Prevention of nosocomial bloodstream infections in preterm infants

Onno Helder

PREVENTION OF NOSOCOMIAL BLOODSTREAM INFECTIONS IN PRETERM INFANTS

Preventie van zorggerelateerde bloedbaaninfecties
bij prematuur geboren kinderen

Onno Helder

MIX
Papier van
verantwoorde herkomst
FSC® C004472

ISBN: 978-94-6169-365-5

Printing of this thesis was financially supported by Abbott B.V., J.E. Jurriaanse Foundation, and Erasmus MC-Sophia Children's Hospital, division of Neonatology.

Cover design: Harrie Remie, www.harrietehuur.nl
Painting: without title, by Tjibbe Spruit (the Netherlands), 1988, private collection Taal en Helder
Layout and print: Optima Grafische Communicatie, Rotterdam

Prevention of Nosocomial Bloodstream Infections in Preterm Infants

Preventie van zorggerelateerde bloedbaaninfecties bij prematuur geboren kinderen

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 17 april 2013 om 15.30 uur

door

Onno Klaas Helder
geboren te Hamilton, Verenigd Koninkrijk

ERASMUS UNIVERSITEIT ROTTERDAM

Promotiecommissie

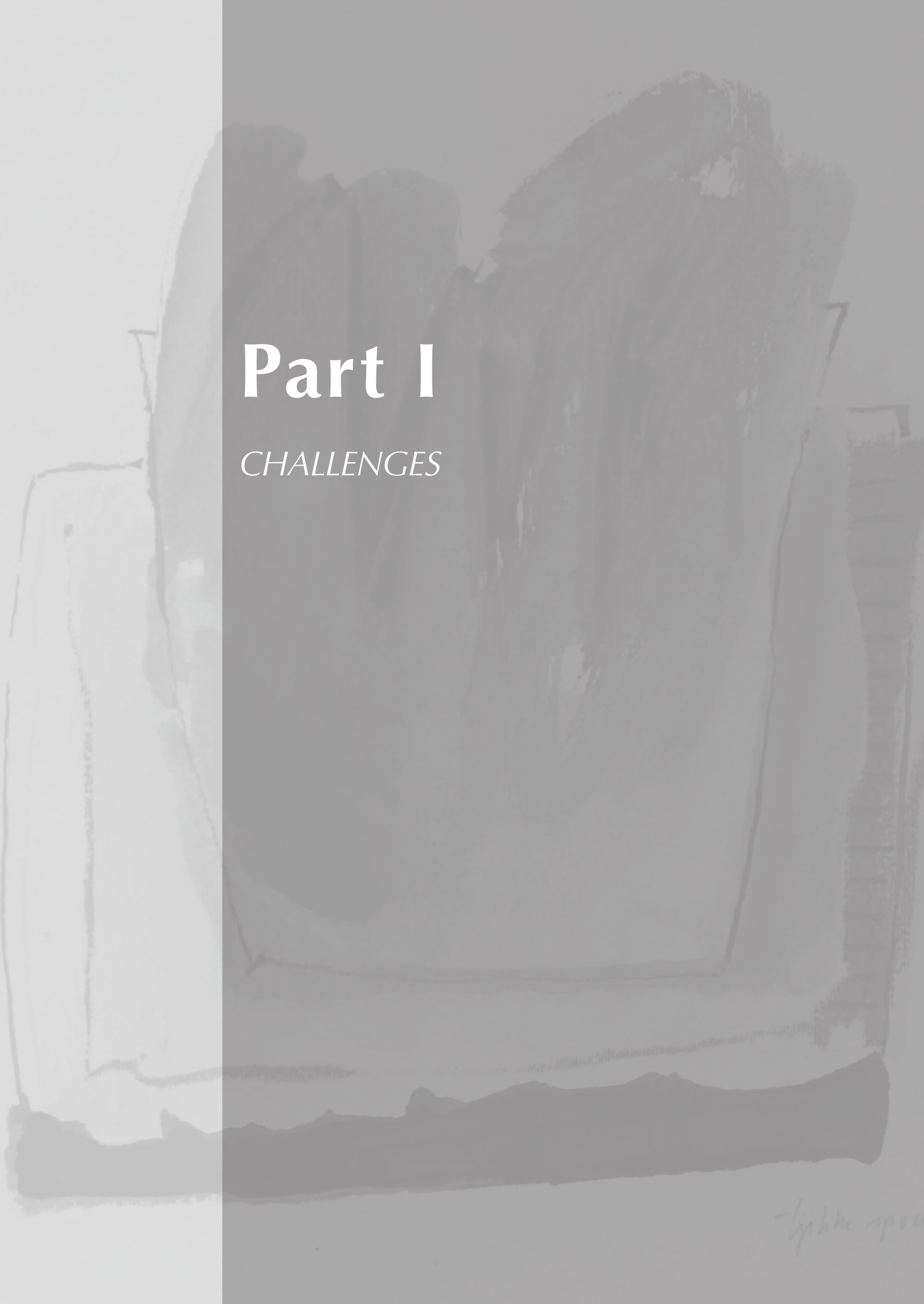
Promotoren:	Prof.dr. J.B. van Goudoever
	Prof.dr.ir. J. Brug
Overige leden:	Prof.dr. I.K.M. Reiss
	Prof.dr. R.M.H. Wijnen
	Prof.dr. H.A. Verbrugh
Copromotor:	Dr. R.F. Kornelisse

CONTENTS

Part I	**Challenges**	
Chapter 1	General introduction	9
Chapter 2	Reduction of catheter related bloodstream infections in intensive care: one for all, all for one?	23
Chapter 3	Undergraduate nurse students' education in infection prevention: is it effective to change the attitude and compliance with hand hygiene?	29
Chapter 4	Effectiveness of non-pharmacological interventions for the prevention of bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review	35
Part II	**Tools and interventions**	
Chapter 5	The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban Neonatal Intensive Care Unit: An intervention study with before and after comparison	61
Chapter 6	Hand disinfection in a neonatal intensive care unit: continuous electronic monitoring over a one-year period	79
Chapter 7	Computer screen saver hand hygiene information curbs a negative trend in hand hygiene behavior	89
Chapter 8	Reduced nosocomial bloodstream infection rate among very low birth weight infants by sequential hand hygiene promotion: a ten-year experience	103
Part III	**Discussion**	
Chapter 9	Implementation of a children's hospital-wide central venous catheter insertion and maintenance bundle	121
Chapter 10	General discussion and future perspectives	145
Chapter 11	Summary	161
Appendices	Nederlandse samenvatting	168
	List of abbreviations	172
	List of publications	174
	Curriculum Vitae	177
	PhD Portfolio	178
	Dankwoord	180

Part I

CHALLENGES



Chapter 1

General introduction

INTRODUCTION

"I will do no harm to the patient" [Hippocratic Oath, modern version] (1)

Protecting patients from harm is the overarching theme of the studies presented here. More precisely, this thesis places a focus on the prevention of nosocomial or hospital-acquired bloodstream infections in preterm infants, thus saving them from further harm. A nosocomial infection is an infection acquired during hospitalization 48-72 hours after admission or birth (2-3). These infections are a threat to patients' health worldwide (4-6).

RELEVANCE

Nosocomial infections are the most common adverse events in our modern healthcare system; at any time they affect worldwide over 1.4 million people in hospitals and are associated with considerable morbidity, mortality, costs, and use of additional resources (7). Severe pneumonia, urinary tract infections, and bloodstream infections (BSIs) are examples of these nosocomial infections. The European Centre for Disease Prevention and Control reported an average prevalence of 7.1 nosocomial infections per 100 hospitalised patients in European countries (8). Prevalence is defined as number of infection episodes or infected patients per 100 patients admitted to a healthcare setting or ward at a given point in time (9). For the United States of America (USA) the estimated incidence is 4.5 nosocomial infections per 100 hospitalised patients (10). Incidence is defined as number of new infection episodes on new patients acquiring an infection per 100 patients followed up for a defined time period (9). The different definitions may explain differences in reported prevalence and incidences. The reported prevalence for developing countries is substantially higher than that reported for European countries, i.e. 15.5 nosocomial infections per 100 patients (10). Nosocomial infections are responsible for 80,000 deaths in the USA and 5,000 in the United Kingdom (UK) (11).

Very few countries systematically collect nosocomial BSI data. In the USA an estimated 80,000 catheter related BSIs annually occur in intensive care units, which are responsible for approximately 28,000 deaths (12). Individual studies reported BSI rates ranging from 0.8 to 4.4 BSIs per 1000 patient days (13-15).

The costs of catheter-associated BSIs in terms of additional hospital charges and extra hospital days are overwhelming (7, 10). The average costs for a patient with a catheter-associated BSI in the USA varies between $16,000 to $45,000, therefore the total additional costs of these infections are up to $2.3 billion annually (12, 16-17). The average additional cost of every nosocomial BSI in infants is about $17.000 and the average neonatal intensive care unit (NICU) hospitalization is extended with approximately two weeks (17-19).

Nationwide numbers of nosocomial BSIs among infants in the Netherlands are not available. However, a point prevalence measurement among infants admitted to several Dutch NICUs found a prevalence of 10.4 (95% CI 7.3-14.5) (20). Two other Dutch studies, that included all admitted infants, reported 14.9 BSIs per1000 patient days (21) and an incidence of 11.3% (22), respectively. Preterm infants, particularly very low birth weight (VLBW) infants (< 1500 grams) and extremely low birth weight (ELBW) infants (< 1000 grams) are at high risk for nosocomial BSIs. The reported incidence among ELBW infants is very high with approximately 32% (23). The incidence of BSIs among VLBW infants in NICUs varies between 10% and 25% (17, 24-26). Up to 75% of all nosocomial infections in these infants are nosocomial BSIs; versus between 5% and 8% in adult settings (27-28).

Nosocomial BSIs in preterm infants are associated with serious complications such as severe intraventricular haemorrhage, hearing loss, cerebral palsy, necrotising enterocolitis, chronic lung disease and retinopathy (23, 26). Most of these complications result in lifelong morbidity during their further entire life (26). Furthermore, BSIs carry a 20% mortality rate among VLBW infants, especially due to Gram-negative pathogens and fungi (2, 29).

WHY ARE PRETERM INFANTS AT HIGH RISK?

Several intrinsic and extrinsic factors are responsible for the high incidence of BSI in NICUs.

Intrinsic factors. The infants' immature immune system is the most important intrinsic factor. VLBW infants or very premature infants have an immature gastrointestinal tract and therefore need parenteral nutrition for an extended period of time which is usually provided by central venous catheters (30). Infants with the lowest birth weight are most at risk for catheter related BSIs; the number per 1000 catheter days was reported to be (25, 29, 31-32):

< 750 gram	13.6
751 – 1000 gram	12.6
1001 – 1500 gram	7.7
1501 – 2500 gram	3.2
> 2500 gram	1.6

The preterm infants' innate immune system is not capable to respond adequately to invading pathogens. The innate immune system consists of *anatomical barriers, inflammatory response, humoral immunity* including complement system, and immunoglobulins (33). The term *anatomical barriers* refers to epithelial surfaces that form a physical barrier and act as a first line of defense for most pathogens. However, barriers such as skin, mucous membranes, and gastrointestinal tract mucosa are not yet well developed in preterm infants. The immature epithelial surfaces are not capable enough to prevent pathogens from invading, with greater risk of BSIs as result (34). Premature infants have a diminished *inflammatory response* to invading pathogens. Chemical factors are produced during inflammation, which sensitize pain receptors, cause vasodilatation of blood vessels at the affected tissue, and attract phagocytes. The febrile reaction mechanism which improves metabolic reaction, like migration of leukocytes, is underdeveloped in preterm infants (33, 35). *Humoral immunity* encompasses the complement system and immunoglobulins. The complement system forms a complex biochemical cascade that contains over 20 different proteins and helps antibodies clear pathogens or flag pathogens for destruction by other cells. The activated complement system organises all involved proteins to trigger an inflammatory response by producing chemotaxis which attracts macrophages and neutrophils, forming holes in the membrane of the pathogen resulting in cytolysis, and causing the destruction of the pathogen. Immunoglobulins are proteins and are also involved in humoral immunity found intravascular and extravascular. The immune system uses immunoglobulins to identify and neutralize pathogens by binding or coating immunoglobulin to pathogens. This process results in immobilization and agglutination of pathogens (33, 35). Immunoglobulin G is the major immunoglobulin in the serum of premature born infants. During the third trimester of pregnancy maternal-fetal transfer of immunoglobulin takes place (35). So, the earlier a preterm infant is born, the lower the quantity of maternal immunoglobulin transferred by the placenta. For preterm infants it takes several months to achieve an adequate immunoglobulin concentration. Therefore, the youngest preterm hospitalised infants are more prone to BSIs (32).

Extrinsic factors: Major extrinsic risk factors for BSI in preterm infants are invasive procedures, parenteral nutrition, and prolonged hospitalization (25, 34). Invasive procedures, such as inserting centrally placed intravenous devices (CVCs) provide a portal of entry (30, 36-38). Microorganisms could affect infants when hygienic prevention measures during the insertion procedure are inadequate, or when pathogens migrate at the intraluminal or less likely extraluminal of the catheter (30, 39). Abandoning CVCs is not a realistic option because they are urgently needed for the administration of medication or total parental nutrition (40). Most preterm infants need total parental nutrition because of the prolonged time needed to get on full enteral feeding (41-44). Adequate amounts of carbohydrates, proteins, and fat are needed for their growth (45).

