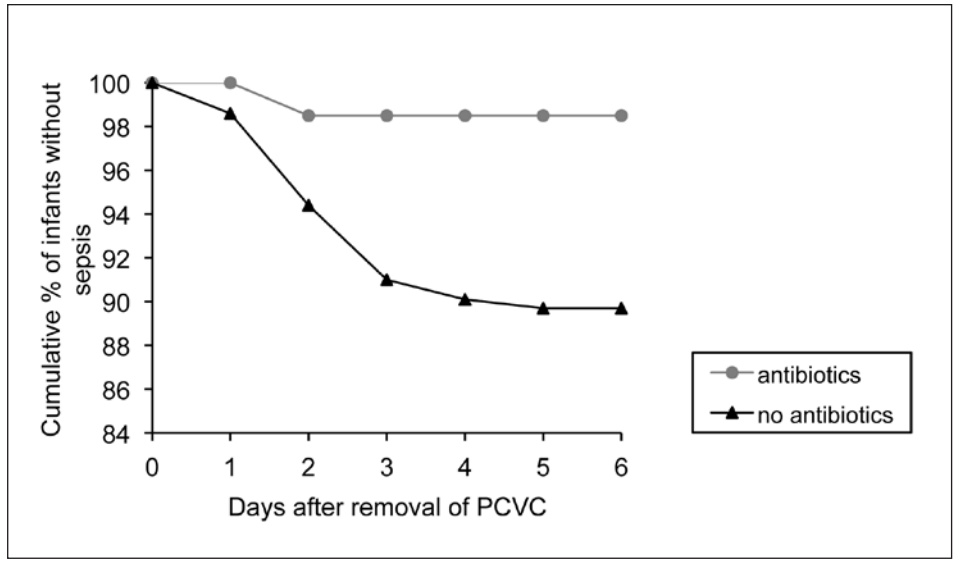
DISCUSSION

CVC-associated sepsis remains an important complication in NICUs. We found that sepsis occurred during an indwelling PCVC in 56% of the cases and in 44% after removal of the PCVC. Of these latter cases more than half (60%) occurred within 5 days after removal of the PCVC, with a peak after 24-72 h. It is hypothesized that with the removal of a catheter the biofilm that is formed on the catheter is stripped off, which causes an influx of bacteria

into the bloodstream. Bacteria escaping the host defence mechanisms will be able to multiply and cause bloodstream infection. However, the amount of bacteria released into the bloodstream, bacterial growth rate and host factors determine the interval between removal of a catheter and onset of sepsis, which may explain the variability in the time of onset of sepsis after removal. There was a clear clustering of cases, however, within 24-72 h after removal. Short gestational age and low birth weight are generally recognized risk factors for catheter-associated sepsis among neonates.[3] Our study showed that these risk factors also apply to infants with sepsis occurring after removal of a PCVC.

A variety of measures have been reported on the issue of reduction of the risk for bloodstream infections in infants with indwelling catheters and among these the administration of antibiotics, that is vancomycin, during catheterization has been shown to be effective in the prevention of catheter-associated sepsis.[5-7] However, the risk of long-term use of vancomycin must be weighed against the benefit of reducing the risk of bacteraemia.[8,9] For these reasons continuous antibiotic prophylaxis for the duration of an indwelling PCVC is not our policy. As we found a high incidence of sepsis within 3 days after removal of a PCVC, we were interested to know whether the use of antibiotics (cefazolin and gentamicin) during the moment of removal of the PCVC influenced the occurrence of sepsis, and found a significant, 7-fold lower incidence of sepsis among infants who received antibiotics at the time of removal of the PCVC. However, the antibiotics were not administered merely for the purpose to prevent

Figure 1 Kaplan Meier Curves of the incidence of sepsis after removal of the PCVC, in the group of infants with antibiotics (N=132) and without antibiotics at the time of removal (N=213). The difference in the incidence between the two groups was significant as estimated by the Log-rank test (p =0.0019)



PCVC removal-associated sepsis. Therefore, future prospective studies are warranted to evaluate the effect of selective administration of cefazolin on PCVC removal-associated staphylococcal sepsis.

In conclusion, our study suggests that peripherally inserted central venous catheters are associated with sepsis, not only during the indwelling period of the catheter, but also after removal. Administration of antibiotics targeted at the time of removal of the catheter significantly reduced the incidence of sepsis. Future prospective studies are warranted to confirm this observation.

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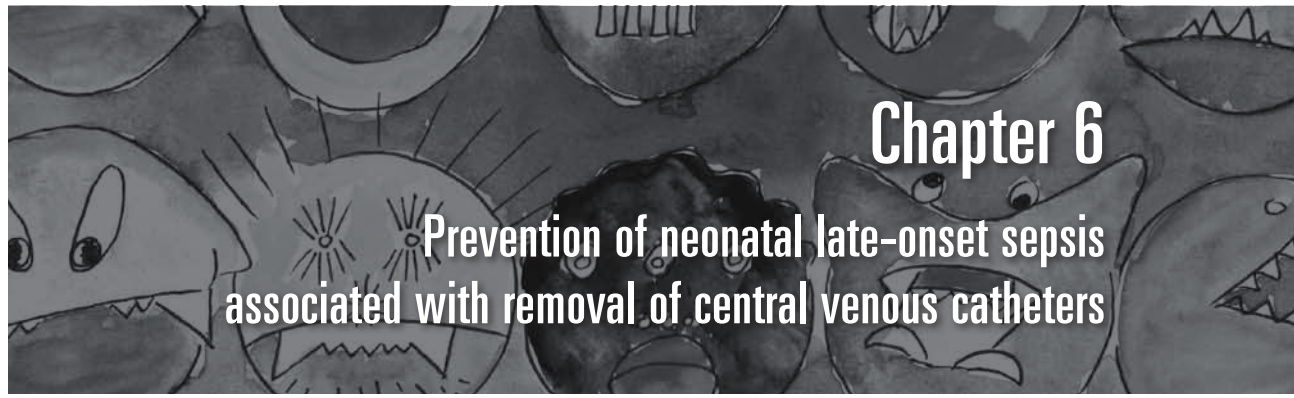

Chapter 6

Prevention of neonatal late-onset sepsis associated with removal of central venous catheters

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ABSTRACT

Background:
Indwelling central venous catheters (CVCs) are an important risk factor for blood stream infections in neonatal intensive care units (NICUs). A retrospective study showed that removal of percutaneously inserted CVCs (PCVCs) was an additional risk factor for sepsis caused by coagulase-negative staphylococci (CoNS) and that antibiotics administered at the time of removal reduced the incidence of sepsis. The prophylactic administration of cefazolin during the procedure of removal of a PCVC was evaluated in a prospective study.

Methods:
Infants with an inserted PCVC, admitted between April 2007 and May 2009, were randomized into the study group receiving cefazolin 100 mg/kg/day in two doses, 1h before and 12h after removal of the PCVC, or into the control group receiving no antibiotics.

Results:
From 173 infants with inserted PCVC, 56 were included, 29 in the study group and 27 in the control group. In 5/27 infants in the control group sepsis due to CoNS occurred, whereas no cases of sepsis occurred in the study group (p = 0.015). In addition in 3 infants of the control group clinical signs of sepsis occurred within 2 days after removal of a PCVC with increased values of C-reactive protein (CRP), but without positive blood culture. CRP was abnormal in 1 infant of the study group on the 3rd day after removal of a PCVC, which infant did not show clinical signs of infection.

Conclusions:
Administration of cefazolin during the removal of a PCVC prevents the occurrence of CoNS sepsis in preterm infants related to the catheter removal. Implementation of this regimen in the guidelines on management of central venous catheters may be indicated.

INTRODUCTION

Central venous catheters (CVCs) are associated with blood stream infections and account for the major part of nosocomial sepsis cases in neonatal intensive care units (NICUs).[1-3]
The most common causative pathogens in CVC-associated sepsis are coagulase-negative staphylococci (CoNS).[3] Although CoNS have a relatively low virulence and the mortality of infections due to CoNS is low, CoNS sepsis is a frequent and significant cause of morbidity in preterm and very low birth weights (VLBW) infants.[4]
Percutaneously inserted central venous catheters (PCVCs) are used in NICUs for long-term venous access to deliver total parenteral nutrition (TPN) and medication, especially in VLBW infants, the category of infants with a high risk for CVC-associated sepsis.[2,5]
The administration of vancomycin during catheterization has been shown to prevent catheter-associated sepsis.[6-9] However, the long-term use of vancomycin is not advocated in NICUs, because of the threat of development of resistance.[10, 11]
In an earlier retrospective analysis we have shown that the administration of antibiotics during the procedure of removal of a PCVC was associated with a 7-fold lower incidence of sepsis, occurring within 72h after removal of the PCVC, compared with infants who did not receive antibiotics.[12] Sepsis associated with PCVC removal was caused by CoNS in all cases. To confirm the findings from this retrospective study a prospective study was carried out to evaluate the effect of the administration of cefazolin during the procedure of removal of a PCVC on the prevention of PCVC-removal associated CoNS-sepsis.

PATIENTS AND METHODS

Study design
We conducted a prospective, randomized controlled intervention study. The study was approved by the local Medical Ethical Committee. After parental informed consent, patients were randomly assigned to either the intervention group (receiving cefazolin) or the control group (no antibiotics) during the procedure of removal of a PCVC. Infants assigned to the intervention group received cefazolin 100 mg/kg/day in two doses, 1h before and 12 hours after removal of the PCVC. Cefazolin is the anti-CoNS antimicrobial agent of first choice in our unit.