Others require medication for vital function support, such as inotropes, which can be administered by CVCs only due to its incisive effect to blood vessels (31, 36).

Above we described the common reasons for infants to be at risk for BSI and usual ways to get infected. However, rare causes in NICU settings have been reported; for example, a cleaning bucket contaminated with Klebsiella spread pathogens over all surfaces (46). Twenty-eight infants were infected with Klebsiella and two of them died as result of the pathogen spread. Others reported an outbreak of Bacillus cereus found on the hands of nursing staff and inside balloons used for manual ventilation. Thirty-five infants were colonised; three developed a BSI; and one of these deceased (47). As a final example, contaminated breast milk caused an outbreak of extended-spectrum ß-lactamase (ESBL) producing Klebsiella pneumonia, spread by insufficient hygienic barriers (48). In total 58 infants were affected; one infant acquired a BSI.

SELECTION OF PREVENTIVE MEASURES

Healthcare workers employed at a NICU may encounter two major risk factors in daily practice: invasive procedures and parenteral nutrition (25, 34). Many different workers are involved in patient care and the preterm infants' environment can be characterised as a high activity level setting (49) in which there is great risk of patient-to-patient transmission of pathogens via healthcare workers' hands (50). Cross-transmission of pathogens requires five steps: (1) pathogens are present on the patient's skin or have been shed at surfaces in the patient's immediate environment; (2) organisms must be transferred to healthcare workers' hands; (3) organisms must be capable of surviving on healthcare workers' hands (4); hand hygiene must be inadequate; and (5) the health-care workers' contaminated hands must come into contact with the patient or a surface nearby the patient (5, 50-51).

Intravenous procedures, as well as the preparation and administration of parenteral nutrition need to be performed aseptically to prevent contamination of the devices used. The weak link in this process is noncompliance with hand hygiene protocols (50). In a systematic review on this subject, improvement of compliance with hand hygiene protocols was therefore found to be the most important intervention to prevent nosocomial infections, and is why we focused on this preventive measure (49). In addition, there is sufficient evidence that improved hand hygiene results in a reduction of nosocomial BSIs in adult settings (52-53).

Other potential preventive measures such as pharmacological interventions, adequate staffing, avoidance of overcrowding, promotion of human milk feeding, involvement of patient families in BSI prevention were not selected for this thesis (54).

Hand hygiene is also designated the most important keystone of infection prevention by the Centers for Disease Control and Prevention, the World Health Organization, and others (5, 37, 49, 55-56). Hand hygiene behavior is a result of so-called behavioral determinants. Three broad categories of behavioral determinants can generally be distinguished: motivation, abilities and opportunities. I.e. if people are motivated, have the abilities and are provided with the right opportunities to comply to hand hygiene practices, they are much more likely to do so. Interventions to promote hand hygiene behavior should this try to improve the healthcare workers motivation to comply, their abilities to comply with the right hand hygiene practices, and should try to create a physical and social environment that makes hand hygiene compliance as easy, self-evident and socially desirable as possible.

HAND HYGIENE PRACTICES

Hand hygiene can be performed by washing with water and soap and drying with paper towels, or by applying hand alcohol. Hand washing with water and soap is recommended if hands are visually soiled, after visiting the bathroom, after contact with food, or in case pathogens are not sensitive to hand alcohol. Examples of the latter pathogens are Clostridium and gastrointestinal tract viruses such as noro-, rota-, adeno-, and astrovirus (57). A few environmental resources are required such as a sink and water supply. A disadvantage of hand washing is its time consuming nature. The complete procedure takes approximately three minutes. In addition, it has only selective bactericidal effects and is only effective for elimination of transient pathogens. Last but not least, frequent use of soap raises the risk of skin breakdown (56). Compliance with hand hygiene can be suboptimal due to poor knowledge of indications for hand hygiene, lack of time, difficulty integrating it into daily practice, absence of social norms promoting hand hygiene, and lack of leadership to promote hand hygiene (4).

Hand disinfection with an alcohol-based solution has superior antimicrobial efficacy compared to hand washing (56, 58). It has been estimated that improved hand disinfection can reduce the nosocomial infection rate by up to 40% (58). To reach the desired effect, all parts of the hands (hand back, palm of the hands, between fingers, finger tops, wrists, and thumbs) should be rubbed with at least 3 ml ethanol 80% solution till all alcohol is evaporated (56). This method carries the advantage of easy application; the relatively short time needed (30 seconds); the bactericidal effect affecting pathogens deep in the skin; and reduced risk of skin breakdown (4, 56).

Hand disinfection with hand alcohol is the preferred method of hand hygiene for most opportunities (56). Despite healthcare professionals' awareness of the need for hand hygiene, compliance with hand hygiene protocols in general is low at approximately 45% (3-4, 59). Many interventions to persuade healthcare professionals to improve compliance have been tested, such as education and information, performance feedback, adjusted sinks, and introduction of new soap or hand rub (4). Regrettably they seem to be effective at the short term only. The effectiveness of other interventions, such as use of opinion leaders and mass media campaigns, remains unclear (4, 60). One study regarded the effectiveness of multifaceted interventions as promising (4); others, however, reported modest effects of multifaceted interventions (61). Therefore, we cannot but conclude that we are lacking a true evidence-based or gold-standard implementation technique to alter healthcare professionals' hygienic behavior (62).

OUTLINE OF THE THESIS

To alter healthcare workers hygienic behavior is a challenge, but needed for patient safety (25, 54). The overall challenge is to persuade them to act according to the hygienic guidelines and retain this behavior on the long term to ensure durable infection prevention effects.

This problem-driven thesis intends to contribute to building empiric evidence for the implementation of effective interventions aimed to reduce BSIs in infants admitted to a NICU.

The aims of this thesis are:

1. To investigate effective non-pharmacological preventive measures to reduce nosocomial BSIs in VLBW infants.
2. To evaluate whether a multifaceted hand hygiene promotion program would alter hand hygiene practises and change nosocomial BSI rates.
3. To evaluate the utility of electronic devices to measure the frequency of hand disinfection.
4. To study whether gain-framed screen savers messages change hand hygiene behavior.
5. To determine the effect of multiple interventions aimed to improve hand hygiene and reduce nosocomial BSIs.
6. To develop a children's hospital wide strategy for a CVC care bundle implementation.

This thesis is divided into three sections.

Part I: Challenges. Prevention of nosocomial infections has challenged the medical world for decades. Two letters to the editor will introduce the outline of the thesis. In an editorial we claim that infection prevention needs joint efforts of all healthcare professionals involved in patient care **(chapter 2)**. Healthcare professionals are held to update their knowledge on infection prevention and act accordingly. **Chapter 3** discusses the need for repeated hand hygiene education to improve hand hygiene adherence and calls for a sense of accountability regarding infection prevention among healthcare professionals. **Chapter 4** is a literature review about the effectiveness of non-pharmaceutical interventions to reduce the number of nosocomial BSIs at a NICU.

Part II: Interventions and tools. This section presents three studies. The first study in **chapter 5** showed the effectiveness of a multifaceted hand hygiene promotion program on hand hygiene compliance and the incidence of nosocomial BSIs. **Chapter 6** deals with the utility of an electronic device that counts the frequency of actuations of hand alcohol dispensers; this device could be used supplementary to observations of hygienic behavior. The effect of screen saver messages on hand disinfection is presented in **chapter 7**. Finally, the long-term effect of sequential hand hygiene-promoting interventions on nosocomial BSIs is analyzed and longitudinal trends in causative pathogens for BSIs are discussed in **chapter 8**.

Part III: Discussion. The general discussion section in part III presents a research protocol (**chapter 9)** as a directive for further research to implement effective hospital-wide guidelines. The main findings of this thesis and recommendations for further research are provided in **chapter 10.** Finally, the findings are summarized in **chapter 11**.

REFERENCES

1. Biesma DH LJ, Houwaart ES, van Dijk G, et al. Nederlandse artseneed. Utrecht: Nederlandse Federatie van Universitair Medische Centra; 2010.
2. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
3. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114(5):e565-571.
4. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
5. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37(10):827-834.
6. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. J Clin Microbiol 2011;49(5):1866-1871.
7. WHO. World Alliance for Patient Safety, Global Patient Safety Challenge 2005 - 2006: Clean Care is Safer Care. Geneva: World Health Organization; 2005.
8. ECDC. Annual epidemiological report on communicable diseases in Europe 2008: report on the state of communicable diseases in the EU ans EEA/ EFTA countries; 2008.
9. WHO. Report on the Burden of Endemic Health Care-Associated Infection Worldwide. Geneva: World Health Organization; 2011.
10. Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377(9761):228-241.
11. Donaldson L. Dirty hands: the human cost. London: UK Department of Public Health; 2006.
12. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355(26):2725-2732.
13. Hugonnet S, Sax H, Eggimann P, et al. Nosocomial bloodstream infection and clinical sepsis. Emerg Infect Dis 2004;10(1):76-81.
14. Lyytikainen O, Lumio J, Sarkkinen H, et al. Nosocomial bloodstream infections in Finnish hospitals during 1999-2000. Clin Infect Dis 2002;35(2):14-19.
15. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: Incidence, risk factors, and associated mortality rate. Crit Care Med 2002;30(11):2462-2467.
16. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention, U.S. Pediatrics 2002;110(5):e1-24.
17. Donovan EF, Sparling K, Lake MR, et al. The Investment Case for Preventing NICU-Associated Infections. Am J Perinatol 2012 Jul 26.
18. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.

19. Apostolopoulou E. Nosocomial bloodstream infections in neonatal intensive care unit: excess of length of stay, extra costs of antibiotics. ICUs & Nurs Web J 2004(19):7.
20. Prezies. Referentiecijfers maart 2007 t/m maart 2011: Prevalentieonderzoek: Prezies; 2011.
21. van der Zwet WC, Kaiser AM, van Elburg RM, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infect 2005;61(4):300-311.
22. van den Hoogen A, Brouwer AJ, Verboon-Maciolek MA, et al. Improvement of adherence to hand hygiene practice using a multimodal intervention program in a neonatal intensive care. J Nurs Care Qual 2011;26(1):22-29.
23. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
24. Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. Semin Perinatol 2003;27(4):293-301.
25. Payne NR, Barry J, Berg W, et al. Sustained reduction in neonatal nosocomial infections through quality improvement efforts. Pediatrics 2012;129(1):165-173.
26. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
27. Zingg W, Posfay-Barbe KM, Pittet D. Healthcare-associated infections in neonates. Curr Opin Infect Dis 2008;21(3):228-234.
28. Sax H, Hugonnet S, Harbarth S, et al. Variation in nosocomial infection prevalence according to patient care setting:a hospital-wide survey. J Hosp Infect 2001;48(1):27-32.
29. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network. Pediatr Infect Dis J 1998;17(7):593-598.
30. Stevens TP, Schulman J. Evidence-based approach to preventing central line-associated bloodstream infection in the NICU. Acta Paediatr Suppl 2012;101(464):11-16.
31. Zingg W, Posfay-Barbe KM, Pfister RE, et al. Individualized catheter surveillance among neonates: a prospective, 8-year, single-center experience. Infect Control Hosp Epidemiol 2011;32(1):42-49.
32. Barbadoro P, Marigliano A, D'Errico MM, et al. Gestational age as a single predictor of health care-associated bloodstream infections in neonatal intensive care unit patients. Am J Infect Control 2011;39(2):159-162.
33. Wright Lott JW, Kenner, C. Assessment and Management of Immunologic Dysfunction In: Kenner C, Wright Lotte, J., Applewhite Flandermeyer, A., editor. Comprehensive neonatal nursing: a physologic perspective. Second edition ed. Philadelphia: W.B. Saunders Company; 1998.
34. Saiman L. Risk factors for hospital-acquired infections in the neonatal intensive care unit. Semin Perinatol 2002;26(5):315-321.
35. Stern CM. Neonatal immunology. In: Rennie J.M. RNRC, editor. Textbook of Neonatology Edinburgh: Harcourt Publishers Limited; 1999.
36. Perlman SE, Saiman L, Larson EL. Risk factors for late-onset health care-associated bloodstream infections in patients in neonatal intensive care units. Am J Infect Control 2007;35(3):177-182.

37. Garland JS, Uhing MR. Strategies to prevent bacterial and fungal infection in the neonatal intensive care unit. Clin Perinatol 2009;36(1):1-13.
38. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect 2003;54(4):258-266.
39. Garland JS, Alex CP, Sevallius JM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. Infect Control Hosp Epidemiol 2008;29(3):243-249.
40. Grisaru-Soen G, Friedman T, Dollberg S, et al. Late-onset Bloodstream Infections in Preterm infants: a Two-Year Survey. Pediatr Int 2012;54:748-753.
41. Elward AM, Fraser VJ. Risk factors for nosocomial primary bloodstream infection in pediatric intensive care unit patients: a 2-year prospective cohort study. Infect Control Hosp Epidemiol 2006;27(6):553-560.
42. Geffers C, Gastmeier A, Schwab F, et al. Use of central venous catheter and peripheral venous catheter as risk factors for nosocomial bloodstream infection in very-low-birth-weight infants. Infect Control Hosp Epidemiol 2010;31(4):395-401.
43. Graham PL, 3rd, Begg MD, Larson E, et al. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. Pediatr Infect Dis J 2006;25(2):113-117.
44. van der Zwet WC, Kaiser AM, van Elburg RM, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infect 2005;61(4):300-311.
45. van Goudoever JB. Abandoning growth failure in neonatal intensive care units. J Pediatr Gastroenterol Nutr 2011;53(5):472.
46. Reiss I, Borkhardt A, Fussle R, et al. Disinfectant contaminated with Klebsiella oxytoca as a source of sepsis in babies. Lancet 2000;356(9226):310.
47. van der Zwet WC, Parlevliet GA, Savelkoul PH, et al. Outbreak of Bacillus cereus infections in a neonatal intensive care unit traced to balloons used in manual ventilation. J Clin Microbiol 2000;38(11):4131-4136.
48. Rettedal S, Lohr IH, Natas O, et al. First outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a Norwegian neonatal intensive care unit; associated with contaminated breast milk and resolved by strict cohorting. APMIS 2012;120(8):612-621.
49. Erasmus V, Daha TJ, Brug H, et al. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol 2010;31(3):283-294.
50. Pittet D, Allegranzi B, Sax H, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. Lancet Infect Dis 2006;6(10):641-652.
51. Pittet D, Dharan S, Touveneau S, et al. Bacterial contamination of the hands of hospital staff during routine patient care. Arch Intern Med 1999;159(8):821-826.
52. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356(9238):1307-1312.
53. Kirkland KB, Homa KA, Lasky RA, et al. Impact of a hospital-wide hand hygiene initiative on healthcare-associated infections: results of an interrupted time series. BMJ Qual Saf 2012;21(12):1019-1026.