Study population
All preterm infants with gestational age (GA) <37 weeks admitted at the NICU of the Wilhelmina Children's Hospital, University Medical Centre Utrecht, the Netherlands, between April 2007 and May 2009, with inserted PCVC were eligible for the study.
Infants with signs of sepsis or receiving antibiotics <24h before the moment of removal of the PCVC were excluded from the study.
Clinical characteristics, including gestational age, birth weight, gender, indication for PCVC, number of catheter days, indication for removal of the PCVC, clinical signs

of sepsis during and after removal of the PCVC, C-reactive protein- (CRP) value at 24, 48 and 72h after removal of the PCVC and mortality were collected in a clinical record form.
The diagnosis sepsis was based on clinical signs of infection (apneic attacks, bradycardias, respiratory distress, tachycardia, hypotension, diminished peripheral circulation, poor skin colour, lethargy, irritability, feeding problems, abdominal distension, fever and temperature instability) and a positive blood culture. Blood cultures yielding CoNS were considered significant when the time to positivity was less than 48 hours.[13]

PCVC management
Single-lumen, silastic or polyurethane PCVCs (Vygon®) were used, inserted aseptically (including the use of sterile gowns, caps and masks and application of appropriate hand hygiene) as a bedside procedure. Insertion sites were covered with a transparent adhesive dressing (Tegaderm®). The preferred position of the catheter tip was in the vena cava superior or inferior. PCVCs were removed electively, preferably when TPN-fluids were less than 50% of the total required intake or, when intravenous access was no longer necessary.

Statistics
Differences between the groups were tested by Student t-test and Chi Square where appropriate, using SPSS® for Windows, version 15.1 (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed for $p < 0.05$.

Table 1 Clinical characteristics of the intervention group (receiving cefazolin during removal of the PCVC) and controls

	Cefazolin N=29	Controls N=27
Sepsis	0*	5
GA (wks) (median, range)	30 (25-36)	29 (26-32)
BW (g) (median, range)	1260 (750-3240)	1120 (660-1870)
Male (%)	58,6	59,3
PCVC (days) (median, range)	8 (3-28)	8 (4-17)
Mortality (n)	0	0

* *p = 0.015*

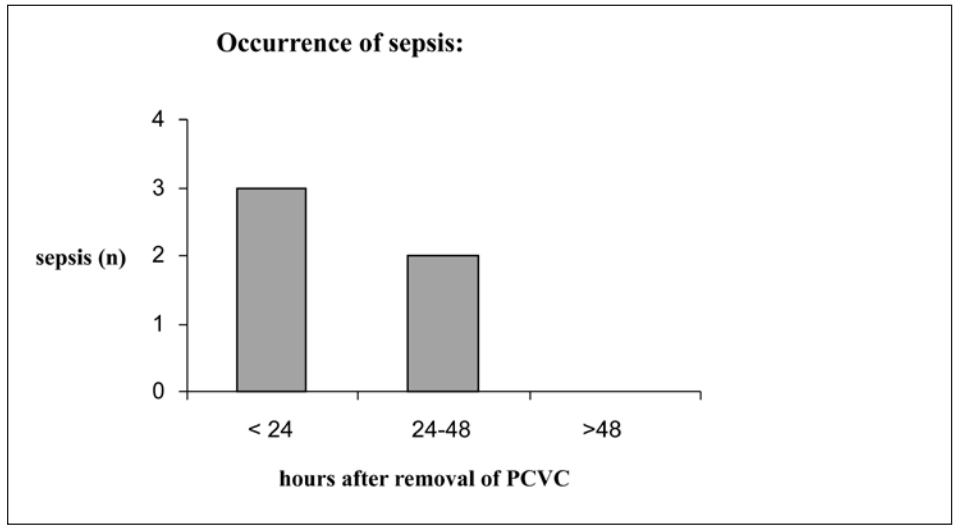
RESULTS

From 173 infants with a PCVC, 56 infants (32%) were included in the study. 117/173 (68%) infants were excluded because of diverse reasons: antibiotic use until < 24h before removal of the PCVC (35%), no informed parental consent obtained (18%), clinical signs of sepsis and for that reason removal of the PCVC (17%), removal of the PCVC because of extravasation (10%) or occurrence of phlebitis (9.5%), or because the infant was transferred while the PCVC was still in situ (7%) or because of death (3.5%).
Of the 56 included infants, 29 were assigned to the intervention group and 27 to the control group. The clinical characteristics and incidence of sepsis are summarized in table 1. The groups were comparable as to demographic data and catheter duration.
Table 1 shows that none of the 29 infants who received cefazolin at the moment of removal of the PCVC developed sepsis, as opposed to 5/27 (18.5%) infants from the control group ($p = 0.015$). Sepsis was caused by CoNS in all 5 cases and all CoNS blood isolates were susceptible to cefazolin.
The median duration of catheter insertion in the 5 infants with sepsis was 9 days (range 7-15) which was not significantly different from the duration of those without sepsis in the control group (median 8, range 4-17).
Figure 1 shows that sepsis developed within the first 2 days after removal of the PCVC in these 5 infants. CRP-values, measured < 24h before the removal of the PCVC, were normal (< 2 mg/L) in all infants in both the intervention group and the control group, except for one infant in the intervention group (CRP 20 mg/L). This infant received cefazolin for 24h on the day of removal of the PCVC, however no clinical signs of infection occurred and CRP normalized. CRP-values measured within 24h after removal of the PCVC were increased to above the normal range in 9/56 infants, 8 from the control group and 1 from the intervention group ($p = 0.008$). The 8 infants from the control group comprised the 5 infants with proven CoNS sepsis and 3 other infants with clinical signs of sepsis but negative blood culture. In these 3 infants anti-sepsis treatment with the combination of cefazolin and gentamicin was initiated according to the protocol in use in our NICU.
The single infant from the intervention group with increased CRP value had a 'normal' CRP value within 24h after removal of the PCVC, but a value of 24 mg/L between 48 and 72h. This infant did not develop clinical signs of sepsis and no antibiotic treatment was initiated.
Gestational age, birth weight and catheter duration of the infants with proven sepsis were not significantly different from values in the infants without sepsis.

DISCUSSION

The present study confirms the results from our earlier retrospective study that removal of a peripherally inserted central catheter imposes a risk for sepsis due to CoNS.[12] In addition the administration of an antimicrobial agent directed to CoNS prevents CoNS sepsis to occur after removal of the PCVC.

Figure 1 Occurrence of sepsis in hours after removal of PCVC



The higher CRP-values in 8 infants from the control group, not receiving anti-CoNS antimicrobials suggest that removal of a PCVC initiates an inflammatory process. In 5 of these infants the blood culture yielded CoNS, whereas in 3 infants sepsis was not confirmed by a positive blood cultures. In only one infant from the study group, receiving cefazolin during removal of the PCVC, CRP value was increased after 48-72h. This infant did not show clinical signs of sepsis. It is suggested that the administration of cefazolin may have prevented sepsis and/or an inflammatory process in this infant. The one infant from the group receiving cefazolin during PCVC removal who showed an increased CRP value just before removal of the PCVC may have been protected from development of catheter-related sepsis, either by the administration of cefazolin during 24h or simply by the removal of the PCVC.

The median gestational age of the 5 infants with proven sepsis was 27.6 (27.2-31.1) weeks, which was not significantly different from the GA of all other included infants. However, it is suggested that infants < 32 weeks of gestation are at risk to develop sepsis after removal of a PCVC. Catheter duration is a recognized risk factor for catheter-related sepsis.[3, 12] However, catheter duration of the infants with proven sepsis was not significantly different from the infants without sepsis.

We have selected cefazolin as an anti-CoNS antimicrobial agent, saving the use of vancomycin for cases with cefazolin-resistant CoNS strains. Ninety-five percent of all CoNS blood isolates from our NICU are susceptible to cefazolin, whereas most isolates are methicillin-resistant (data not shown). For this reason, cefazolin is the antimicrobial agent of first choice for the treatment of CoNS sepsis in our unit.

In addition, we have arbitrarily chosen to treat the infants for a period of 24 hours, starting at 1 hour before removal of the PCVC and administering a second dose 12 hours later. To administer a single dose of cefazolin may be as effective as a 24 hour dose, as may be the administration of an alternative antimicrobial agent.

In conclusion, administration of cefazolin during the removal of a PCVC prevents the occurrence of CoNS sepsis in preterm infants related to the catheter removal.

Implementation of this regimen in the guidelines on management of central venous catheters, may be indicated, although alternative measures, such as limiting the duration of an indwelling catheter, or use of antibiotic-coated or silver-impregnated catheters may have a similar preventive effect.

Further studies are warranted to evaluate these alternative strategies.

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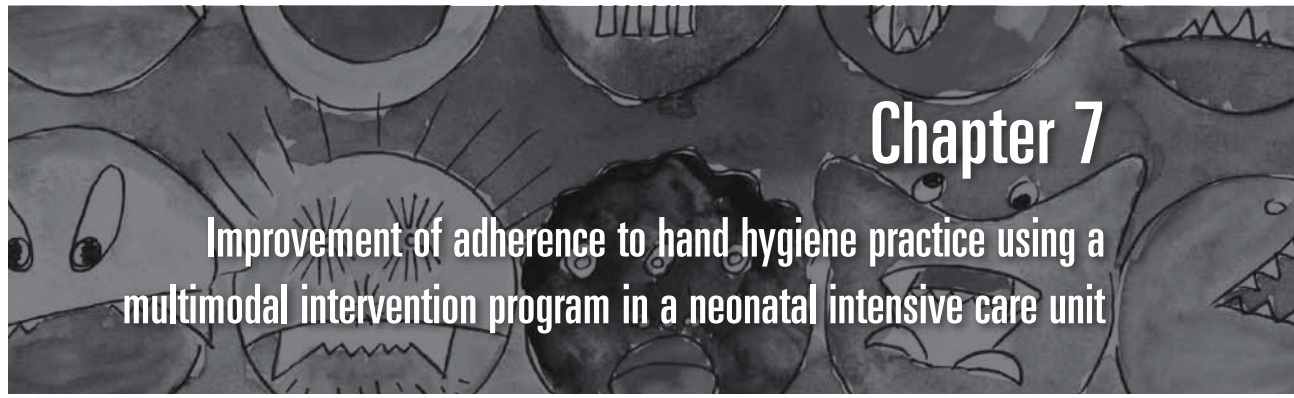

Chapter 7

Improvement of adherence to hand hygiene practice using a multimodal intervention program in a neonatal intensive care unit

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Submitted

SUMMARY

Background:
Nosocomial infections are serious complications among premature infants admitted to neonatal intensive care units (NICUs) and contribute considerably to neonatal morbidity. Hand hygiene is considered as one of the most effective measures to prevent hospital-acquired infections.

Aim:
To assess, promote and improve hand hygiene practices in the NICU of the Wilhelmina Children's Hospital, University Medical Centre, Utrecht.