54. Suresh GK, Edwards WH. Central line-associated bloodstream infections in neonatal intensive care: changing the mental model from inevitability to preventability. Am J Perinatol 2012;29(1):57-64.
55. Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory C, et al. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 2002;51(RR-16):1-45.
56. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clin Microbiol Rev 2004;17(4):863-893.
57. Kaltsas A, Sepkowitz K. Community acquired respiratory and gastrointestinal viral infections: challenges in the immunocompromised host. Curr Opin Infect Dis 2012;25(4):423-430.
58. Kampf G, Loffler H. Hand disinfection in hospitals - benefits and risks. J Dtsch Dermatol Ges 2010;8(12):978-983.
59. van den Hoogen A, Brouwer AJ, Verboon-Maciolek MA, et al. Improvement of Adherence to Hand Hygiene Practice Using a Multimodal Intervention Program in a Neonatal Intensive Care. J Nurs Care Qual 2011;26(1)22-29..
60. Gould DJ, Drey NS, Moralejo D, et al. Interventions to improve hand hygiene compliance in patient care. J Hosp Infect 2008;68(3):193-202.
61. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8(6):iii-iv, 1-72.
62. Pittet D. The Lowbury lecture: behaviour in infection control. J Hosp Infect 2004;58(1):1-13.

Chapter 2

Reduction of catheter related bloodstream infections in intensive care: one for all, all for one?

Onno Helder and Jos Latour

Nursing in Critical Care 2009;14(3):107-108

Critically ill patients, regardless of their age, are often subject to hospital-acquired infections. The risk of iatrogenically acquired infection while in intensive care unit (ICU) is extremely high. This risk cannot be reduced without an 'all for one' approach by professionals to reduce infections.

Life-saving central venous catheters (CVC's) are widely used in critical care settings. Unfortunately, these devices are often the cause of catheter related bloodstream infections (CRBI) in patients. CRBI significantly contributes to high rates of mortality and morbidity, increase in length of stay and consequently increase in the healthcare costs. Critically ill children and infants are a particularly vulnerable population in hospitals to acquire bloodstream infections because of the immature or impaired host defense, invasive procedures, suppressed immune systems and other causes. Bloodstream infections in the pediatric ICU (PICU) varied from 3.5 to 8 infections per 1000 catheter days (1-3). In Neonatal ICU (NICU), a study documented that the infection rates in infants vary per birth weight and rage from a median of 4.4 (birth weight > 2500 g) to a median of 12.8 (birth weight < 1000 g) infections per 1000 catheter days (4). The lower the birth weight and gestational age at birth, the higher the risk of infection and extremely low-birth weight infants (below 1000 g) developed up to 43% CRBI (5).

Various strategies have been initiated to reduce nosocomial infections. The report *To Err is Human* (6) and the Surviving Sepsis Campaign (7) contributed to raising healthcare professions' awareness of their role in reducing iatrogenic infection. Subsequently, a variety of projects to reduce nosocomial infections in critical care have been initiated, such as practice reviews, clinical guidelines and studies on the effectiveness of specific clinical practice. The Michigan Health and Hospital Association Keystone Center for Patient Safety and Quality Keystone ICU project, evaluating the effects of five Centers for Disease Control and Prevention (CDC) recommendations is one of the most recent initiatives in the fight against CRBI (8). The recommendations are hand-washing, use of full barrier precautions, use of chlorhexidine for skin cleaning, avoiding the femoral site for catheter insertion and prompt removal of unnecessary lines. This bundle of interventions resulted in a reduction of catheter related infections in adult intensive care patients from 2.7 infections per 1000 catheter days at baseline to zero infection per 1000 catheter days measured at 3 and 18 months post-intervention.

A reduction of CRBI to *zero* infection per 1000 catheter days has not been achieved in eider the NICU or PICU population. The challenging question remains, is *zero* CRBI per 1000 catheter days a realistic goal? Pronovost et al. suggest this is not unrealistic if a simple bundle of interventions are implemented, citing the findings that the majority of infections arose from insertion and removal of CVCs (9). However, the majority of these findings do not rule out other cause of infections. The CDC recommends appropriate hand hygiene to be observed in *all* activities relating to CVC handling to avoid cross-infections (10-11).

In many studies hand washing has been emphasized instead of hand disinfection. Current evidence suggests hand disinfection, by the use of an alcohol solution, is for more effective, less time consuming and applicable compared to hand washing (12,13). Hand washing followed by hand disinfection is recommended when undertaking an asceptic technique or invasive procedure such as handling a CVC [International Federation of Infection Control (IFIC) 2009] (14).

For critical care nurses, CVC handling is part of their daily care and therefore it is the nurses' responsibility to maintain a clean CVC insertion site (15). Knowledge of the current evidence is only one part of the chain to prevent nosocomial infections. Awareness is not enough; critical care nurses need *to act* according to recognized guidelines if they are to reduce the incidence of CRBI.

A recent study on European intensive care nurses' illuminated poor knowledge of the guidelines for preventing CVC related infections (15). A convenience sample of 3405 European intensive care nurses' knowledge was tested using a 10-item survey regarding CVC related infection prevention. The results of this knowledge test were generally poor, although the knowledge scores were significantly better for experienced nurses and those working in smaller ICUs.

Several strategies might increase the knowledge concerning CDC guidelines of CVC. They include:

- More emphasis on infection prevention in the critical care curriculum and continuing education programmes (15);
- Experienced nurses emphasizing infection prevention strategies during bed-side training of student nurses and junior staff and finally;
- By increasing compliance with infection prevention protocols specially designed for the care of CVC lines (16).

Initiatives for improvements to save the lives of our patients have been addressed by many colleagues and education seems one of the keystones for success (17). However, educational programmes that solely focus on theory without addressing behavior change in practice will not accomplish the ultimate goals. All healthcare practitioners working in adult, pediatric and neonatal ICUs need to consider how they can change their practice to reduce CRBI.

The phrase 'Yes We Can' has moved a whole nation lately. These encouraging words might inspire the critical are workforce to take action to decrease nosocomial infections.

REFERENCES

1. Costello JM, Morrow DF, Graham DA, et al. Systematic intervention to reduce central line-associated bloodstream infection rates in a pediatric cardiac intensive care unit. Pediatrics 2008;121(5):915-923.
2. McKee C, Berkowitz I, Cosgrove SE, et al. Reduction of catheter-associated bloodstream infections in pediatric patients: experimentation and reality. Pediatr Crit Care Med 2008;9(1):40-46.
3. Smith MJ. Catheter related bloodstream infections in children. Am J Infect Control 2008;36(10):S173 e171-173.
4. Stover BH, Shulman ST, Bratcher DF, et al. Nosocomial infection rates in US children's hospitals' neonatal and pediatric intensive care units. Am J Infect Control 2001;29(3):152-157.
5. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
6. Kohn LT, Corrigan JM, Donaldson MS. To Err is human: Building a safer health system. Washington: The National Academy Press; 2000.
7. Townsend SR, Schorr C, Levy MM, et al. Reducing mortality in severe sepsis: the Surviving Sepsis Campaign. Clin Chest Med 2008;29(4):721-733.
8. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355(26):2725-2732.
9. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
10. Pittet D, Boyce JM. Revolutionising hand hygiene in health-care settings: guidelines revisited. Lancet Infect Dis 2003;3(5):269-270.
11. Voss A, Widmer AF. No time for handwashing!? Handwashing versus alcoholic rub: can we afford 100% compliance? Infect Control Hosp Epidemiol 1997;18(3):205-208.
12. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clin Microbiol Rev 2004;17(4):863-893.
13. International Federation of Infection Control (IFIC) Infecton control: basic concepts and practice, 2nd edition edn; Chapter 4 Hand Hygiene, downloaded from (www.ific.narod.ru/Manual/Hands.htm) (assessed 20/02/2009).
14. Labeau SO, Vandijck DM, Rello J, et al. Centers for Disease Control and Prevention guidelines for preventing central venous catheter-related infection: results of a knowledge test among 3405 European intensive care nurses. Crit Care Med 2009;37(1):320-323.
15. Vandijck DM, Labeau SO, Secanell M, et al. The role of nurses working in emergency and critical care environments in the prevention of intravascular catheter-related bloodstream infections. Int Emerg Nurs 2009;17(1):60-68.
16. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356(9238):1307-1312.

Chapter 3

Undergraduate nurse students' education in infection prevention: is it effective to change the attitude and compliance with hand hygiene?

Onno K. Helder and Jos M. Latour

Nursing in Critical Care 2010;15(1):39-40

In response to Vandijck and colleagues' comment (1) on our editorial (2) concerning the improvement of hand hygiene in order to decrease infection rate in patients, we would like to raise the following issues. Vandijck and colleagues argue that registered critical care practitioners and undergraduate nursing students should receive appropriate education in hand hygiene techniques. We agree that knowledge and competence in hygienic practices should be established from the start of a nursing career. However, we doubt that the intervention suggested by Vandijck and colleagues is sufficient to achieve the desired outcome of improved adherence to hand hygiene. This is supported by a study observing nursing students illustrating an improbable level of compliance with hand hygiene (3). Healthcare professionals have to change their attitude and behavior towards proper hand hygiene before every patient contact at any time. The challenge is improving hand hygiene compliance. In this perspective, two issues related to changing attitude of critical care nurses are worthy of further elaboration.

The first issue is related to compliance with hand hygiene technique over time. A systematic review concluded that there was no convincing evidence on the effective interventions to increase hand hygiene compliance (4). One observational study, measuring the impact of an educational programme on intensive care professionals' hand washing compliance, documented a decline in performance over four repeated measures, taken after the initial educational intervention at 5, 11, 13, and 24 months respectively. Among nurses the effect was diminished from 90%, 71%, 84%, to 58%, and among physicians it was diminished from 85%, 76%, 74%, to 68% (5). In contrast, a randomized control trial observed a sustained effect over a 4-month period in the experimental group who received a comprehensive teaching course while the control group showed no improvement (6). However, this study did not report on the validity of the observational tool nor the inter-rater reliability among the three observers. Despite the promising results, it can be argued that the Hawthorne effect might have effected the time-series observations. The question is, 'would proper hygiene recommendations be sustained without an observer effect?' Such research would demand a covert observer role, the ethics of which could be highly contested. Rather than seeking research answers to this question perhaps we should turn our attention to practice development activities. We should strive for total adherence to the evidence-based recommendations of hand hygiene to achieve full compliance with hand washing and we argue that this can be achieved by repeated unit-based educational activities to raise staff awareness that ultimately improves patient care.

The second issue concerns changing healthcare professionals' attitude towards healthcare-associated infections (HAI). Once a patient has an infection, the challenge is not only to treat a HAI with antibiotics but rather ask yourself -and question others- why has this patient got an infection? Did we strictly follow the infection prevention protocols? Could I have contributed to prevent this infection? Did I empower colleagues to work according to the standard guidelines? Did I point out to my colleagues when he/ she did not perform according to the hygienic guidelines? In fact, we should become curious to the cause of every infection occurred in our patients. Such inquiry should be an essential part of the critical care team clinical reviews. We contest that every HAI is now seen as a nursing/ medical error.

The Medicare Program in the USA aims to accelerate the improvement of patient safety by withholding funding to hospitals where it is deemed that patient infection could have been reasonably prevented by using evidence-based guidelines (7). The issue will be in how 'reasonable preventative measures' are to be interpreted. In this example we can see how healthcare finance has prompted a strategy to motivate healthcare professionals to prioritise patient safety in this area (8). Regardless of what kind of sanctions is proposed, we believe that changing attitude might be the ultimate goal for success.

Vandijck and colleagues (1) stated that education on evidenced-based recommendations alone does not improve infection prevention. We believe that collaborative efforts are needed in all education nursing programmes, including specialised critical care courses to achieve this outcome. Furthermore, ongoing unit-based education programmes focussing on changing reactive attitudes to proactive behaviors might be the decisive intervention to achieve reduction in hospital-acquired infections.

REFERENCES

1. Vandijck DM, Blot SI, Labeau SO. Reduction of catheter related bloodstream infections in intensive care: one for all, all for one? Nurs Crit Care 2009;14(5):273.
2. Helder OK, Latour JM. Reduction of catheter related bloodstream infections in intensive care: one for all, all for one? Nurs Crit Care 2009;14(3):107-108.
3. Cole M. Exploring the hand hygiene compliance of student nurses: a case of flawed self assessment. Nurse Educ Today 2009;29(4):380-388.
4. Gould DJ, Drey NS, Moralejo D, et al. Interventions to improve hand hygiene compliance in patient care. J Hosp Infect 2008;68(3):193-202.
5. Salemi C, Canola MT, Eck EK. Hand washing and physicians: how to get them together. Infect Control Hosp Epidemiol 2002;23(1):32-35.
6. Huang J, Jiang D, Wang X, et al. Changing knowledge, behavior, and practice related to universal precautions among hospital nurses in China. J Contin Educ Nurs 2002;33(5):217-224.
7. Milstein A. Ending extra payment for “never events”—stronger incentives for patients’ safety. N Engl J Med 2009;360(23):2388-2390.
8. Rosenthal MB. Nonpayment for performance? Medicare’s new reimbursement rule. N Engl J Med 2007;357(16):1573-1575.

Chapter 4

Effectiveness of non-pharmacological interventions for the prevention of bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review

Onno Helder*, Agnes van den Hoogen*, Coby de Boer, Johannes van Goudoever, Malgosia Verboon-Maciolek, and René Kornelisse

International Journal of Nursing Studies 2012, online ahead of print

** Helder and Van den Hoogen equally contributed to this paper*

ABSTRACT

Background: Bloodstream infections are associated with increased morbidity and mortality in very low birth weight infants admitted to neonatal intensive care units.
Objective: To evaluate the available evidence for the effectiveness of non-pharmacological bloodstream infection-preventive measures in infants admitted to a neonatal intensive care unit.
Design: A systematic review of randomized, controlled trials, controlled clinical trials, interrupted time series, and pretest-posttest studies.
Data sources: PubMed, CINAHL, Web-of-Science, Cochrane Central Register of Controlled Trials, and Embase were searched.
Review methods: The systematic review was carried out according to the guidelines of the Center for Reviews and Dissemination. The methodological quality of the individual studies was evaluated with the quantitative evaluation form of McMaster University. The review included randomized, controlled trials, controlled clinical trials, interrupted time series, and pre-posttest studies published from January 1990 to January 2011.

Quantitative pooling of the results was not feasible due to the high heterogeneity of the interventions, methods and outcome measures. Instead, we present the studies in tabular form and provide a narrative account of the study characteristics and results.
Results: Fifteen studies out of 288 generated hits were selected and categorized as research on: hand hygiene (5), intravenous (IV) bundles (4), closed IV sets/ patches/ filters (4), surveillance (1), and percutaneously inserted central catheter teams (1). IV bundles including proper insertion and proper maintenance showed to be the most effective intervention for preventing bloodstream infection in infants; in three out of four studies on IV bundles, a statistically significant reduction of bloodstream infections was mentioned.
Conclusions: Although the methodological quality of most studies was not very robust, we conclude that IV bundles may decrease bloodstream infections in infants. However, differences in IV bundle components and in practices limited the underpinning evidence. There is limited evidence that the introduction of a percutaneously inserted central catheter team results in bloodstream reduction. Hand hygiene promotion increases hand hygiene among healthcare workers, but there is inconclusive evidence that this intervention subsequently leads to a bloodstream infection reduction in infants. Future studies must be well designed, with standardized outcome measures.

What is already known about the topic?

- Infants admitted to neonatal intensive care units are at increased risk for bloodstream infections.

- Previously designed preventive measures do not unanimously reduce the number of bloodstream infections.

What this paper adds

- IV bundles may effectively reduce bloodstream infections in infants.
- A 'percutaneously inserted central catheter' team is promising; however, additional studies are needed to confirm this finding.
- Hand hygiene promotion programs improve hand hygiene compliance; however, there is inconclusive evidence that this intervention subsequently leads to a bloodstream infection reduction in infants admitted to neonatal intensive care units.

INTRODUCTION

Bloodstream infections are a major health threat to hospitalized patients worldwide (1-3). Infants admitted to neonatal intensive care units are at increased risk for bloodstream infections. In particular, very low birth weight infants (< 1500 g) are at risk for bloodstream infections due to their compromised immunological defense systems and multiple invasive procedures. Neonatal bloodstream infections are acquired during hospitalization and, according to the Centers for Disease Control and Prevention (CDC), are defined as bloodstream infections starting at least 48 hours after birth (4) or at least 72 hours after admission (5-6).

The incidence of bloodstream infections among very low birth weight infants in different neonatal intensive care units ranges from 11% to 53% (1, 7-8). Very low birth weight infants affected by bloodstream infections are at higher risk for chronic lung disease (1), periventricular leukomalacia (3), necrotizing enterocolitis (1), severe retinopathy of prematurity (1), poor neurodevelopmental outcomes (3), prolonged hospitalization (9), and death (10). In Europe, the additional costs of one bloodstream infection in a neonatal intensive care unit are €11.750 (9), and in the United States of America, the costs can be as much as $25.090 (≈ €17.469) (11).

Various interventions to reduce bloodstream infections in infants have been studied, with their focuses on healthcare professionals' hands (e.g., the improvement of compliance with hand hygiene protocols, the use of gloves, the introduction of hand alcohol), the usage of intravenous (IV) devices (e.g., closed IV administration devices, the introduction of IV teams, IV care bundles) or 'other aspects' (e.g., multimodal interventions, neonatal intensive care unit design, and feeding the infant with human milk). However, the results of these studies have not been unanimous, and a recent systematic overview of the effectiveness of various interventions is lacking.

Objective

The objective of this review is to present a systematic overview of the available evidence for the effectiveness of non-pharmacological bloodstream infection-preventive measures in infants admitted to a neonatal intensive care unit.

METHODS

Study design

To conduct this systematic review, the 'Center for Reviews and Dissemination Guidance for Undertaking Reviews in Health Care' (CRD, 2009) was used. The review team (OH and AvdH) a priori adapted this protocol to the study purposes, and post hoc changes were not made. The advisory group (RK, CdB, MV) critically commented on this adjusted review protocol and later discussed the findings presented in this paper.

Study identification

To list all possibly relevant studies that may have met the inclusion criteria, the following databases were searched from January 1990 to January 2011: PubMed, CINAHL, Web-of-Science, Cochrane Central Register of Controlled Trials, and Embase. The following keywords were identified if they appeared in the title or abstract: 'nosocomial infection', 'infection prevention', 'infant', and 'cross-infection'. For example, we used the following syntax for the PubMed search: (cross infection/pc[mesh] OR ((infectio*[tw] OR pathogen*[tw]) AND (cross[tw] OR transmiss*[tw] OR nosocom*[tw] OR hospital*[tw]) AND prevent*[tw])) AND (blood-born*[tw] bloodborn*[tw] OR blood-stream*[tw] OR bloodstream*[tw] OR catheter-relat*[tw] OR catheterrelat*[tw] OR catheter-associat*[tw] OR catheterassociat*[tw]) AND (infan*[tw] OR newborn*[tw] OR neonat*[tw]) AND (newborn intensive care unit*[tw] OR neonatal intensive care unit*[tw]). In the second phase, reference lists of the relevant studies were screened to retrieve additional literature. Furthermore, we contacted three international experts in the field of bloodstream infections prevention in neonatal intensive care unit settings and asked them to add potential relevant literature to our compiled list.

Inclusion/exclusion criteria

Studies were considered for inclusion if they met the following criteria: (a) reporting on non-pharmacological interventions aimed to reduce bloodstream infections; our primary outcome of 'reduction of bloodstream infections' was expressed as bloodstream infections per 1000 patient days or bloodstream infections per 1000 catheter days; (b) using a randomized, controlled trial (RCT) design; controlled clinical trial design; interrupted time series having observed at least three data points in the pre- and post-intervention period (12); or pretest-posttest design; (c) reporting on primary research; (d) undertaken in a neonatal intensive care unit; and (e) published in English, French, German, Spanish, Portuguese, or Dutch. Excluded were studies with mixed patient groups that did not allow for subgroup analyses.

Screening of study eligibility

The members of the review team independently decided whether the studies were eligible using an evaluation form based on the inclusion and exclusion criteria. Disagreements were solved by discussion until a consensus was reached. In case one of the authors' own work (OH or AvdH) had to be screened, a member of the advisory group (CdB) replaced that reviewer to avoid potential assessor bias.

Data extraction

This review presents the study design, setting and patient characteristics, (co-)interventions, outcome measurements, conclusions, comments, and quality assessments from the articles that were considered to be eligible. The members of the review team independently extracted these data by using the standard extraction form, conforming to the guidelines of the Center for Reviews and Dissemination. Discrepancies between the reviewers were resolved through discussion until a consensus was obtained.

Quality assessment

The members of the review team independently appraised the design, methods and outcomes reported in each selected article by using the McMaster tool for quantitative studies (13). The assessment tool had 15 criteria that assess the study quality. The reviewers scored 'yes' if the concerning criterion was met or 'no' if the criterion was insufficiently met. Each 'yes' generated one point, with a maximum of 15 points. This quality assessment included the following items: Was the study purpose stated clearly? Was relevant literature reviewed? Was the design appropriate for the study question? Was the sample described in detail? Was the sample justified? Were the outcome variables valid and reliable? Was the intervention described in detail? Were contamination in the intervention group and co-intervention group avoided? Were the results described in terms of statistical significance? Were the analysis methods appropriate? Was the clinical importance reported? Were dropouts reported? and Were the conclusions appropriate given the study methods and results?

Data analysis and evidence synthesis

Given the heterogeneity of the interventions, methods and definitions of bloodstream infections, it seemed unfeasible to pool the results in a meta-analysis. Instead, we present a detailed, narrative account of the study characteristics, designs, settings, and effectiveness of the interventions.

The strength of evidence was determined using an assessment tool adapted from Gartner et al. (14). Six levels of evidence were distinguished based on the study design, the number of tested relationships per theme, and the proportions of statistically significant results. The levels of evidence were: (1) strong evidence, i.e., statistically significant results among 50% of the tested relationships in longitudinal studies; (2) moderate evidence, i.e., statistically significant results in cross-sectional studies; (3) limited evidence, i.e., statistically significant results in one study; (4) expert evidence, i.e., an indication from one or more narrative reviews; (5) inconclusive evidence, i.e., statistically significant results in a cross-sectional study and 50% of the relationships or less were statistically significant; and (6) inconsistent evidence, i.e., statistically significant results were found, but they were in different directions.

RESULTS

Selected studies

The electronic database search yielded 288 manuscripts. The initial selection by the review team, based on titles and abstracts, included 33 manuscripts that seemed to fulfill the pre-defined criteria; if the abstract did not provide sufficient data to determine eligibility, then the full manuscript was reviewed. Additionally, reference lists of these 33 manuscripts were screened for new relevant titles, and this step retrieved two studies; one is included in this review (15), and one did not meet the inclusion criteria (16). After closer inspection by reading the full manuscripts, 20 of these 35 articles did not meet the inclusion criteria, and were therefore excluded (six reviews, four descriptive papers, two epidemiological articles, and eight remaining articles). Finally, 15 studies describing interventions among 7526 infants met the inclusion criteria for the systematic review (Figure 1). The details of the 15 included studies are presented in Table 1.

Interventions in the selected studies with regard to bloodstream infection reduction could be categorized by intervention type: improving compliance with hand hygiene; IV bundles (e.g., proper central venous catheter (CVC) insertion, aseptic preparation, and the administration of IV medication/ fluids); devices (e.g., IV filter, aseptic patch, or closed IV sets); the provision of information concerning the infection rate; and the installation of a 'percutaneously inserted central catheter' team.

There was no general consensus concerning the definition of bloodstream infection in the selected studies. Some used the definition of the CDC's National Healthcare Safety Network (17-22), while others used the definition according to Stoll et al. (8, 23), the definition of the National Nosocomial Infections Surveillance (15) or other alterna-

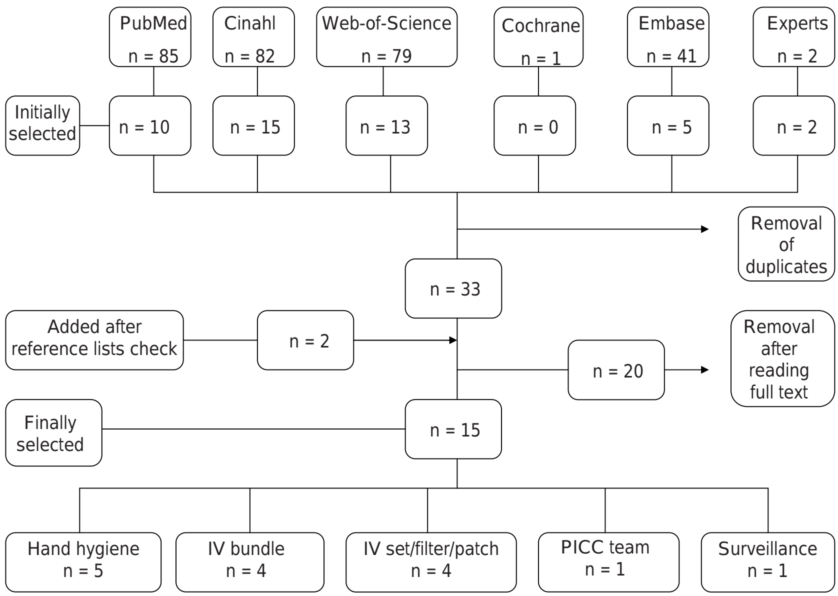


Figure 1. Flowchart of the inclusion process.

tives (24-28). Additionally, in four studies (18, 20, 24, 28), there was no distinction made between late-onset and early-onset sepsis.