Methods:
Adherence to hand hygiene guidelines among all Health Care Workers (HCWs) were compared between a baseline assessment and a second assessment performed after a period of 9 months with multimodal interventions, including observation sessions, questionnaires, presentations on hand hygiene and actual data on nosocomial infections, posters and videos.

Results:
The compliance with hand hygiene increased from 23% in the baseline assessment to 50% in the second assessment ($p < 0.05$). Evaluation of specific procedures failed due to a low number of observations. Presentations on the prevalence of nosocomial infections and spread of multiresistant Gram-negative microorganisms had a high impact on compliance with hand hygiene.

Conclusion:
This study highlights the importance of multimodal intervention programs for adherence to hand hygiene guidelines in a NICU. The compliance with hand hygiene among HCWs of the NICU increased after implementation of a multimodal intervention program. Although the increase in adherence was significant, a result of 50% adherence is still too low and requires further improvement.

INTRODUCTION

Nosocomial infections are serious complications among critically ill infants admitted to neonatal intensive care Units (NICUs) and contribute considerably to neonatal morbidity and mortality.[1,2] The incidence of nosocomial, late-onset infections in NICUs is high (11.5 -32.4 %), especially among very low birth weight premature infants.[2,3] Advances in medical care have resulted in a significant improvement in both survival and outcome in these critically ill infants. However, some of the technological advances that have provided this improvement in care imply an increased risk for health care associated infections. Preterm infants have a functionally limited immune system while they are exposed to multiple invasive procedures which are risk factors for the acquisition of nosocomial infections.[4-6] Adherence to hygienic guidelines is one of the key factors in the reduction of the incidence of nosocomial infections.[7] Especially hand hygiene has been shown to be a key measure to prevent transmission of microorganisms between patients via the hands of health care workers (HCWs). Previous studies have shown that in hospitals, including neonatal wards, strict adherence to hand hygiene guidelines reduces the occurrence of health care associated, nosocomial infections.[8-10] Hand hygiene is a general term to describe hand disinfection with a soap-solution or the use of a microbicidal agent (e.g. alcohol).[11] Despite the relatively simple procedure and the widespread knowledge that hand hygiene is one of the most effective measures in the prevention of nosocomial infections, the adherence to hand hygiene procedures remains low, often being less than 50%.[8-10] Promotion of hand hygiene is therefore a challenge for infection control practitioners in health care institutions. Single interventions to promote hand hygiene compliance have been shown to be ineffective.[12] Multidisciplinary and multimodal interventions to promote hand hygiene practices appeared to have more impact.[12,13] Education and workshops on hand hygiene practices to improve the knowledge of guidelines, the distribution of information leaflets and posters and observation sessions with performance feedback for the HCWs are factors that have been proven to have a positive effect on compliance rates. Negative influences on compliance to hand hygiene are skin irritation by the frequent application of hand hygiene agents, high workload and understaffing.[14] The wearing of gloves can result in an unrealistic sense of compliance to hygienic guidelines. Accessibility to, and type of hand hygiene agents are also important factors in the adherence to hygienic guidelines.[13,15]

In an intensive care setting the need for patient contact is high. This also applies to the NICU, despite the adherence to the policy of minimal handling, with clustering of nursing care from the point of view of developmental care.[16] With clustered nursing care, patient contact is reduced, which may lead to decreased transmission of microorganisms.[8]

Since the nosocomial infection rate in our NICU is high (15.3%), we intensified the attention to the current hygienic guidelines and implemented a multimodal intervention program to improve hand hygiene practices. The aim of the present study was to evaluate the effect of this program on the adherence to the hygienic guidelines among all HCWs in the NICU.

METHODS

Setting

Our NICU is a modern 28-bed level III unit with 570 annual admissions, covering an area with 30,000 live births. The 28 beds are divided over 4 units with 7 beds each. Each unit is equipped with 2 hand washing facilities with touch taps and supply of soap and paper towels, each accommodating 3-4 patients. In addition to the soap dispenser a second dispenser with alcohol-based hand rub is provided at each washing sink. Moreover, next to each incubator an additional dispenser for alcohol-based hand rub is available. The mean distance between a patient and a washing sink is 4 m (range 2-6).
An example of the protocol used in our NICU is shown in table I.

Multimodal Intervention Program

The first issue of this program was an episode of observation (baseline assessment) of all NICU HCWs including physicians and laboratory and radiology personnel, for their adherence to the current hygienic guidelines, during a period of 3 months (February through April 2006). The observation period for baseline assessment was planned without prior acknowledgement of personnel.
The observations were performed by 5 members of the NICU nursing staff, trained to observe hand hygiene practice. The training consisted of 2 practical and theoretical lessons on how to observe and what to observe, and how to score the hand hygiene practice among the HCWs. After the training, Cohen's' Kappa coefficient, a chance-adjusted measure of agreement between observers, was established between the 5 members of the nursing staff to ensure the inter-observer reliability, which was 0.75 for this study.

Table I

Current hand hygiene protocol
All guidelines apply for all HCWs who enter the NICU.
Before entrance to the NICU:
1. It is not allowed to enter the NICU wearing rings, watches and bracelets.
2. HCWs must wash their hands thoroughly, when hands are visibly dirty by using water and soap, followed by using an alcohol rub based on 80% w/w ethanol (Sterillium®) applied to hands and arms. In case of clean hands the alcohol rub (2 plunges = 4 ml) must be applied to hands and arms up to the elbows and left to dry.
After entering the NICU:
3. Before entering and after leaving the patient site (incubator or heated platform) an alcohol rub has to be used on both hands, up to the elbows.
Re-apply alcohol rub:
4. Before and after touching equipment (monitors, thermometers, keyboards, observation charts, etc.).
5. Before shifting from a contaminated to a clean body site of an infant and after contact with the infants' body fluids.
6. Before and after the use of gloves.
7. Before and after the manipulation of catheters, drains and tubes within the patient site.

During the observation session the application of hand hygiene was registered during all handling procedures for which hand hygiene was required. In addition, the wearing of rings, watches and bracelets was registered and hair-dress was scored for correctness. Hand hygiene was categorized into three groups: 1 Correct (applied according to the protocol); 2 Insufficient (applied incompletely, i.e. washing the hands but not the arms, using an alcohol rub on hands only, using an insufficient volume of the alcohol rub, or failure to let hands dry before handling) and 3 No hand hygiene.
After each observation session the observed person was asked to directly return a questionnaire after which feedback was given by the observer.

The questionnaire included questions on the general knowledge of hand hygiene and the current hand hygiene protocol. In a last question the observed person was asked whether he or she had been aware of being observed. Each observation session was followed by a prompt feedback by the observer and discussion of the questionnaire. In addition, the working experience of each observed person was registered, expressed as number of years.
After completion of the baseline observations, the questionnaires were studied for issues that required special attention.
As part of the multimodal intervention program, all HCWs were informed about the current results of surveillance cultures and antimicrobial resistance. Routine weekly surveillance cultures from rectal swabs are performed in our NICU to detect colonization and spread of multiresistant Gram-negative microorganisms.
The third issue of the intervention program was presentation of the results of the baseline assessments to all HCWs and presentation of the incidence of nosocomial infections and the results of the surveillance cultures during the study period. In addition, the most frequent mistakes and omissions in hand hygiene practices, as observed during the observation sessions, were copied in a fake clinical situation by one of the observers, recorded on videos and presented to all HCWs. Subsequently, the videos were installed on every computer on the NICU, accessible for all HCWs. During the presentations, the concept of minimal handling was emphasized, with the advantages for a possible reduction in the transmission of microorganisms.
Furthermore, posters with cartoons and drawings, emphasizing good hand hygiene practice, were put up on every unit, clearly visibly near every sink and in all toilet facilities. For sustained attention these illustrations were renewed every three weeks.
In addition to the measures mentioned above hand hygiene was given special attention in the introduction program for all new HCWs.

A second observation assessment was carried out during a second episode of 3 months (November 2006 -January 2007). After each observation session the observed person

Table II Characteristics of all observed HCWs during two assessment episodes, before and after multimodal interventions.

	Baseline assessment	Second assessment	*p*-value
HCWs	101	104	NS
Male/female, n	4/97	5/99	NS
Nursing staff, n (%)	88 (87)	92 (88)	NS
Other HCWs, n (%)	13 (13)	12 (12)	NS
Experience, years median (range)	20 (1-36)	20 (0.5-39)	NS

was asked to return a questionnaire, with the same questions as used after the first, baseline assessment session.
The results of the observation during the first and the second assessment were compared for the correct application of hand hygiene during the described manipulations.

Statistics

Statistical analyses were performed using SPSS® for Windows, version 15 (SPSS Inc., Chicago, Ill, USA). Chi Square analysis and Student's-test were used to compare differences between the baseline and the second assessment. Correlations were performed using Pearson's correlation coefficient. All statistical tests were 2-tailed. The results were considered statistically significant at $p < 0.05$.

RESULTS

Table II shows the characteristics of all HCWs during the baseline and the second observation-assessments. The majority of HCWs was observed in both assessments. It was ascertained that all HCWs who participated in the second assessment were informed during the presentations as described in the multimodal intervention program. The great majority (97 and 99% during the first and second assessment respectively) of the observed HCWs were female and belonged to the nursing staff. No difference was noted in working experience.
Table III shows the frequency of applied hand hygiene according to category, during both observation episodes. During the baseline observation assessment, hand hygiene was applied in 23% of all procedures, which increased to 50% during the second assessment ($p < 0.05$). Table III also shows that hand hygiene was applied either sufficiently, or not at all, since insufficient hand hygiene was infrequently observed (4% and 1% respectively, during both episodes). The duration of the observation period was significantly longer during the second assessment ($p = 0.00$) with a higher number of assessed handling procedures (899 versus 688).
Table IV shows the compliance to hand hygiene in patient contacts during both observation assessments, showing significant improvement during the second assessment ($p = 0.00$). Although hand hygiene improved during all other specific procedures, (the application of correct hand hygiene before and after manipulations of catheters and other devices, before and after bronchial suctioning, and the use of gloves) the observed number of these procedures was too low to draw conclusions. During both observation periods the codes for wearing rings, watches and bracelets as well as hair dress were strictly followed by all HCWs.

During the baseline assessment period, increased colonization with *Klebsiella pneumoniae* (resistant to aminoglycosides and ESBL positive) was observed. During the period of 9 months with multimodal interventions, surveillance revealed increased colonization with *Proteus mirabilis* (not multiresistant to common antibiotics). Results of the surveillance cultures during the second assessment episode did not reveal a specific pattern of microorganisms.
HCWs were highly impressed by the information on the periods of increased colonization during educational sessions, given the comments received during the feedback interviews (data not shown). Several meetings were organised to discuss methods to prevent the transmission of Gram-negative microorganisms including hygienic measures.

Table III Application of hand hygiene practice during baseline and second assessment episodes, categorized as no, insufficient or sufficient hand hygiene, and duration of observation period.

Manipulations N = 1577	Baseline assessment N=688	Second assessment N= 889	*p*-value
No hand hygiene applied n (%)	533 (77)	442 (50)	< 0.05
Insufficient hand hygiene applied n (%)	26 (4)	10 (1)	< 0.05
Sufficient hand hygiene applied n (%)	129 (19)	437 (49)	< 0.05
Duration of observation minutes, median (range)	10 (3 – 23)	15 (5 – 60)	0.00

Table IV Correct application of hand hygiene in relation to the number of procedures for which hand hygiene is required, during baseline and second assessment episodes.

Procedures (N,%)	Baseline assessment	Second assessment	*p*-value
Before direct patient contact	65/267 (25)	180/297 (61)	0.000
After direct patient contact	65/227 (29)	158/272 (58)	0.000
Before entrance patient site	30/93 (33)	103/171 (60)	0.000
After leaving patient site	44/99 (45)	104/178 (58)	0.000

In total, 203 out of 205 questionnaires were returned (99 during the baseline assessment and 104 during the second assessment) and all respondents received feedback from the observer during both assessments. Two respondents in the baseline assessment refused to return the questionnaire.
All respondents appeared to be fully aware of the necessity and benefit of good hand hygiene. Compared with the baseline assessment, significantly more respondents were aware of being observed during the second assessment (11.9% and 44.2%, respectively, $p< 0.001$). All other questions were answered equally during both assessments.
The feedback interviews revealed that the most common reasons for not applying good hand hygiene were skin breakdown by repeated friction and application of antiseptic agents, the opinion that hand hygiene is not required when wearing gloves and lack of time due to heavy workload and understaffing, or simply forgotten. Simply forgotten, heavy workload and understaffing were the main excuses to apply good hand hygiene in both assessment sessions. Two HCWs did not agree with their observation report and were of the opinion that they used appropriate hand hygiene when recommended even after being confronted with the registered observation that they failed to perform hand hygiene as required by the guidelines.

DISCUSSION

The compliance with hand hygiene among HCWs significantly improved during the second observation session, 9 months after the baseline assessment. During a period of 9 months a multimodal intervention program was implemented in our NICU. The program was based on prompt feedback after each observation session, presentations on the actual nosocomial infections and episodes of increased colonization with multiresistant Gram-negative microorganisms and the display of posters and videos with examples of mistakes or omissions in hand hygiene practice. Subsequently teaching programs on the proper use of alcohol based agents, presentation of the hygienic guidelines and the concept of minimal handling were provided to all HCWs. The poster campaign was conducted during the entire study period.
Overall adherence to hand hygiene guidelines improved from 23% during the baseline episode to 50% during the second episode. This increase in adherence is remarkable, concerning the longer duration of observation and the higher number of manipulations during the second assessment observation. However, adherence of 50% is still too low and requires further improvement. An additional observation of the study is that HCWs either apply good hand hygiene or no hand hygiene at all, suggesting that either there is no time for appropriate hand hygiene, or HCWs are aware of the fact that hand hygiene is required and behave accordingly. This is confirmed by the questionnaire results: HCWs are fully aware of the importance of hand hygiene practice and they all know the risk for cross transmission of microorganisms. Information on the incidence of nosocomial infections and the presentations on the patterns of spread of multiresistant microorganisms among the infants were important issues for all HCWs to sharpen the awareness of the importance of good hand hygiene practice,
Several reasons for non adherence to hand hygiene were given, such as lack of time because of heavy workload and understaffing or simply forgotten, skin breakdown from repeated friction, application of antiseptic agents and the false notion that wearing gloves is safe and therefore no hand hygiene is required. Pittet et al showed that a high demand for hand hygiene practice as is prevalent in NICUs combined with a heavy workload, are the most important risk factors for non compliance and therefore, full compliance may be unrealistic.[14]
Improvement in hand hygiene practice and infection control requires continuous assessment of behaviour and interventions for improvement.[17,18,19]
Awareness of being observed improved hand hygiene practice significantly in our study. Being observed may change a persons' behaviour, at least during a short period. This could be seen as a bias of the study results, however this finding is in agreement with other studies in which it was also found that social pressure influences hand hygiene behaviour.[10,19] The observation rounds had the effect of an intervention to improve hand hygiene practice and changed behaviour for at least the duration of the observation session.[13]
Unfortunately we were not able to analyse differences between nurses and other HCWs because the observed group of other HCWs was too small. In addition, we were not able to analyse differences between the sexes, because of the small group of males (4 in baseline and 5 in second the assessment).

In conclusion, our study shows a significant improvement in the compliance of hand hygiene among HCWs of the NICU using a multimodal intervention program including feedback, education, the display of posters, presentation of the prevalence of healthcare related infections and information on colonization with multiresistant microorganisms, emphasis on the concept of minimal handling and paying attention to hand hygiene as part of the introduction program for new HCWs. Lessons on hand hygiene practice and being observed made HCWs aware of the need of good hand hygiene practice. Improvement in hand hygiene practice requires continuous assessment of behaviour and interventions such as feedback and observation sessions. For this reason hand hygiene and updates on the nosocomial infection rate and microbiological surveillance results are constant issues during monthly nursing meetings.

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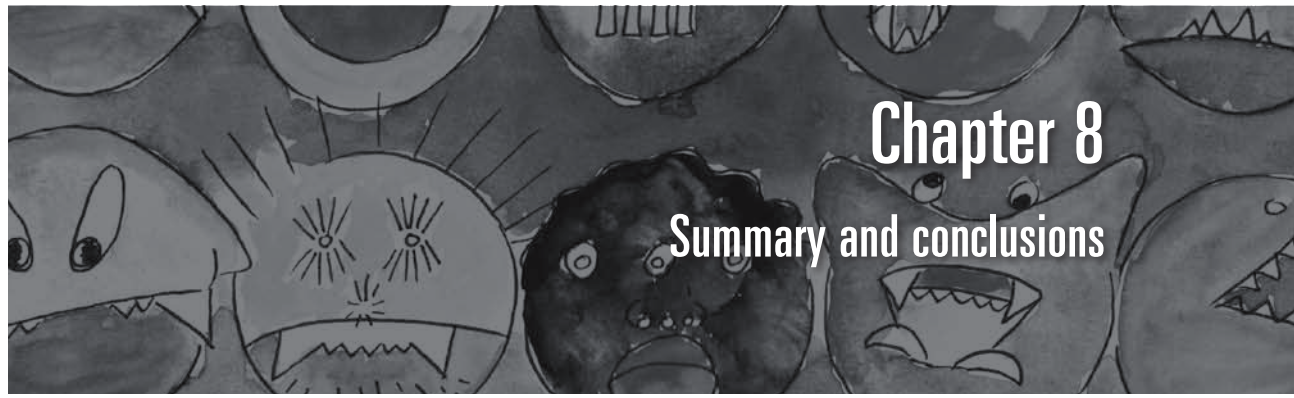

Chapter 8

Summary and conclusions

SUMMARY AND CONCLUSIONS

Neonatal infections are an important cause of morbidity and mortality in neonatal intensive care units.[1,2] Epidemiological studies have shown shifts in causative agents.
At present Gram-positive microorganisms, in particular group B streptococci, are major causative microorganisms in early-onset sepsis, although the incidence of group B streptococcal sepsis is decreasing due to antimicrobial prophylaxis to the mother.[3,4] Coagulase-negative staphylococci are the major causative agents of late-onset nosocomial sepsis [5,6], although Gram-negative microorganisms and Candida species are increasingly important.

In **Chapter 2** longitudinal trends in causative microorganisms for neonatal sepsis were demonstrated over a 29-year period in the neonatal intensive care unit (NICU) of the Wilhelmina Children's Hospital. In addition, the antibiotic susceptibility of all blood isolates of infants with sepsis was analyzed.
A remarkable finding was the decreasing incidence of early-onset sepsis since 1978-1982 (4%) to 2003-2006 (1.2 %). Moreover, a shift was noted from a greater proportion of preterm infants with GBS sepsis (78% of all infants with GBS sepsis were premature during 1978-1982 to less than 50% during 2003-2006), since the increased maternal antibiotic use for the purpose of GBS-prophylaxis and to postpone premature birth.
The incidence of early-onset Gram-negative infections remained low during the complete period of 29 years, which is in contrast to recent reports on an increasing incidence of Gram-negative infections, particularly caused by *E.coli*. A remarkable increase in incidence of late-onset sepsis was shown, from 7.1 to 13.9%, to which the increased use of central venous catheters was attributed. Infections due to fungi or yeasts were rare (incidence < 0.3%). In our study, the predominant causative agents were CoNS and *S. aureus,* which is comparable to other studies. However, in contrast to the reported increasing incidence of sepsis caused by Gram-negative agents and yeasts, the incidence of sepsis due to these microorganisms is still low in our NICU.
The majority of CoNS blood isolates was oxacillin-resistant. However, 95% of the CoNS blood isolates was susceptible for first generation cephalosporins, which is the antibiotic of first choice for the treatment of neonatal CoNS sepsis in our unit.

In **Chapter 3** we described the antibiotic use in the NICU over a 16-year period from 1990-2006. Monitoring antibiotic susceptibility patterns and antibiotic use is essential to determine the optimal antibiotic therapy for the treatment of neonatal sepsis.
A remarkable result of this long-term study was that 85 - 90% of all admitted infants was treated with antibiotics, whereas the incidence of proven early-, and late-onset sepsis was much lower (range 1.2-2.4% and 7.1-14%, respectively). However, a significant decrease in length of antibiotic treatment was noted over the period of 16 years, for the most frequently used antibiotics, i.e. amoxicillin-clavulanic acid *(p*=0.011), aminoglycosides (*p*=0.003) and cephalotin/cefazolin (*p*=0.002). Vancomycin and other antimicrobial agents were used infrequently. An additional finding was that the guidelines for antibiotic therapy for neonatal sepsis were unchanged during 16 years. The results of this study emphasize that correct identification of infants with sepsis is difficult and remains a major challenge in attempts to further reduce antibiotic use and postpone the emergence of antibiotic resistant microorganisms.