Quality assessment

The quality of the included studies varied, and none of the studies fulfilled all 15 quality criteria. One study had a 'quality score' between 12 and 15 (17), eight studies received a score from eight to 11 (15, 20, 22-26, 28), and six studies received a score of seven or less (18-19, 21, 27, 29-30). Frequently observed weaknesses were a lack of power analysis, a low number of studied infants, the absence of a clear statement concerning how contamination was avoided, and a lack of reporting of the clinical importance of the results. Table 2 provides a detailed overview of the included studies' quality.

Study description

Hand hygiene promotion

Five studies evaluated the impact of hand hygiene promotion programs on the number of bloodstream infections per 1000 CVC days or on the number of bloodstream infections per 1000 patient days.

Helder et al. studied the impact of a hand hygiene promotion program on compliance with hand hygiene protocols and the subsequent reduction of bloodstream infections

Table 1. Key characteristics of included studies.

Citation/design/ location	Quality	Group: Control	Group: Intervention	Conclusions
Hand hygiene				
Helder et al. 2010 Pre- and posttest and ITS The Netherlands	11/15	n = 429 GA 28 (27-30)[c] BW 1075 (880-1275)[c] 5-minute Apgar score 8 (7-9)c H observations 575 Conventional care without HH education program	n = 274 GA 29 (27-30)[c] BW 1040 (870-1260)[c] 5-minute Apgar score 9 (7-9)[c] HH observations 725 HH education program and feedback	HH compliance significant improved ($p < 0.001$) BSIs per 1000 patient days significantly reduced ($p = 0.03$)
Lam et al. 2004 Pre- and posttest China	10/15	n = 116 Patient characteristics were not reported Hand washing with soap and conventional care	n = 121 Patient characteristics were not reported HH with hand alcohol (or washing) and minimal handling	HH compliance significant improved ($p < 0.001$) BSI per 1000 CVC days was reduced, however not significant ($p = 0.16$)
Larson et al. 2005 Crossover USA	14/15	n = 1516 admissions GA 35.1 (23-42)[a] BW 2456 (± 1015)[b] Severity of illness missing HH with antiseptic soap	n = 1416 admissions GA 34.6 (23-49)[a] BW 2380 (± 1047)[b] Severity of illness missing HH with hand alcohol	No significant difference in microbial counts ($p = 0.38$) No significant reduction of BSIs per 1000 CVC days ($p = 0.94$)
Pessoa-Silva et al. 2007 Pre- and posttest Swiss	12/15	n = 296 GA 35.5 (24.9-41.4)[a] BW 2300 (620-4740)[a] CRIB 3 (0-13)[a] Conventional care	n = 554 GA 35 (25.6-41.4)[a] BW 2305 (650-4560)[a] CRIB 2 (0-15)a Multimodal HH promotion program	HH compliance significant improved ($p = 0.037$) BSI per 1000 patient days was reduced; p-value NA
Rogers et al. 2010 Pre- and posttest UK	4/15	Number and patient characteristics not reported Not clearly stated	Number and patient characteristics not reported HH education program (posters, education, demonstration HH techniques)	HH improved, p-value NA BSIs per 1000 CVC days was reduced; p-value NA

Table 1. Key characteristics of included studies. (continued)

Citation/design/ location	Quality	Group		Conclusions
		Control	Intervention	
IV bundle				
Aly et al. 2005 Pre- and posttest USA	10/15	n = 169 GA 30.1 (± 3.6)[b] BW 1393 (± 576.1)[b] 5-minute Apgar score 7.9 (± 1.3)[b] Open stock medication system, no limitation IV access	n = 367 GA 31.2 (± 4)[b] BW 1594 (± 585.9)[b] 5-minute Apgar score 7.8 (±1.6)[b] IV bundle (incl. closed medication system, IV access for medication once per 24 hour, daily change of dressing, tube change max. sterile barrier by two nurses)	The IV bundle significant reduced the BSIs per 1000 CVC days (p = 0.001)
Bizzarro et al. 2010 Pre- and posttest USA	10/15	n = 417 GA 30.9 (± 4.8)[b] BW 1640 (± 898)[b] Severity of illness missing Conventional care	n = 159 GA 30.2 9 (± 5.2)[b] BW 1572 (± 942)[b] Severity of illness missing Bundle of IV improvements (incl. proper CVC placement, dressing, HH education, daily evaluation CVC need, infection surveillance)	The IV bundle significant reduced BSI per 1000 CVC days; mean difference -6.73 (95% CI -9, -4.46)
Sannoh et al. 2010 Pre- and posttest USA	11/15	n = 163 GA 29 (23-42)[a] BW 1275 (499-5418)[a] 5-minute Apgar score < 7 15% (n = 25) Conventional care without education	n = 210 GA 30 (21-41)[a] BW 1365 (305-4495)[a] 5-minute Apgar score < 7 20% (n = 43) IV bundle (incl. hub care by using chlorhexedine with alcohol, CVC database, education program, HH, and glove use promotion)	The IV bundle significant reduced BSI per 1000 CVC days in PICCs; OR 0.33 (95% CI 0.12, 0.91), no BSI reduction in umbilical catheters
Wirtschafter et al. 2010 pre-, during and posttest	7/15	Number and patient characteristics were not reported Conventional care without IV bundle education	Number and patient characteristics were not reported IV bundle (incl. CVC insertion with max. sterile barrier, HH education, closed tubing system, hub care, glove use, feedback in case of protocol violations)	The IV bundle reduced BSIs per 1000 CVC days; p-value NA

Table 1. Key characteristics of included studies. (continued)

Citation/design/ location	Quality	Group		Conclusions
		Control	Intervention	
IV device				
van den Hoogen et al. 2006 RCT The Netherlands	11/15	n = 214 GA 34 (26-43)[a] BW 2003 (600-4640)[a] 5-minute Apgar score 9 (1-10)[a] IV set without in-line filter changed every 24 h	n = 228 GA 32 (25-42)[a] BW 1653 (610-4410)[a] 5-minute Apgar score 8 (0-10)[a] IV set with in-line filter changed every 96 h	In-line filters did not reduce the BSI per 1000 CVC days ($p = 0.65$)
Khattak et al. 2010 RCT USA	8/15	n = 25 GA 27.2 (± 1.85)[b] BW 955 (± 250)[b] Severity of illness missing Silver dressing was not applied	n = 25 GA 27.3 (± 2.03)[b] BW 913 (± 209)[b] Severity of illness missing Silver patch dressing	Silver patch dressings reduce BSIs; p-value NA
Reiter et al. 2010 Cohort study USA	5/15	n = 150 GA 32 (± 5.3)[b] BW 1867 (± 1022)[b] Severity of illness missing Open drug Delivery system	n = 150 GA 29.7 [± 4.3][b] BW 1418 [± 895][b] Severity of illness missing Closed drug delivery system	Closed drug delivery systems did not reduce BSIs ($p = 0.054$)
Urrea Ayala et al. 2009 Pre- and posttest Spain	6/15	Number and patient characteristics were not reported. Conventional care	Number and patient characteristics were not reported. Closed IV system and labeling medication line	Closed IV systems did not reduce BSIs; p-value NA

Table 1. Key characteristics of included studies. (continued)

Citation/design/ location	Quality	Group		Conclusions
		Control	Intervention	
Surveillance				
Leboucher et al. 2006 Pre- and posttest France	6/15	n = 254 GA < 28 (n = 12), 28-32 (n = 50), > 32 (n = 192) BW < 1000 (n = 10), 1001-1500 (n = 37) > 1501 (n = 207) Severity of illness missing Conventional care without surveillance information	n = 240 GA < 28 (n = 14), 28-32 (n = 43), > 32 (n = 183) BW < 1000 (n = 14), 1001-1500 (n = 29), > 1500 (n = 197) Severity of illness missing Monthly report to HCWs concerning infections (epidemiologic, bacteriologic and sensitivity)	Monthly report significant reduced BSIs in ELBW infants ($p < 0.01$) and infants with a GA < 28 weeks ($p < 0.01$)
PICC team				
Golombek et al. 2002 Pre- and posttest USA	11/15	n = 89 GA 26 (± 0.4)[b] BW 769 (± 19)[b] Severity of illness missing Conventional care without PICC team	n = 47 GA 25.6 (± 0.3)[b] BW 743 (± 20)[b] Severity of illness missing Introduction of a PICC maintenance team	Introduction of a PICC team significant reduced BSIs ($p < 0.05$)

Data presented as median (range)[a], mean (± standard deviation)[b], or median (interquartile range)[c].
Gestational age (GA) is expressed in weeks and birth weight (BW) in grams.
Abbreviations: n = number; GA = gestational age; BW = birth weight; CRIB = clinical risk index for babies; NICU = neonatal intensive care unit; HH = hand hygiene; RCT = randomized clinical trial; ITS = interrupted time series; IV = intravenous; h = hours; CVC = central venous catheter; PICC = percutaneously inserted central catheter; CI = confidence interval; NA = not available

Table 2. Quality assessment of selected studies with the McMaster tool for quality assessment.

Author	Item[a]															Total quality score
	1 Purpose	2 Literature	3 Design	4 Sample detail	5 Sample justified	6 Outcome valid	7 Outcome reliable	8 Intervention	9 Contam-ination	10 Contam-ination	11 Results	12 Analysis	13 Clinical	14 Drop-outs	15 Conclusions	
Hand hygiene																
Helder et al. 2010	x	x	x	x	x	x	x	x	x	x	x	x			x	11
Lam et al. 2004	x	x	x			x	x	x			x	x	x		x	10
Larson et al. 2005	x	x	x			x					x		x		x	7
Pessoa-Silva et al. 2007	x	x	x	x	x	x	x	x			x	x	x		x	12
Rogers et al. 2010	x	x	x					x								4
IV bundle																
Aly et al. 2005	x		x	x		x		x	x		x	x	x		x	10
Bizzarro et al. 2010	x		x	x		x	x	x			x	x	x		x	10
Sonnoh et al. 2010	x	x	x	x		x	x	x			x	x	x		x	11
Wirtschaft-er et al. 2010	x	x	x			x	x	x					x			7
IV device																
van den Hoogen et al. 2006	x	x	x	x		x	x	x			x	x		x	x	11
Khatttak et al. 2010	x	x	x	x		x	x	x					x			8
Reiter et al. 2006	x	x	x			x					x					5
Urrea Ayala et al. 2009	x	x	x					x					x			5
Surveillance																
Leboucher et al. 2006	x		x	x							x		x		x	6
PICC-team																
Golombek et al. 2002	x	x	x	x		x	x	x			x	x	x		x	11
Total item score	15	12	15	9	2	12	9	12	2	1	11	8	11	1	10	10 (6-11)[b]

PICC = percutaneously inserted central catheter,

[a] The subsequent following items were assessed, [b] Median (interquartile range): 1. Was the study purpose stated clearly? 2. Was relevant literature reviewed? 3. Was the design appropriate for the study question? 4. Was the sample described in detail? 5. Was the sample size justified? 6. Were the outcome variables valid? 7. Were the outcome variables reliable? 8. Was the intervention described in detail? 9. Was contamination avoided in the intervention group? 10. Was contamination avoided in the co-intervention group? 11. Were the results described in terms of statistical significance? 12. Were the methods of analysis appropriate? 13. Was the clinical importance reported? 14. Were dropouts reported? and 15. Were the conclusions appropriate given the study methods and results?

per 1000 patient days (23). The authors performed a single neonatal intensive care unit trial with repeated pre- and posttests and an interrupted time series design. Healthcare workers in the experimental group received an education program, including individual performance feedback on hand disinfection, while healthcare workers in the control group did not receive this education. A bloodstream infection in a very low birth weight infant was defined as a positive blood culture, obtained ≥ 72 h after admission and C-reactive protein > 10 g/L (8). The compliance with hand hygiene statistically significantly improved, from 65% to 88% ($p < 0.001$). In addition, the median (interquartile range) amount of hand alcohol solution used for bedside hand disinfection increased from 40 mL/day/patient (25-56) to 54 mL/day/patient (40-71) ($p < 0.001$). This improved hand hygiene resulted in a reduction of 17.3 bloodstream infections per 1000 patient days to 13.5 bloodstream infections per 1000 patient days ($p = 0.03$).

In a pre- and posttest design, Lam et al. compared hand hygiene and the minimal handling of infants with hand washing with water and soap combined with the conventional handling of infants (15). The patient characteristics were not reported. Bloodstream infection was defined according to the National Nosocomial Infections Surveillance system: blood culture confirmed in presence of a CVC within 48 hours of the onset of infection (31), with an unreported minor modification. Compliance with hand hygiene improved from 40% to 53% ($p < 0.001$), and the number of bloodstream infections decreased, although not statistically significantly, from 6.8 to 1.2 bloodstream infections per 1000 CVC days ($p = 0.16$).

Larson et al. compared antiseptic soap and hand alcohol for their effectiveness on hand disinfection (29). This multi-center, crossover study was performed in two neonatal intensive care units. All infants with a CVC were included, and bloodstream infection was defined according the National Nosocomial Infections Surveillance definition. The bacterial colonization on the hands of nurses during both interventions was not different (mean $\log_{10}$ counts 3.21 vs. 3.11; $p = 0.38$). There were no statistically significant differences between bloodstream infections in the two interventions (14.8 bloodstream infections per 1000 CVC days and 18.2 bloodstream infections per 1000 CVC days, respectively; $p = 0.94$).