The use of In-line filters in central venous catheters in neonates was described in **Chapter 4**. In-line filters in the intravenous (IV) administration sets are used to prevent the infusion of particles, endotoxins and bacteria, which may reduce infectious complications. We randomized infants to treatment with in-line filter (for clear fluids and lipid emulsions) or no filter placement. This study showed that in-line filters did not result in a significant decrease in nosocomial sepsis: sepsis occurred in 16% of the infants both with and without filters. However, a difference was found in nursing time needed to change the intravenous-administration sets, which was significantly shorter in the filter-group ($p< 0.05$). There was no difference in costs of materials. A substantial advantage of the use of in-line filters is that a more continuous administration of intravenous medication (especially cardio-inotropics) and parenteral nutrition was guaranteed, since the IV-administration sets are used for 4 days with the use of in-line filters, whereas the systems have to be changed daily when no filters are used. For the purpose of patient safety the use of in-line filters in all IV-administration systems may be recommended in neonatal intensive care units.

Chapter 5 describes a retrospective study on percutaneously inserted central venous catheter (PCVC) – removal associated sepsis. Indwelling central venous catheters (CVCs) are a major risk factor for late-onset sepsis among infants admitted at neonatal intensive care units. Among a group of 345 infants with a PCVC, 90 cases of sepsis were identified (26%), which could possibly be attributed to the PCVC. In 50/90 cases (56%), sepsis occurred during indwelling PCVC, whereas in 40/90 of these cases (44%) after removal of the PCVC. In 21/40 cases (53%) sepsis developed within 72 hours after removal. Sepsis was caused by CoNS in all cases.
Administration of antibiotics during removal of the PCVC significantly reduced the occurrence of sepsis within 72 hours after removal in this group of 345 infants. In 22/213(10.3%) cases, sepsis occurred when no antibiotics were administered, versus 2/132 cases of sepsis (1.5%) when antibiotics were administered (p=0.002). This study suggests that removal of peripherally inserted central venous catheters is a risk for sepsis. Administration of antibiotics targeted at the time of removal of the catheter significantly reduced the incidence of sepsis. These results needed to be substantiated in a prospective study.

In **Chapter 6** a prospective study on the effect of prophylactic administration of cefazolin during the procedure of removal of a PCVC was described. In a group of 56 infants with a PCVC, 5/27 (22.7%) infants who did not receive cefazolin during the procedure of removal of the PCVC, CoNS-sepsis occurred within 48h after removal, whereas none of the infants who received cefazolin developed sepsis within 72 h. The groups were

comparable for gestational age, birth weight and duration of indwelling PCVC. This study suggests that prophylactic administration of cefazolin may prevent CoNS-sepsis associated with the removal of a PCVC. Implementation of the prophylaxis might especially be beneficial in the group of infants with increased risk for CVC-related sepsis, i.e. with a gestational age < 32 weeks.

In **Chapter 7** the effect of a multimodal intervention program to improve the adherence to hand hygiene guidelines was studied among all Health Care Workers (HCWs) in the NICU. Multimodal intervention programs have been proven to be effective in the adherence to hygienic rules. The study comprised baseline observation sessions on adherence to hygienic rules, which were compared with observation during a second assessment performed after a period of 9 months with multimodal interventions, which included presentations on hand hygiene and actual data on nosocomial infections and drawing attention by posters and videos. The multimodal intervention program resulted in a significant increase in adherence to hygienic rules, from 23% adherence in the baseline assessment to 50% in the second assessment is. However, a result of 50% adherence is still too low and requires further improvement.

RECOMMENDATIONS AND FUTURE RESEARCH

We noticed in our studies that most neonatal infections are bloodstream infections, most probably associated with intravascular catheters, including peripherally inserted central venous catheters, umbilical catheters and surgically inserted central venous catheters. Prevention of these infectious complications is a major challenge. To achieve this, the following topics are important:

Hygiene
Of major importance is a sustained attention to hygienic rules, which has been proven to increase with the use of a multimodal intervention program, such as described in this thesis.[7]

Critical judgement on invasive procedures
A great proportion of neonatal late-onset sepsis is associated with invasive procedures that are considered necessary in neonatal intensive care.[8-11]
The use of invasive procedures has to be judged with criticism.

Decrease the duration of parenteral nutrition
Early introduction of enteral feeding in newborns limits the duration of total parenteral nutrition and the need for central venous access, which may decrease the incidence of infectious complications.

Intravenous therapy team
Implementation of a special "IV"-team, responsible for the insertion and management of central venous catheters in the NICU, may be beneficial to prevent and decrease adverse outcomes in the management of central lines. Efforts to decrease catheter related infections include proper antisepsis of the skin before insertion, antiseptic precautions during insertion, aseptic technique when entering the line and minimizing the number of entry into the line and decreasing catheter duration.
An IV-team should be informed on new developments in intravenous access, including in-line filters, new catheter material, such as antibiotic-coated or silver-impregnated catheters.

Infectious Disease Team
An infectious disease team (IDT), including paediatric infectious disease specialist, medical microbiologist, hospital hygiene specialist and neonatologist, plays an important role in the decision on treatment of infants with infectious diseases.
In addition, there is an important role for an IDT in the education and training of HCWs on neonatal infectious diseases and antibiotic therapy.

FUTURE RESEARCH

Several topics discussed in this thesis are candidates for further research:

Antibiotic use
Decrease antibiotic use by correctly identifying the infants with infection, and by strictly monitoring antibiotic use as for choice of antibiotics and duration of therapy. Especially in infants with CoNS sepsis, which generally is a mild disease, the duration of antibiotic therapy may be limited. A study on this subject is in process in our unit.

Diagnosis of infants with infection
Combinations of diagnostic tools such as CRP, interleukins and procalcitonin should be studied for their discriminative power to detect and rule out a patient with an infectious disease. Especially in infants admitted to the neonatal ward because of risk factors for infection that, according to the protocol, receive antibiotic treatment until infection is ruled out, these parameters could be used in the decision not to administer antibiotics when the results are normal. This item is currently under investigation in our unit.

Prevention of CVC-removal associated CoNS sepsis
As is described in chapter 6 the first results of the prospective study on the effect of prophylactic administration of cefazolin during the procedure of removal of a PCVC are promising. Further research including more respondents is necessary to confirm this outcome.

Research on impregnated or coated catheters

Research on silver-impregnated or antibiotic-coated catheters to prevent catheter related blood stream infections in neonates is still scarce. Studies in adults and infants > 3kg have shown promising data on the use of these catheters.[12] A study on the use of impregnated and coated catheters is scheduled in our unit for the near future.

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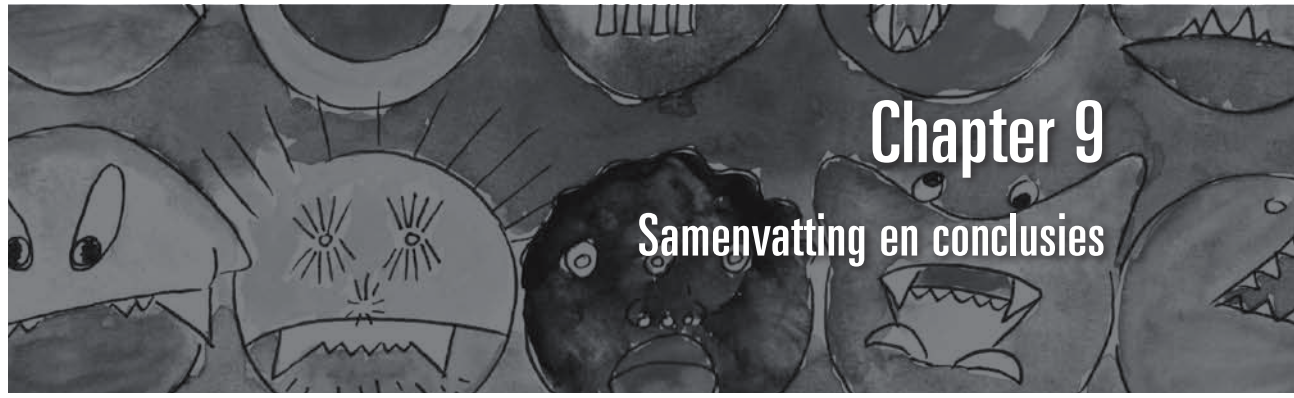


Chapter 9
Samenvatting en conclusies

Neonatale infecties zijn een belangrijke oorzaak van morbiditeit en mortaliteit in neonatale intensive care units (NICUs). Uit epidemiologische studies is gebleken dat er verschuivingen zijn geweest in de verwekkers van neonatale infecties. De laatste jaren zijn Gram-positieve bacteriën, vooral groep B streptokokken, de belangrijkste verwekkers van vroege neonatale infecties, hoewel de incidentie afneemt waarschijnlijk doordat profylaxe met antibiotica gegeven wordt aan de moeder. De belangrijkste verwekkers van late neonatale infecties zijn coagulase-negatieve staphylokokken (CoNS). Gram-negatieve bacteriën en *Candida* species worden in toenemende mate gezien als verwekker.
De incidentie van neonatale bacteriële infecties varieert van 1 tot 4 gevallen per 1000 levend geborenen. Prematuur geboren kinderen of kinderen met een erg laag geboortegewicht vormen een belangrijke risicogroep voor het krijgen van infecties. Infecties komen 3- tot 10-maal vaker voor bij premature kinderen dan bij voldragen kinderen met een normaal geboortegewicht. Een infectie van de moeder kan vroeggeboorte veroorzaken. Bovendien hebben prematuur geboren kinderen een onrijp immuunsysteem waardoor de afweer tegen infecties verminderd is.
Bacteriën kunnen overgedragen worden van moeder op kind via de placenta, via het bloed of 'opstijgend' via het geboortekanaal. Vooral wanneer de vliezen breken kan er een opstijgende infectie ontstaan. Besmetting van het kind kan ook optreden tijdens passage door het geboortekanaal, of na de geboorte via de omgeving.

Neonatale infecties kunnen onderverdeeld worden in twee grote groepen gebaseerd op het tijdstip van optreden: vroege infecties (early-onset) en late (late-onset) infecties.

Vroege infecties treden op in de eerste levenweek, meestal voordat het kind 48-72 uur oud is en worden verkregen door 'verticale overdracht', afkomstig van de moeder.
Groep B streptokokken (GBS) en *Escherichia coli* (*E. coli*) zijn de meest voorkomende bacteriën die vroege infecties veroorzaken.

Late neonatale infecties kunnen optreden na verticale overdracht van micro-organismen of worden verkregen door 'horizontale overdracht' van bacteriën, welke afkomstig zijn van omgeving, personeel, ouders of andere patiënten of door contact met besmet materiaal. Late infecties treden op na de derde levensdag, maar meestal na de eerste levensweek. De incidentie van ziekenhuisinfecties bij gezonde pasgeborenen is laag (<1%). De incidentie is hoger bij te vroeg geboren kinderen en stijgt wanneer de zwangerschapsduur en het geboortegewicht afnemen (20-25% bij kinderen <1500 gr).
Er zijn, vooral bij prematuren, naast het onrijpe afweer systeem verschillende risicofactoren aan te geven voor ziekenhuisinfecties. Centraal veneuze en arteriële katheters, totale parenterale voeding (vooral de vetoplossingen), beademing, het gebruik van antibiotica en langdurige ziekenhuisopname zijn risicofactoren voor ziekenhuisinfecties in deze groep van kinderen.
De belangrijkste verwekkers van late infecties zijn Gram-positieve bacteriën waarvan CoNS het meest frequent voorkomen (48% van alle neonatale infecties en 68% onder de kinderen met een extreem laag geboorte gewicht).

Stafylococcus aureus is een tweede belangrijke veroorzaker van late infecties. De incidentie van sepsis met *S. aureus* is laag (8% van alle gevallen van late infecties) maar het ziektebeeld kan een ernstig verloop hebben en kan gepaard gaan met het ontstaan van endocarditis, osteomyelitis en artritis.
Bacteriën zoals *E. coli, Klebsiella, Pseudomonas, Enterobacter* en *Serratia* worden in toenemende mate gezien als veroorzakers van neonatale ziekenhuisinfecties.
Schimmels en gisten, in het bijzonder *Candida* species, zijn ook belangrijke veroorzakers van neonatale infecties, vooral onder kinderen met een laag geboorte gewicht. Bekende risicofactoren voor het ontstaan van *Candida* infecties zijn het langdurig toedienen van antibiotica en het veelvuldig gebruik van instrumentatie.

In dit proefschrift gaat het om bacteriële infecties van de bloedbaan (sepsis) bij pasgeborenen op de NICU, optredend rondom de geboorte en tijdens de opname (ziekenhuis- of nosocomiale infecties).

De diagnose sepsis wordt gesteld wanneer er klinische verschijnselen van sepsis zijn in combinatie met een positieve bloedkweek. De klinische verschijnselen van neonatale sepsis zijn niet-specifiek en zijn vaak moeilijk te onderscheiden van symptomen die voorkomen bij andere ziektebeelden. Tot de meest voorkomende klinische verschijnselen van neonatale sepsis behoren koorts en/of een instabiele temperatuur, geel zien, ademhalingsmoeilijkheden, voedingsproblemen, sloomheid, bleek of cyanotisch zien, het optreden van apneu aanvallen en/of bradycardiën en een opgezette buik. Naast het optreden van klinische verschijnselen kunnen laboratoriumparameters, zoals het aantal leukocyten en differentiatie en het acute fase eiwit C-reactive protein (CRP), een toegevoegde waarde hebben bij het stellen van de diagnose neonatale sepsis. In sommige klinieken worden tevens cytokinen, zoals interleukine (IL)-6 en IL-8 routinematig bepaald.

Strategieën om risicofactoren van neonatale vroege infecties te minimaliseren zijn het voorkomen van vroeggeboorte, antibiotica profylaxe ter voorkoming van GBS infecties en het minimaliseren van obstetrische handelingen.
Ziekenhuisinfecties moeten vooral voorkomen worden door strikte hygiëne maatregelen zoals goede handen hygiëne bij ieder patiënten contact, duidelijke richtlijnen met betrekking tot hygiënische maatregelen en het voorkomen van een tekort aan verpleegkundigen.

Hoofdstuk 2 toont trends in de bacteriële verwekkers van neonatale sepsis over een periode van 29 jaar van de NICU van het Wilhelmina Kinderziekenhuis. Tevens werd de gevoeligheid voor antibiotica van alle bacteriën uit bloedkweken geanalyseerd.
De incidentie van vroege infecties bleek afgenomen te zijn van 4% (1978-1982) tot 1.2% (2003-2006). Bovendien bleek het percentage te vroeg geboren kinderen met GBS infecties afgenomen te zijn van 78% van alle kinderen met GBS infecties in de periode 1978-1982 naar minder dan 50% gedurende 2003-2006. Deze afname van

GBS infecties bij te vroeg geboren kinderen kan verband houden met het toegenomen antibioticagebruik van moeders ter voorkoming van GBS infecties en om vroeggeboorte uit te stellen wanneer de vliezen gebroken zijn.
De incidentie van vroege infecties door Gram-negatieve bacteriën bleef laag gedurende de hele onderzoeksperiode van 29 jaar. Dit is in tegenstelling tot wat uit andere studies komt, welke een toename van Gram-negatieve infecties, vooral veroorzaakt door *E.coli* lieten zien. Onze studie toonde ook een opvallende toename in de incidentie van late infecties van 7.1% tot 13.9%. Infecties veroorzaakt door schimmels en gisten waren zeldzaam in onze NICU (incidentie <0.3%). Vergelijkbaar met andere studies liet ook onze studie zien dat CoNS en *S. aureus* de belangrijkste verwekkers voor late sepsis zijn. In tegenstelling tot andere studies werd geen toename van incidentie van late sepsis veroorzaakt door Gram-negatieve bacteriën en schimmels gezien.
Het grootste gedeelte van de CoNS bloedkweken (95%) was gevoelig voor eerste generatie cephalosporines (cefazoline), wat het antibioticum van eerste keus voor het behandelen van CoNS sepsis is op onze afdeling.

In **Hoofdstuk 3** hebben we het antibioticagebruik in de NICU bestudeerd over een periode van 16 jaar (1990-2006). Een opmerkelijke bevinding van deze lange termijn studie was dat 85-90% van alle opgenomen kinderen behandeld werd met antibiotica, terwijl de incidentie van bewezen vroege en late infecties veel lager was (1.2-2.4% en 7.1-14%, respectievelijk). Er werd echter een significante daling gezien in de duur van antibioticagebruik voor de meest gebruikte antibiotica, amoxicilline-clavulaanzuur, aminoglycosides en cephalotin/cefazolin. Het gebruik van vancomycine en andere antibiotica was laag. Gedurende de gehele periode van 16 jaar is het niet nodig geweest wijzigingen aan te brengen in het protocol voor de behandeling van neonatale sepsis. Wanneer het correct stellen van de diagnose sepsis direct na de geboorte beter mogelijk zou zijn zou het antibioticagebruik waarschijnlijk belangrijk verder kunnen afnemen.

In **Hoofdstuk 4** is het gebruik van in-line filters in de intraveneuze toedieningssystemen bij pasgeborenen bestudeerd. In-line filters in het infuus toedieningssysteem worden gebruikt om partikels, endotoxines, micro-organismen en luchtbellen tegen te houden, die infectieuze complicaties kunnen veroorzaken. Er werd gerandomiseerd voor gebruik van een filter (voor heldere vloeistof en voor vetoplossing) of geen filter in het toedieningssysteem. Het gebruik van filters bleek geen verandering van de incidentie van infecties te geven. Zestien procent van de patiënten kreeg een infectie, zowel in de groep met als zonder filter. De tijd die verpleegkundigen nodig hadden om de toedieningssystemen te verwisselen was significant korter in de filter groep. Er werd geen verschil gevonden in de kosten van de materialen. Een ander groot en niet voorzien voordeel van het gebruik van filters was dat er met het gebruik van een filter een meer stabiele toediening was van medicatie en parenterale voeding doordat het niet meer dagelijks nodig was deze te onderbreken voor het verwisselen van het infuussysteem. Dit voordeel werd voornamelijk gezien bij de toediening van inotropica (dopamine, dobutamine), waarbij kinderen met een filter een stabielere bloeddruk hadden gedurende de uren rondom het verwisselen van de toedieningssystemen dan de kinderen die geen filter hadden en waarbij het infuussysteem dagelijks verwisseld moest worden.
In het kader van patiëntveiligheid zou het gebruik van in-line filters in infusie toedieningssystemen aanbevolen kunnen worden op neonatale intensive care afdelingen.

Hoofdstuk 5 toont in een retrospectief onderzoek aan dat pasgeborenen met een centraal veneuze katheter naast een verhoogd risico op kathetersepsis ook meer kans hebben op sepsis na het verwijderen van de katheter.
In een groep van 345 kinderen met een percutaan ingebrachte centrale veneuze katheter (PCVC) traden 90 gevallen van sepsis op (26%). In meer dan de helft van de gevallen (50/90, 56%) trad sepsis op tijdens de periode waarin de PCVC in situ was. Opmerkelijk was dat in iets minder dan de helft van de gevallen (40/90, 44%) sepsis optrad na verwijdering van de PCVC , waarbij dit in 21 van de 40 (53%) gevallen binnen 72 uur na het verwijderen van de PCVC was. In alle gevallen werd sepsis veroorzaakt door CoNS.
Het toedienen van antibiotica rondom het moment van het verwijderen van de PCVC deed het optreden van sepsis significant verminderen in de groep van 345 kinderen. In 22 van 213 (10.3%) gevallen trad sepsis op terwijl er geen antibiotica toegediend waren op het moment van verwijderen van de PCVC, in tegenstelling tot 2 van 132 (1.5%) die antibiotica kregen op het moment van verwijderen van de PCVC. Het verwijderen van een PCVC lijkt een verhoogd risico te geven op sepsis. Antibiotica toegediend ten tijde van het verwijderen van de PCVC verminderde de kans op infectie significant. De resultaten van dit onderzoek zouden bevestigd moeten worden in een prospectieve studie (hoofdstuk 6).