Pessoa-Silva et al. studied the impact of hand hygiene promotion on healthcare workers' compliance by comparing a baseline assessment with both a post-intervention assessment and admitted to the neonatal intensive care unit were included, and bloodstream infection was defined according to the CDC (17). The results demonstrated that compliance with hand hygiene improved in the follow-up (49%, 48%, and 61% for baseline, intervention, and follow-up respectively; p-value not reported). Bloodstream infections decreased from 5.1 bloodstream infections per 1000 patient days to 3.1 bloodstream infections per 1000 patient days; p-values were not reported.

Rogers et al. compared the efficacy of a hand hygiene education program with an unclearly reported baseline intervention (19). In this multicenter study with a pre- and posttest design, only very low birth weight infants were included. Bloodstream infection was defined according to the National Nosocomial Infection Surveillance. Self-reported compliance with hand hygiene improved from 24% to 53%; no *p*-values were reported. Bloodstream infections decreased from 31 bloodstream infections per 1000 CVC days to 19 bloodstream infections per 1000 CVC days; *p*-values were not reported.

In sum, there is strong evidence that hand hygiene promotion programs may result in increased compliance with hand hygiene among healthcare workers. There is limited evidence that improved adherence to hand hygiene protocols subsequently leads to a statistically significant reduction of bloodstream infections per 1000 CVC days or bloodstream infections per 1000 patient days. Only one study reported a statistically significant decline in bloodstream infections.

IV bundle introduction

Four papers described the effects of the introduction of IV bundles on the reduction of bloodstream infections per 1000 CVC days or bloodstream infections per 1000 patient days.

Aly et al. compared the effect of an IV bundle (closed IV medication system, IV access for medication only once per 24 h, sterile tubing change by two nurses and daily change of dressing) with an open stopcock medication system with conventional care (24). This multicenter (16 neonatal intensive care units) study was performed using a pre- and posttest design. Infants admitted to the neonatal intensive care unit with a birth weight < 2500 g were included, and bloodstream infection was defined as a positive blood culture and antibiotics for more than 72 h. In the control group, 15.2 bloodstream infections per 1000 CVC days occurred, whereas in the intervention group, 2.1 bloodstream infections per 1000 CVC days occurred ($p < 0.001$).

Bizzarro et al. compared a bundle of IV improvements (proper CVC placement, hand hygiene lessons, skin disinfection with povidone-iodine in 70% alcohol, dressing replaced on indication only, the daily evaluation of the need for CVC removal, surveillance discussed among staff) with standard care (22). In this single-center study with a pre- and posttest design, all infants admitted to the neonatal intensive care unit with a CVC were included. The National Healthcare Safety Network definitions of sepsis were used, or the bloodstream infection was a laboratory-confirmed bloodstream infection with coagulase-negative staphylococci. Bloodstream infections decreased from 8.4 bloodstream infections per 1000 CVC days in the control group to 1.7 bloodstream infections per 1000 line days in the intervention group; the mean difference was -6.73 days (95% CI -9, -4.46).

Sannoh et al. compared a multimodal intervention (CVC database, instruction DVD: nine steps of catheter hub care, hand hygiene and non-sterile gloves, CVC cart in every room, and CVC dressing change when soiled) with custom care without education using a pre- and posttest design in a single center study (20). All infants admitted to the neonatal intensive care unit with a CVC were included. CDC guidelines were used to define bloodstream infections. Bloodstream infections in infants with percutaneously inserted central catheter lines decreased from 23 infections per 1000 catheter days in the control group to 12 infections per 1000 catheter days in the intervention group (OR 0.33, 95% CI 0.12, 0.91). Bloodstream infections in infants with umbilical arterial catheters and umbilical venous catheters decreased from 15 per 1000 catheter days in the control group vs. 5 per 1000 catheter days in the intervention group (OR 0.47 95% CI 0.17, 0.91).

Wirtschafter et al. compared the impact of a multimodal IV bundle (consisting of five features: developing leadership commitments, describing potential best practices, developing collaborative processes between members, developing audit and feedback processes and teaching quality improvement techniques) with unspecified custom care as applied before introduction of the IV bundle (21). This multicenter study (13 neonatal intensive care units) was performed using a pre- and posttest design. The characteristics of the admitted infants were not specified, and the CDC definition of bloodstream infection was used. The number of catheter related bloodstream infections was reduced by 25%, from 4.32 to 3.22 per 1000 catheter days; p-values were not reported.

In sum, there seems to be evidence that IV bundles may decrease bloodstream infections per 1000 patient days or per 1000 CVC days in infants admitted to the neonatal intensive care unit. However, the IV bundle components were different in the studies under review and contradictory; e.g. the daily dressing change in one study or dressing change on indication only in another study. Therefore, the effectiveness of the individual components has to be assessed before clear recommendations can be provided.

Introduction of IV devices (filter, dressing, closed IV set)

Four studies tested utilization of different IV devices.

Van den Hoogen evaluated the effect of in-line filters in central venous catheters in a randomized, controlled trial (28). All admitted infants were randomized either to the no filter control group or to the in-line filter intervention group. Bloodstream infections per 1000 catheter days, nursing time and costs were assessed. Sepsis was defined as a positive blood culture and the presence of clinical signs (not further defined) of sepsis. Bloodstream infections occurred in 16.3% of infants without filters and in 16.2% of the infants with in-line filters. Using in-line filters in central venous catheters did not decrease bloodstream infections ($p = 0.65$).

Khattak et al. studied systemic silver absorption by using silver-impregnated alginate central catheter dressings in very low birth weight infants, and additionally, bloodstream infections were monitored. Bloodstream infection was defined as bacterial or fungus growth in a single blood culture (26). In this randomized, controlled trial, each patient was assigned either to the standard dressing control group or to the silver alginate dressing group. Serum silver concentrations were obtained on days 1, 7 and 28. Serum silver concentrations in the treatment group were statistically significantly higher than among the controls, although below toxic levels. The silver alginate group had a 45.8% reduction of bloodstream infections per 1000 CVC days, although too few patients were enrolled (n = 25/ group) to draw meaningful conclusions.

Reiter et al. evaluated the effects of a closed drug-delivery system on the incidence of bloodstream infections, and catheter related bloodstream infections were evaluated in a multicenter, prospective cohort study (18). Site A used a closed drug-delivery system, while site B used an open drug-delivery system. The bloodstream infection rate was assessed in all infants admitted for > 7 days at the neonatal intensive care unit. Only infants with a percutaneously inserted central catheter or Broviac catheter were included. Bloodstream infection was defined using the CDC and National Nosocomial Infections Surveillance criteria. There was no statistically significant difference in the rate of bloodstream infections per 1000 catheter days between the two sites (16.2 ±39 vs. 8.9 ±24; p = 0.054). The closed drug-delivery system failed to reduce the incidence of bloodstream infections; however, the patient characteristics of both sites were statistically significantly different with respect to gestational age and birth weight, and therefore it was difficult to draw conclusions about the effectiveness of the closed drug-delivery system.

Urrea Ayala and Rozas Quesada studied a new protocol for manipulation, including maintenance of CVCs and introduction of catheters with proximal sealed connections (27). This single center study was performed on different patient groups, including infants, and a pre- and posttest design was used; the characteristics of the admitted infants were not specified. Bloodstream infection was defined as the occurrence of fever and a positive blood culture. After the introduction of the protocol, proximal sealed connectors were used in 95% of cases, and 85% of the CVCs were labeled with the date of insertion, as prescribed in the protocol. The bloodstream infection rates per 1000 catheter days before and after the start of the new protocol were 24.6 and 18.0, respectively; no p-values were reported.

In sum, compliance to the introduced protocols was demonstrated in only one study. There is insufficient evidence that the three devices evaluated effectively reduced bloodstream infections in infants.

Provision of information concerning the infection rate and introduction of a 'percutaneously inserted central catheter' team

The two remaining studies did not fit into the previous intervention themes and are discussed separately below.

Leboucher et al. studied the effectiveness of a nosocomial infections report, including epidemiologic, bacteriologic, and sensibility information, which was published monthly (30). In this single center study with a pre- and posttest design, all infants admitted to the neonatal intensive care unit were stratified according to gestational age and birth weight. Bloodstream infection was defined according to the criteria of 'du réseau Reaped' a Network of French neonatal intensive care units and special care nurseries (32). Bloodstream infections per 1000 patient days decreased from 3.4 to 1.4, and bloodstream infections per 1000 CVC days decreased from 11.3 to 5.2; $p = 0.08$. The reduction was, however, statistically significant in two subgroups (infants < 1000 g and infants with a gestational age of < 28 weeks).

Golombek et al. studied the effectiveness of a 'percutaneously inserted central catheter' team on bloodstream infections in extremely low birth weight infants (< 1000 g) (25). The 'percutaneously inserted central catheter' team assessed the need for percutaneously inserted central catheter placement and removal, inspected the dressing on a daily basis, and replaced the dressing before the disruption of sterility could occur. In this single center study with a pre- and posttest design, all extremely low birth weight infants with a peripherally inserted central catheter were included. Bloodstream infection was defined as clinical signs of infection and a positive blood culture requiring antibiotics. After the introduction of the 'percutaneously inserted central catheter' team, bloodstream infections decreased from 15.8 bloodstream infection per 1000 CVC days to 5.1 bloodstream infection per 1000 CVC days; $p < 0.05$.

In sum, there was inconclusive evidence that the provision of information concerning the infection rate alone could reduce bloodstream infections, and there was limited evidence that the introduction of a 'percutaneously inserted central catheter' team could effectively reduce the number of bloodstream infections in extremely low birth weight infants. However, the authors did not report adherence.

DISCUSSION

This systematic evaluation of the available evidence for the effectiveness of non-pharmacological bloodstream infection preventive measures in infants admitted to a neonatal intensive care unit shows that, until now, there has been no evidence for a 'gold standard bloodstream infection-preventive intervention' that could be effectively applied to all categories of infants and in all settings. Our results suggest that there is limited evidence that IV bundles, including proper insertion and proper maintenance, and limited evidence that the introduction of 'percutaneously inserted central catheter' teams may effectively reduce bloodstream infections in infants; the evidence for hand hygiene in this respect is limited as well.

Consistency of the results

Our review shows that the introduction of IV bundles may be an effective non-pharmacological intervention for the prevention of bloodstream infections in the neonatal intensive care unit. Within the different studies on IV bundles, the results were relatively consistent. Four of the five studies showed that the introduction of IV bundles was effective with respect to reduction of bloodstream infections. However, the consistency of the results with regard to compliance with the IV bundle was reported in only one study (20).

This finding is not in line with recently published reviews: three out of four non-systematic reviews concluded that hand hygiene is the most effective measure in infants (33-35). The non-systematic origin of these reviews may underlie the different conclusions drawn regarding the most effective preventive measure. Furthermore, in one non-systematic review, it was documented that infection prevention by IV management, combined with hand hygiene, was the most effective measure to reduce bloodstream infections (36). It should be recognized, however, that these authors a priori hypothesized that preventive measures should be founded in IV management solutions.

In the 'hand hygiene promotion' group, two studies evaluated more complex interventions that combined hand hygiene with additional measures (i.e., an education program and individual feedback or minimal handling) (15, 23); one study simply compared water and antiseptic soap hand washing with alcohol hand disinfection (29), and two studies solely evaluated hand hygiene promotion (17, 19). The results from these studies showed marked improvement of compliance with hand hygiene; in three of these studies, this improvement was statistically significant (15, 17, 23). Hand hygiene promotion campaigns seem to be effective in increasing hand hygiene adherence. The long-term effect was studied twice and showed a sustained effect of the intervention (17, 23). A statistically significant positive effect of improved hand hygiene on the reduction of bloodstream infections in infants admitted to the neonatal intensive care unit was found in one study (23). In the remaining studies on hand hygiene, lower bloodstream infection rates were found in the intervention groups, but the results were not statistically significant (15, 29), or the significance was not given (17, 19). Although the installation of promotion programs seems to improve compliance with hand hygiene, the positive effect on bloodstream infections among infants is weak, which is in contrast with studies among adults showing that improved adherence to hand hygiene statistically significantly reduced infection rates (37-38). In addition, an authoritative institution like the World Health Organization has stated that hand hygiene is the single most important measure to prevent healthcare-associated infections (39-40).

Design and methods

This review highlights the lack of appropriately designed studies that use unambiguous outcome measures. Studies should be designed according to the ORION statement, which was designed to evaluate the effectiveness of infection prevention interventions (41). The ORION statement emphasized the need for interrupted time series analysis, which could determine the longitudinal effects of an intervention. Furthermore, power analyses must be performed to ensure that the number of patients is large enough to draw firm conclusions concerning effects.

Limitations

The limited number of eligible studies showed inconsistency in unambiguous description within the interventions such as IV bundles. In addition different bloodstream infections definitions were used which also made comparison between the interventions and the different studies difficult. Due to the lack of homogeneity among the study populations, study designs, and bloodstream infection definitions, we were not able to pool the data for meta-analysis. Second, two included studies were the authors' own work. This potential limitation with respect to quality assessment was solved by the replacement of the concerned author by a member of the advisory group (CdB). Finally, four studies did not report patient characteristics; therefore, generalization to other patient populations was impossible.