In **Hoofdstuk 6** worden de eerste resultaten beschreven van de prospectieve studie naar het effect van profylactische toediening van antibiotica (cefazoline) rondom het moment van verwijderen van een PCVC. Een groep van 56 premature kinderen met een PCVC werden gerandomiseerd voor het wel of niet toedienen van cefazoline rondom het verwijderen van een PCVC. Vijf van de 27 (22.7%) kinderen die geen cefazoline kregen gedurende het verwijderen van de PCVC ontwikkelden sepsis, in alle gevallen binnen 48 uur na het verwijderen van de PCVC en bij allen was de bloedkweek positief voor CoNS. In de groep van 29 prematuren die cefazoline toegediend kregen rondom het verwijderen van de PCVC trad geen enkel geval van sepsis op. De groepen waren vergelijkbaar voor zwangerschapsduur, geboortegewicht en het aantal dagen dat de PCVC in situ was.
Het profylactisch toedienen van cefazoline rondom het verwijderen van een PCVC lijkt CoNS sepsis te voorkomen.

Hoofdstuk 7 beschrijft het effect van een multimodaal interventie programma naar het toepassen van hand hygiëne en hygiëne regels onder medewerkers van de NICU.
Multimodale interventie programma's hebben bewezen effectief te zijn in het bevorderen van de toepassing van hand hygiëne. In deze studie worden observaties van het

toepassen van hand hygiëne vergeleken tussen een eerste meting (nulmeting) en een tweede meting na een periode van 9 maanden waarin een aantal interventies plaatsvond. De interventies bestonden uit onderwijs aan de medewerkers over het toepassen van goede hand hygiëne, terugkoppeling van feiten over ziekenhuisinfecties op de NICU en het attenderen op het belang van het opvolgen van de hygiëne regels door middel van posters welke bevestigd werden op prominente en duidelijk zichtbare plaatsen. Tevens werd er een film over hand hygiëne en hygiëne regels op het bureaublad van iedere computer op de afdeling geplaatst. Dit multimodale programma resulteerde in een toename van het toepassen van hand hygiëne van 23% in de eerste observatieronde tot 50% in de tweede observatieronde. Echter, een resultaat van 50% is te laag en vereist verdere verbetering.

AANBEVELINGEN EN TOEKOMSTIG ONDERZOEK

Uit de onderwerpen beschreven in dit proefschrift komen enkele belangrijke aanbevelingen naar voren en onderwerpen voor toekomstig onderzoek.

Aanbevelingen

Hygiëne
Van groot belang is dat er een strak beleid gevoerd wordt ten aanzien van het toepassen van hygiëne regels. Regelmatig uitgevoerde multimodale interventie programma's hebben een positieve invloed op het gedrag rond hand hygiëne. Het verdient aanbeveling deze programma's regelmatig uit te voeren op (neonatale) intensive care afdelingen.

Team 'Intraveneuze therapie' (IV-team)
De invoering van een speciaal IV-team dat verantwoordelijk is voor het proces van inbrengen en behandeling van centraal veneuze katheters en andere intraveneuze en arteriële toegangswegen op de NICU zou belangrijk kunnen zijn voor de preventie van het aantal infectieuze complicaties. Een IV-team moet bewaken dat de maatregelen die nodig zijn om katheter gerelateerde infecties te doen dalen worden opgevolgd, zoals het zorgvuldig ontsmetten van de huid voor het inbrengen van een katheter, aseptische voorzorgsmaatregelen tijdens het in situ zijn van een katheter, aseptische technieken wanneer een lijn onderbroken moet worden en het beperken van het aantal keren dat dit gebeurt.
Een IV-team moet geïnformeerd zijn over nieuwe ontwikkelingen op het gebied van infuustechnologie, zoals in-line filters, naaldloze toegangspoorten in infuussystemen, nieuwe katheter soorten, zoals katheters gecoat met antibiotica of met zilver geïmpregneerd.

Infectieteam
Een infectieteam, ten minste bestaande uit een kinderarts die zich gespecialiseerd heeft in infectieziekten, medisch microbioloog, ziekenhuis hygiënist en neonatoloog, speelt een belangrijk rol in de beslissingen rondom de behandeling van pasgeborenen met infectie. Tevens is er een belangrijke rol weggelegd voor het infectieteam in het geven van onderwijs en training aan de medewerkers op het gebied van infectie en antibiotica therapie.

Kritisch beoordelen van invasieve procedures
Een groot deel van neonatale sepsisgevallen is geassocieerd met invasieve procedures, vooral het plaatsen van centraal veneuze katheters die noodzakelijk zijn bij de behandeling van ernstig zieke kinderen opgenomen op de NICU. Een IV-team zou een belangrijke rol kunnen spelen in het kritisch beoordelen van de noodzaak en de duur van deze procedures.

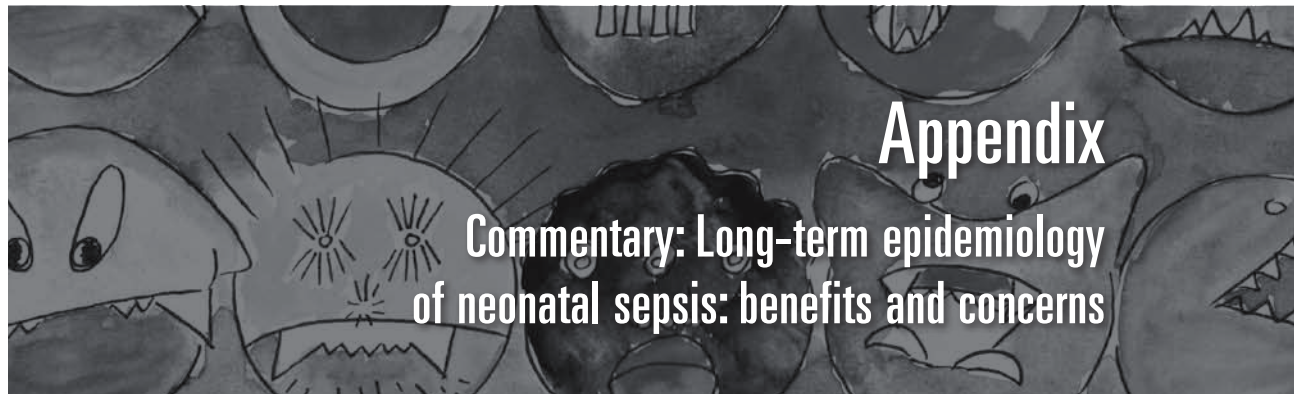
Verminderen van het aantal dagen parenterale voeding
Het vroeg starten met enterale voeding vermindert de duur van totale parenterale voeding en daardoor de noodzaak van een centraal veneuze toegangsweg. Dit zou een positieve invloed kunnen hebben op het aantal infecties. Ook hierin kan een rol weggelegd zijn voor een IV-team.

Toekomstig onderzoek

Antibioticagebruik
Het correct identificeren van kinderen met een infectie en het zorgvuldig monitoren van antibioticagebruik zowel wat betreft de keuze van antibiotica als de duur van de therapie kan het antibioticagebruik doen verminderen. Speciaal voor kinderen met CoNS sepsis, die over het algemeen mild verloopt, zou de duur van de behandeling met antibiotica beperkt kunnen worden. Dit onderzoek is op dit moment in gang op onze afdeling.

Het diagnosticeren van kinderen met infectie
Een combinatie van diagnostische testen zoals CRP, interleukines en procalcitonine zouden verder onderzocht moeten worden op hun voorspellende waarde voor het stellen en uitsluiten van de diagnose sepsis. Dit is vooral van belang voor kinderen die op een neonatale afdeling zijn opgenomen vanwege risicofactoren voor infectie en die behandeld worden met antibiotica totdat infectie is uitgesloten. Deze parameters zouden gebruikt kunnen worden in de besluitvorming om geen antibiotica toe te dienen wanneer de resultaten normaal zijn. Op dit moment loopt er onderzoek op dit gebied op onze afdeling.

Onderzoek naar geïmpregneerde of gecoate katheters
Bij neonaten is er nog weinig onderzoek naar met zilver geïmpregneerde of met antibiotica gecoate centraal veneuze katheters ter voorkoming van katheter gerelateerde bloedstroom infecties. Studies bij volwassenen en kinderen > 3 kg naar het gebruik van deze katheters tonen veelbelovende resultaten. Onderzoek naar het gebruik van deze geïmpregneerde en gecoate katheters is in voorbereiding op onze afdeling.



Appendix

Commentary: Long-term epidemiology of neonatal sepsis: benefits and concerns

Michael P. Sherman

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(Epub ahead of print)

In the United States of America (USA), a historical study of neonatal sepsis from Yale-New Haven Hospital has become a roadmap for health care professionals. In a recent 15-year period, the causes of neonatal sepsis at Yale were compared to the 60 years of preexisting data.[1] Publications related to neonatal sepsis at Yale have helped identify new or emerging bacterial pathogens that cause early-onset sepsis (EOS) and late-onset sepsis (LOS) in neonates.

In this issue of Neonatology [2], van den Hoogen and colleagues report the first long-term epidemiologic study of neonatal sepsis in Western Europe. The 29-year review of EOS and LOS at the Wilhelmina Children's Hospital in the Netherlands shows trends like those seen at Yale with a few exceptions. First, these Dutch investigators show a reduction in EOS caused by group B streptococci after recent increased use of intrapartum antibiotics. A report from Yale had similar findings.[3] Second, van den Hoogen and colleagues found a low incidence of gram-negative infections in neonates caused by *Escherichia coli*.[4] It is plausible that intrapartum use of antibiotics at the University Medical Centre in Utrecht will over time result in increased early- and late-onset sepsis caused by gram-negative bacteria akin to those emerging at Yale.[3,4] The primary cause of LOS at the Wilhelmina Children's Hospital is currently coagulase-negative staphylococci (CoNS). CoNS are now appreciated as a world-wide cause of nosocomial infections in NICUs.[5] In the future, longitudinal reviews of neonatal sepsis from the Wilhelmina Children's Hospital may be informative to caregivers in other neonatal intensive care units (NICUs) of Western Europe.