Implications and suggestion for future research

Hand hygiene promotion is a safe and low-cost intervention that contributes to increased hand hygiene and probably to bloodstream infection reduction; however, the evidence for this intervention is still limited. There is moderately evidence that the introduction of an IV bundle leads to bloodstream infection reduction in infants. Certain devices do not seem useful in reducing the number of infections, e.g., closed IV systems and IV filters. In addition, silver-impregnated patches may reduce bloodstream infections; however, the limited number of enrolled infants hampered the ability to draw a formal conclusion.

This review showed the urgent need for well-designed studies with standardized outcome measures to improve evidence for potentially effective interventions. Therefore, studies need to be designed according RCTs or interrupted time series, and they also should evaluate compliance to the interventions. Outcome measures should include bloodstream infections per 1000 CVC days, and studies should use widely accepted standardized definitions of bloodstream infections suitable for infants cared for at neonatal intensive care units to present unequivocal outcomes. The bloodstream infection definition according the CDC is preferred as the standard definition. Furthermore, comparison between patient groups is more appropriate when patient characteristics are described in a more standardized way, including at least gestational age, birth weight, and the severity of illness. The severity of illness could be expressed by measurements such as the Clinical Risk Index for Babies (CRIB) score and Apgar score (backronym: Appearance, Pulse, Grimace, Activity, and Respiration). Studies that include all infants admitted to the neonatal intensive care unit should also provide results of a subgroup analysis of very low birth weight infants, which is accepted as an extremely vulnerable patient subgroup. Additionally, an extended follow-up period is needed to measure the potential washout effect of the intervention.

CONCLUSION

Methodological limitations, inconsistency in definitions and conflicting results impede universal recommendations concerning the best bloodstream infection preventive intervention in infants. Evidence was found for IV bundles, limited evidence was found for 'percutaneously inserted central catheter' teams, and inconclusive evidence was found for hand hygiene promotion programs to be able to prevent bloodstream infections. Further well-designed research is needed to confirm these findings.

REFERENCES

1. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
2. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
3. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
4. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36(5):309-332.
5. Payne NR, Carpenter JH, Badger GJ, et al. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. Pediatrics 2004;114(2):348-355.
6. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. Clin Microbiol Rev 2004;17(3):638-680.
7. Ng PC, Wong HL, Lyon DJ, et al. Combined use of alcohol hand rub and gloves reduces the incidence of late onset infection in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004;89(4):336-340.
8. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
9. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.
10. Makhoul IR, Sujov P, Smolkin T, et al. Pathogen-specific early mortality in very low birth weight infants with late-onset sepsis: a national survey. Clin Infect Dis 2005;40(2):218-224.
11. Gray JE, Richardson DK, McCormick MC, et al. Coagulase-negative staphylococcal bacteremia among very low birth weight infants: relation to admission illness severity, resource use, and outcome. Pediatrics 1995;95(2):225-230.
12. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27(4):299-309.
13. Law M, Stewart, D., Pollock, N., et al. Guidelines for Critical Critical Review Form - Quantitative Studies. In. Hamilton: McMaster University 1998.
14. Gartner FR, Nieuwenhuijsen K, van Dijk FJ, et al. The impact of common mental disorders on the work functioning of nurses and allied health professionals: a systematic review. Int J Nurs Stud 2010;47(8):1047-1061.
15. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114(5):565-571.
16. Andersen C, Hart J, Vemgal P, et al. Prospective evaluation of a multi-factorial prevention strategy on the impact of nosocomial infection in very-low-birthweight infants. J Hosp Infect 2005;61(2):162-167.
17. Pessoa-Silva CL, Hugonnet S, Pfister R, et al. Reduction of health care-associated infection risk in neonates by successful hand hygiene promotion. Pediatrics 2007;120(2):382-390.

18. Reiter PD, Novak K, Valuck RJ, et al. Effect of a closed drug-delivery system on the incidence of nosocomial and catheter-related bloodstream infections in infants. Epidemiol Infect 2006;134(2):285-291.
19. Rogers E, Alderdice F, McCall E, et al. Reducing nosocomial infections in neonatal intensive care. J Matern Fetal Neonatal Med 2010;23(9):1039-1046.
20. Sannoh S, Clones B, Munoz J, et al. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. Am J Infect Control 2010;38(6):424-429.
21. Wirtschafter DD, Pettit J, Kurtin P, et al. A statewide quality improvement collaborative to reduce neonatal central line-associated blood stream infections. J Perinatol 2010;30(3):170-181.
22. Bizzarro MJ, Sabo B, Noonan M, et al. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31(3):241-248.
23. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.
24. Aly H, Herson V, Duncan A, et al. Is bloodstream infection preventable among premature infants? A tale of two cities. Pediatrics 2005;115(6):1513-1518.
25. Golombek SG, Rohan AJ, Parvez B, et al. “Proactive” management of percutaneously inserted central catheters results in decreased incidence of infection in the ELBW population. J Perinatol 2002;22(3):209-213.
26. Khattak AZ, Ross R, Ngo T, et al. A randomized controlled evaluation of absorption of silver with the use of silver alginate (Algidex) patches in very low birth weight (VLBW) infants with central lines. J Perinatol 2010;30(5):337-342.
27. Urrea Ayala M, Rozas Quesada L. Catheter-associated bloodstream infections: Implementation of a new consensus protocol. An Pediatr 2009;71(1):20-24.
28. van den Hoogen A, Krediet TG, Uiterwaal CS, et al. In-line filters in central venous catheters in a neonatal intensive care unit. J Perinat Med 2006;34(1):71-74.
29. Larson EL, Albrecht S, O’Keefe M. Hand hygiene behavior in a pediatric emergency department and a pediatric intensive care unit: comparison of use of 2 dispenser systems. Am J Crit Care 2005;14(4):304-311.
30. Leboucher B, Leblanc M, Berlie I, et al. Effectiveness of an informative report on the prevention of nosocomial bloodstream infections in a neonatal intensive care unit. Arch Pediatr 2006;13(5):436-441.
31. Horan TC, Emori TG. Definitions of key terms used in the NNIS System. Am J Infect Control 1997;25(2):112-116.
32. Desplanques L, Mahieu G, Gottot S. Infections nosocomiales en réanimation pédriatrique: expérience du réseau REAPED. In: Beafils F, Aujard Y, Bingen E, editors. Les infections nosocomiales en pediatrie. Paris: Arnette Blackwell; 1996.
33. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect 2008;68(4):293-300.
34. Curtis C, Shetty N. Recent trends and prevention of infection in the neonatal intensive care unit. Curr Opin Infect Dis 2008;21(4):350-356.

35. Toltzis P, Walsh M. Recently tested strategies to reduce nosocomial infections in the neonatal intensive care unit. Expert Rev Anti Infect Ther 2010;8(2):235-242.
36. Garland JS, Uhing MR. Strategies to prevent bacterial and fungal infection in the neonatal intensive care unit. Clin Perinatol 2009;36(1):1-13.
37. Allegranzi B, Sax H, Bengaly L, et al. Successful implementation of the World Health Organization hand hygiene improvement strategy in a referral hospital in Mali, Africa. Infect Control Hosp Epidemiol 2010;31(2):133-141.
38. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356(9238):1307-1312.
39. Pittet D, Allegranzi B, Boyce J, et al. The World Health Organization Guidelines on Hand Hygiene in Health Care and their consensus recommendations. Infect Control Hosp Epidemiol 2009;30(7):611-622.
40. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37(10):827-834.
41. Cooper BS, Cookson BD, Davey PG, et al. Introducing the ORION Statement, a CONSORT equivalent for infection control studies. J Hosp Infect 2007;65 Suppl 2:85-87.

Part II

TOOLS AND INTERVENTIONS

Chapter 5

The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban Neonatal Intensive Care Unit: An intervention study with before and after comparison

Onno K. Helder, Johannes Brug, Caspar W.N. Looman, Johannes B. van Goudoever, and René F. Kornelisse

International Journal of Nursing Studies 2010;(47)1245-252

ABSTRACT

Background: Nosocomial bloodstream infections are a major cause of morbidity and mortality in neonatal intensive care units. Appropriate hand hygiene is singled out as the most important measure in preventing these infections. However, hand hygiene compliance among healthcare professionals remains low despite the well-known effect on infection reduction.

Objectives: We studied the effectiveness of a hand hygiene education program on the incidence of nosocomial bloodstream infections.

Design: Observational study with two pretests and two posttest measurements and interrupted time series analysis.

Setting: A 27-bed level IIID neonatal intensive care unit in a teaching hospital in the Netherlands.

Participants: Healthcare professionals who had physical contact with very low birth weight (VLBW) infants.

Methods: The study was conducted during a period of four years. Medical and nursing staff followed a problem-based education program on hand hygiene. Hand hygiene practices before and after the education program were compared by guided observations. The incidence of nosocomial bloodstream infections in VLBW infants was compared. In addition, numbers of nosocomial bloodstream infections per day-at-risk in very low birth weight infants were analyzed by a segmented loglinear regression analysis.

Results: During 1201 observations hand hygiene compliance before patient contact increased from 65% to 88% ($p < 0.001$). Median (interquartile range) drying time increased from 4 s (4-10) to 10 s (7-14) ($p < 0.001$).

The proportion of very low birth weight infants with one or more bloodstream infections and the infection rate per 1000 patient days (relative risk reduction) before and after the education program on hand hygiene intervention decreased from 44.5 to 36.1 (18.9%, $p = 0.03$) and from 17.3 to 13.5 (22.0%, $p = 0.03$), respectively.

At the baseline the nosocomial bloodstream infections per day-at-risk decreased by +0.07% (95% CI -1.41, +1.60) per month and decreased with -1.25% (95% CI -4.67, +2.44) after the intervention ($p = 0.51$). The level of instant change was -14.8% ($p = 0.48$).

Conclusions: The results are consistent with relevant improvement of hand hygiene practices among healthcare professionals due to an education program. Improved hand hygiene resulted in a reduction in nosocomial bloodstream infections.

What is already known about the topic?

- Nosocomial bloodstream infections among very low birth weight infants contribute to mortality and morbidity. These infections result in longer hospitalization.
- The relatively high incidence of nosocomial infections can be reduced by improving hand hygiene compliance.

What this paper adds

- A problem-based hand hygiene education program improved quantity and quality (completeness of hand rubbing and drying time) of hand hygiene.
- Hand hygiene around care for infants nursed in incubators was better than that for infants nursed in cribs.
- The program resulted in a reduction of nosocomial bloodstream infections.

INTRODUCTION

The survival rate of very low birth weight (VLBW) infants (< 1500 g) has improved over the past decades. Consequently, a fragile population survives at high risk of nosocomial bloodstream infections due to immature host defense and invasive procedures. The incidence of nosocomial bloodstream infection among VLBW infants in neonatal intensive care units (NICUs) worldwide varies between 11% and 53% (1-3). These infections are associated with increased mortality and morbidity (4-5). In addition, infected infants need to stay longer in hospital and utilize more resources than non-affected infants (6). Compliance with hand hygiene protocols among healthcare professionals in NICUs is recognized as one of the most important means of preventing hospital-acquired infections (7-8).

Nosocomial bloodstream infections are in part caused by horizontal transmission of commensals or pathogens due to inappropriate hygiene practice (9). Various sources have reported poor compliance among healthcare professionals. Therefore, the most effective strategy to decrease nosocomial bloodstream infections is to improve hand hygiene practices (9,12-13).

Researchers have tested a wide range of interventions and combinations of interventions to improve hand hygiene (10, 14-17). The question whether a combination of interventions would be more effective than a single intervention is still debated however.

The aim of the study reported here was to assess the impact of an education program on compliance with hand hygiene and its influence on the incidence of nosocomial bloodstream infections in VLBW infants. Additionally, differences for infants nursed in incubators and cribs were determined.

METHODS

Study design

We observed hygienic behavior as process outcome in a pretest design and infection rates in an interrupted time series. The study was performed in the level IIID NICU at the Erasmus MC – Sophia Children's Hospital in Rotterdam, the Netherlands, from 1 January 2003 to 31 December 2006. The multifaceted intervention comprised an education program, encouragement of key players to perform correct hygienic behavior, and effecting a culture shift to better hand hygiene. Hand hygiene compliance was observed during two non-consecutive periods before (pretest 1 and 2) and two non-consecutive periods after the intervention (posttest 1 and 2). The intervals between the observation periods ranged from 4 to 6 months. Nosocomial bloodstream infections were continuously documented during 30 months prior and 18 months after the intervention. The Erasmus MC Institutional Review Board approved the study.

This NICU is organised into three identical sub-units with nine beds each. Approximately 750 neonates are admitted annually. The clinical staff included 11 neonatologists, 9 residents, 102 nurses, 12 nursing assistants and 3 nurse practitioners.

Each sub-unit has two conveniently located hand washing sinks. Healthcare professionals wash their hands with plain soap first only when these are visibly soiled. They are required, however, to rub hands with hand alcohol solution as a standard procedure before and after patient contact activities (18). To this aim dispensers are available at each bed, delivering an alcohol-based solution with ethanol 80% (Baktosept E, Bode Chemie GmbH , Hamburg, Germany) at a maximum volume of 1.8 mL per actuation. The manufacturer recommends a drying time of 30 s. The hospital infection control guideline states that rings, wristwatches, and bracelets should be removed on entering the unit. Healthcare worker uniform policies also recommend the wearing of short sleeves.

During the study period the risk factor for nosocomial bloodstream infections remained unchanged in that no other specific measures were implemented to prevent infections.