Neonatal units in developed and developing countries outside of Europe should probably not rely on the information about neonatal sepsis from studies performed at the Wilhelmina Children's Hospital, other NICUs in Western Europe or the USA. Rather, it is recommended that all NICUs conduct their own surveillance of infections.[6] Knowledge of the antibiotic susceptibilities of pathogens causing EOS and LOS in a particular NICU assists clinicians in making decisions about empiric antibiotics before microbiologic studies are available.[7] This strategy may also reduce neonatal morbidity and mortality from infection.[8]

van den Hoogen *et al*. [2] express opinions in their report that requires discussion. Similar to treatment for LOS at the Wilhelmina Children's Hospital, Karlowicz and associates [9] suggest vancomycin can be avoided as an empiric antibiotic for nosocomial infections. The rationale for use of a 1st-generation cephalosporin to treat LOS is based on the finding that deaths are rarely associated with coagulase-negative staphylococcal infections.[9] Several issues must be considered when a caregiver selects a 1st-generation cephalosporin to treat LOS. First, the incidence of 1st-generation cephalosporin- and/or methicillin-resistant *Staphylococcus aureus* in the NICU must be very low or absent. Second, a septic infant with necrotizing enterocolitis (NEC) might benefit from being treated with vancomycin. Coagulase-negative staphylococci, *Enterococcus* spp., and anaerobic bacteria are pathogens associated with NEC, and most of these bacteria are killed by vancomycin. Most importantly, a delay in administering the proper antibiotic [7] might result in a prolonged neonatal inflammatory response syndrome and an unfavorable neurodevelopmental outcome.[8]

The concept that treatment of LOS with a 1st-generation cephalosporin prevents neonatal infections caused by Candida invites debate. When 3rd-generation cephalosporins are used in the NICU, Candida becomes a predominant microorganism in bowel flora.[10] Overgrowth of intestinal Candida facilitates gut translocation of this microbe. There is no information about intestinal overgrowth with Candida when preterm infants receive intravenous 1st-generation cephalosporins compared to 3rd-generation cephalosporins. Preterm infants weighing <1000 g at birth are the highest risk group for systemic candidiasis.[11] The number of infants weighing <1000 g at birth is not stated in the report from the Wilhelmina Children's Hospital. There may have been too few infants with extreme prematurity to delineate the role of 1st-generation cephalosporins as a measure that prevents neonatal candidiasis. One can infer that at the Wilhelmina Children's Hospital, excellent hand washing behaviors and avoidance of unnecessary antibiotics prevented systemic candidiasis.[12] The pathogenesis of neonatal candidiasis is complex. Extreme prematurity, immature skin, an immune system, hyperglycemia, use of parenteral nutrition and intravenous lipids, use of histamine-2 receptor antagonists, excessive environmental humidity, and prolonged use of two or more antibiotics are incriminated in the pathogenesis of Candida infections.[13] The association of neonatal candidiasis with so many risk factors diminishes the usage of a first generation cephalosporin as a sole measure that prevents neonatal infections caused by Candida.

In summary, van den Hoogen and colleagues should be congratulated for reviewing three decades of neonatal sepsis in The Netherlands. The report provokes thought and encourages our continued surveillance of neonatal infections.

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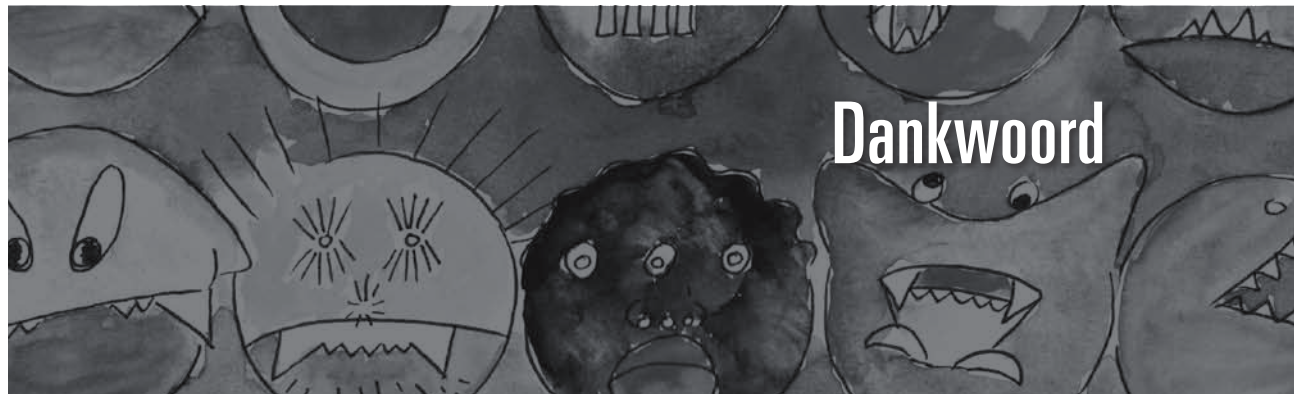

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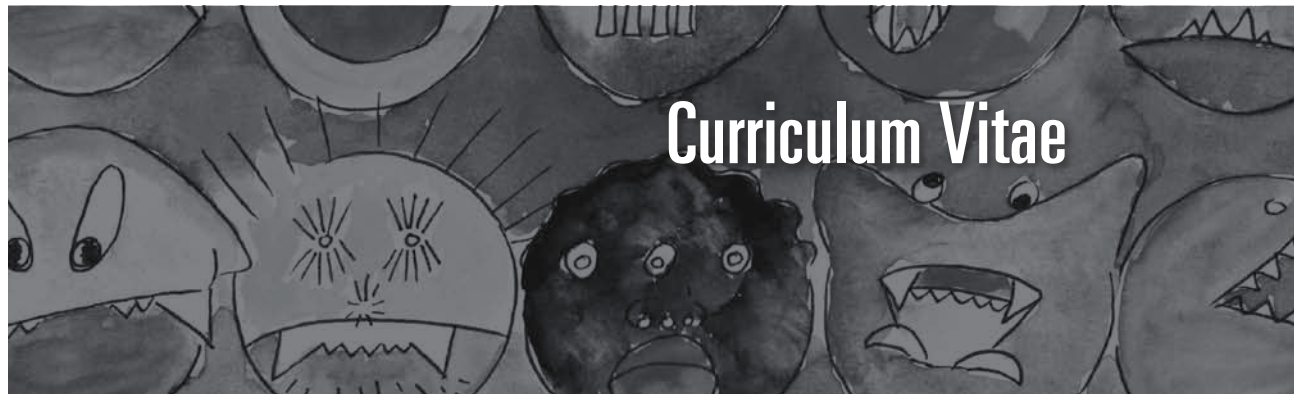
Curriculum Vitae

Agnes van den Hoogen werd geboren op 29 september 1957 in Bunschoten. Na de middelbare school begon zij in 1975 haar opleiding tot verpleegkundige in ziekenhuis de Lichtenberg te Amersfoort. In 1979 ronde zij deze opleiding af en startte met de opleiding tot kinderverpleegkundige in hetzelfde ziekenhuis, waar zij vanaf 1981 waarnemend hoofd van de kinderafdeling was.
Ter voorbereiding op haar werk in Nepal startte zij in 1982 met de tropenopleiding aan het Tropeninstituut in Amsterdam en volgde daarna een Cross Culture Training in London, UK.
In 1983 was zij werkzaam in het Shining Hospital in Pokhara, Nepal voor de International Nepal Fellowship.
Medio 1984 startte zij de specialistische opleiding tot neonatologie verpleegkundige in het Wilhelmina Kinder Ziekenhuis (WKZ) te Utrecht. Na het behalen van het diploma was ze werkzaam op de Neonatale Intensive Care Unit (NICU). In de periode van 1990 tot 1996 was zij werkzaam in het Diaconessen ziekenhuis, locatie Zeist en Utrecht waar zij als gespecialiseerd verpleegkundige de training voor kinderreanimatie heeft ontwikkeld en uitvoerde.
In 1997 startte zij met haar studie Gezondheidswetenschappen aan de University of Wales, Cardiff, UK. Haar afstudeerproject voor de richting 'Nursing Studies', betrof onderzoek naar de functie en de verantwoordelijkheid van de verpleegkundige, binnen het besluitvormingsproces aangaande levensbeëindigend handelen bij de pasgeborenen op de NICU. Dit onderzoek vond plaats op de NICU van het WKZ te Utrecht waar zij vanaf 1998 opnieuw werkzaam is. Haar Master degree behaalde zij in januari 2000.
In 2003 volgde zij de cursus klinische epidemiologie aan het Julius centrum in Utrecht, waarna zij sinds 2004 betrokken is geweest bij het opzetten van wetenschappelijk onderzoek door verpleegkundigen binnen de divisie vrouw en baby van het Universitair Medisch Centrum (UMC) Utrecht. Vanaf die tijd vervult zij zowel de functie van verpleegkundige op de NICU als de functie van wetenschappelijk onderzoeker binnen het onderzoeksprogramma infectie (dr. Tannette G. Krediet en dr. Leo J. Gerards). In 2005 werd ze getraind in de medische microbiologie (dr. André Fleer) en liep zij stage op het klinisch laboratorium van het UMC Utrecht. Medio 2004 startte zij met het uitvoeren van wetenschappelijk onderzoek wat tot dit proefschrift heeft geleid.
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List of abbreviations

List of abbreviations

CDC	Centres for Disease Control and prevention
CFU	Colony forming unit
CoNS	Coagulase negative staphylococci
CRP	C-reactive protein
CSF	Colony-stimulating factor
CVC	Central venous catheter
E.coli	*Escherichia coli*
GA	Gestational age
GBS	Group B streptococci
G-CSF	Granulocyte colony-stimulating factor
HCW	Health care worker
IDT	Infection disease team
IL	Interleukin
IV	Intra Venous
IVIG	Intra venous immunoglobulin
MRSA	Methicillin-resistant *Staphylococcus aureus*
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
PCT	Procalcitonin
PCVC	Percutaneously inserted central venous catheter
PICC	Peripherally inserted central catheter
S.aureus	*Staphylococcus aureus*
TPN	Total parenteral nutrition
UVC	Umbilical venous catheter
VLBW	Very low birth weight

List of publications

1. Long term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, and Krediet TG. *Neonatology* 2009; 97: 22-28 (Epub ahead of print)

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