Education program

Promotion of hand hygiene is a complex issue; it concerns perceptions of individual staff among whom compliance with hand hygiene may vary. This suggests that individual factors play a role in determining hygienic behavior (19-20). Therefore, a hand hygiene education program was developed based on literature (8, 11-12). The education program both had theoretical and practical orientation. It was offered in June 2005 to small groups of healthcare professionals at a time. All who came into contact with infants were obliged to participate. The program lasted 30 min and was structured as follows:

1. Brief overview of the background of infection prevention;
2. Information on the documented incidence of nosocomial bloodstream infections and its consequences. Furthermore, healthcare professionals were made aware of their own poor overall compliance to hand hygiene, a strategy aimed to enhance responsibility awareness and behavioral change;
3. Instructions for optimal hand hygiene procedures. These mainly focused on the timing, the technique and completeness of hand rubbing (e.g. rubbing of the hand back, rubbing the palm of the hand, wrists, finger tops and thumbs);
4. Performance feedback on personal hand hygiene practices. Completeness of hand rubbing was assessed by UV-light after rubbing hands with fluorescent hand rub solution. Only sufficiently rubbed parts will glow in UV-light; non-disinfected parts remain dark;
5. Senior healthcare professionals were encouraged to improve social norms regarding hand hygiene by serving as role models and encouraging junior healthcare professionals to comply with hand hygiene protocols.

Data collection

Three researchers observed hand hygiene practices associated with patient contact using a guided, structured self-designed observation tool. One of the items concerned the nature of the procedure i.e. whether it as elective versus rescue and low-risk versus high-risk. An elective procedure was defined as routinely planned contact; a rescue procedure was defined as an immediately needed intervention. A low-risk procedure was defined as skin contact not associated with invasive procedures, e.g. physical examination or tube feeding (12). A high-risk procedure was defined as prolonged patient skin contact and/ or invasive procedures such as inserting intravenous catheters or endotracheal suction (12). In addition, hand disinfection, completeness of hand rubbing and the applied drying time were observed. The healthcare professionals were not informed about the purpose of the observations.

Data were collected in each sub-unit for several 1-h periods from 8:00 AM to 10:00 PM on weekdays. Hand hygiene compliance before and after patient contact was recorded. Failure to disinfect hands was recorded as noncompliance (12). To determine the influence of the education program on the consumed amount of hand alcohol we recorded the mean 1-week amount of applied hand alcohol per occupied bed during two periods before and two periods after the education program.

Prior to the study the interobserver reliability had been assessed by using Cohen's Kappa. The mean Kappa was above 0.86 which indicates very good agreement.

Nosocomial bloodstream infections

Nosocomial bloodstream infections were determined for 30-month periods prior to (1 January 2003 – 31 June 2005) and 18-month periods after (1 July 2005 – 31 December 2006) implementation of the education program. Nosocomial bloodstream infection was defined as an infection occurring later than 72 hours after admission, at least one positive blood culture and elevated C-reactive protein concentration (> 10 mg/L) (3). The incidence rate was defined as the percentage of infants who had one or more infections in those periods. We also determined the rate of infections per 1000 patient days before and after the intervention.

Additionally, an interrupted time series (ITS) analysis on 2-month periods was performed to determine the longitudinal effects of the hand hygiene education program on the number of nosocomial bloodstream infections. The guidelines of the ORION statement were adhered to Cooper et al. (21). Subsequent nosocomial bloodstream infections in the same patient were defined as another infection when it was caused by another pathogen according to the antibiogram of the same microorganism in combination with a re-elevation of the C-reactive protein concentration.

Statistical analysis

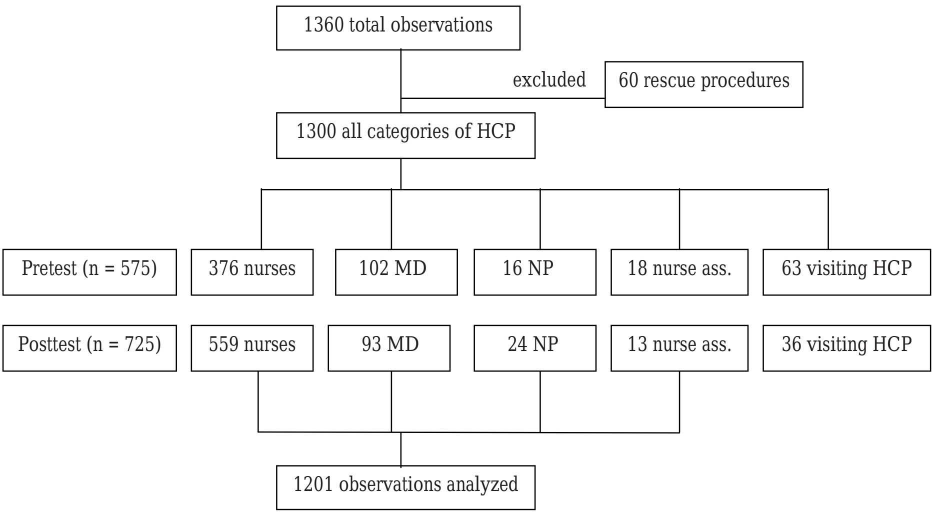
Data are expressed as median and interquartile range (IQR), unless indicated otherwise. Data concerning infections in previous years showed that 50% of VLBW infants developed a nosocomial bloodstream infection. A sample size of approximately 180 infants per period would be required to detect a 30% reduction in the incidence of nosocomial bloodstream infection (80% power with 5% two-sided significance). Differences in frequencies of various findings between groups were analyzed by the Fisher's exact test or Pearson chi-square. As the drying time for the four hand hygiene observation periods showed skewed distribution, differences were analyzed by an ANOVA after log-transformation. This analysis pertained only to those healthcare professionals who performed hand hygiene practices.

The analysis of intervention on the infection rate was carried out with a segmented loglinear regression analysis of interrupted time series data, which divides the time series into a pretest and a posttest segment. The slope or trend of the segments indicates the rate of change in time. An abrupt change in the level at the time of the implantation indicates an immediate effect. Introducing slopes (percentual changes in time in infection rate before and after the implementation) corrects for unassociated background trends. A change in slope may identify a gradual effect of the implantation (21-23). We aggregated nosocomial infections and days-at-risk over 2-months periods. As only infections after 72 h were bookmarked as nosocomial, we started counting days-at-risk from the third day on.

The statistical analysis was performed with SPSS 15 version (Chicago, IL, USA) and R version 2.7.1. (the R Foundation for Statistical Computing, http://rgg.rforge.r.-project.org). *p*-Values of less than 0.01 were considered statistically significant to adjust for multiple testing on the completeness of hand rubbing. For all other tests a *p*-value of less than 0.05 was defined as statistically significant. Observations were not independent from each other, because most healthcare professionals were observed more than once. Characteristics of healthcare professionals were not recorded in the dataset, thus multilevel analysis was not possible.

RESULTS

A total of 1360 structured observations were performed during the two pretests and two posttests periods (Fig. 1). Sixty observations for rescue procedures were excluded from analysis. In these observations the drying time was less than the prescribed 30 s, which, for that matter, is acceptable for emergent life-saving interventions. Ninety-nine observations of visiting healthcare professionals (e.g. laboratory workers and X-ray technicians) were analyzed separately since they did not participate in the education program. Thus, 1201 observations were included in the main analysis. These concerned 751 low-risk and 450 high-risk procedures.



MD = medical doctor, NP = nurse practitioner, nurse ass. = nurse assistants, HCP = healthcare professionals.

Figure 1. Overview of the observed health care workers.

Compliance with and completeness of hand rubbing

Overall hand hygiene compliance before patient contact increased significantly by 26.3% from 352 of 512 (68.8%) pretest to 599 of 689 (86.9%) posttest; $p < 0.001$ (Table 1). Hand hygiene compliance after patient contact also increased significantly by 22.5% from 327 of 512 (68.9%) pretest to 579 of 689 (84%) posttest; $p < 0.001$.

Hand hygiene during high-risk and low-risk procedures

Compliance to hand hygiene prior to high-risk procedures was higher than prior to low-risk procedures. For both types of procedures, compliance had improved after the education program; low-risk: 174 of 270 (64.4%) vs. 413 of 481 (85.8%), $p < 0.001$; high-risk: 178 of 242 (73.6%) vs. 186 of 208 (89.4%), $p < 0.001$.

Table 1. Technique and compliance with hand hygiene before patient contact.

	Pretest 1 (n = 174)	Pretest 2 (n = 338)	Posttest 1 (n = 336)	Posttest 2 (n = 353)
Handpalm (%)	62.1^{ab}	71.6^{cd}	89.9^{ace}	83.6^{bde}
Handback (%)	59.8^{abc}	67.8^{ade}	87.8^{bd}	78.8^{ce}
Wrist (%)	16.1^{abc}	37.0^{ad}	67.9^{bde}	45.3^{ce}
Between fingers (%)	6.9^{abc}	35.8^{ade}	63.4^{bdf}	50.4^{cef}
Finger tops (%)	4.0^{ab}	5.9^{cd}	25.3^{ace}	15.0^{bde}
Thumb (%)	0.6^{abc}	11.8^{ade}	36.6^{bd}	46.5^{ce}
Overall compliance (%)	63.2^{ab}	71.6^{cd}	90.2^{acde}	83.9^{be}

The mutual differences between test periods are compared. Significant comparisons between periods measured by Fisher's exact test at significance level of $p < 0.01$ were coded as a, b, c, d, e and f.

Hand hygiene compliance among visiting healthcare professionals before initiation of patient contact was 45.5%, 31.6%, 57.1% and 50.0%, respectively, for pretests 1 and 2, and posttests 1 and 2.

Table 1 also provides details on completeness of hand rubbing. During all observation periods the palms and backs of the hands were significant better disinfected than wrists, areas between fingers, finger tops and thumbs. The education program improved the completeness of hand rubbing before and after patient contact.

Drying time and usage of hand alcohol

The median hand drying time both before and after patient contact had improved significantly directly after the education program but still remained far below the recommended 30 s (Table 2). Changes in drying time prior to patient contact in comparison with the previous observation periods were +60% (pretest 1 vs. pretest 2), +50% (pretest 2 vs. posttest 1) and -33% (posttest 1 vs. posttest 2) (Table 2). Changes in drying time after patient contact were comparable to those.

Table 2. Drying time before starting and after completing patient contact.

	Pretest 1	Pretest 2	Posttest 1	Posttest 2
Before initiating contact, n	110	242	302	296
Drying time (s)	5 (5–10)^{abc}	8 (4–12)^{ade}	12 (8–15)^{bdf}	9 (6–13) ^{cef}
After completing contact, n	90	238	287	290
Drying time (s)	5 (4-6.25)^{abc}	7 (4-12.25)^{ade}	12 (7-16)^{bdf}	9 (6-13)^{cef}

Data are expressed as median (IQR). The mutual differences between test periods are compared. Significant comparisons tested by ANOVA at significance level of $p < 0.05$ were coded as a, b, c, d, e and f.

The median (IQR) amount of hand alcohol solution used had increased by 35% after the education program; 40 (25-56) vs. 54 mL/day/patient (40-71), $p < 0.001$.

Incubators versus cribs

Hand hygiene compliance was significantly better regarding infants nursed in incubators as compared with infants nursed in cribs during the two pretest observations; pretest 1: incubator 60 of 74 (81.1%) vs. crib 50 of 100 (50%) $p < 0.001$; pretest 2: incubator 145 of 186 (78%) vs. crib 97 of 152 (63.8%), $p < 0.001$. This difference was no longer apparent during the first posttest observation; 140 of 160 (87.5%) vs. 163 of 176 (92.6%), $p = 0.60$. However, 6 months after the education program hand hygiene compliance again was significantly better regarding infants nursed in incubators than for those nursed in cribs; 251 of 284 (88.4%) vs. 45 of 69 (65.2%), $p < 0.001$.

Nosocomial bloodstream infections

Clinical characteristics of the VLBW infants are shown in Table 3. The pretest and posttest groups of patients are comparable.

The incidence of nosocomial bloodstream infections showed a significant reduction after the education program; 191 of 429 (44.5%) vs. 99 of 274 (36.1%), $p = 0.03$. The relative risk reduction was 18.9%. The proportions of infants having two or more infections also decreased significantly; 38 of 429 (8.9%) vs. 12 of 274 (4.4%), $p = 0.02$. Analysis of the pathogens isolated from the blood cultures revealed that coagulase-negative staphylococci were responsible for most of the infections (63.8%). Numbers of nosocomial bloodstream infections in both periods and distribution of the other pathogens did not differ.

The rate of nosocomial infections before the intervention was 17.3 (95% CI 15.2, 19.7) per 1000 patient days and decreased to 13.5 (95% CI 11.2, 16.2) per 1000 patient days after the intervention ($p = 0.03$). The relative risk reduction was 22%. Pretest trend showed a baseline trend (slope, +0.07 per month, 95% CI -1.41, +1.60; $p = 0.93$). Changes in slopes were not significant ($p = 0.51$). The level of infections per day-at-risk decreased immediately after the intervention (-14.8%, $p = 0.48$). The posttest trend

Table 3. Clinical characteristics of the VLBW infants.

	Pretest (n = 429)	Posttest (n = 274)	*p*-Value
Male (%)	227 (52.9)	147 (53.6)	0.88
Gestational age (weeks)	28 (27-30)	29 (27-30)	0.84
Birth weight (g)	1075 (880-1275)	1040 (870-1260)	0.30
APGAR score 5 min	8 (7-9)	9 (7-9)	0.63
Duration of			
Mechanical ventilation (days)	4 (1-12)	3 (1-13)	0.83
CPAP (days)	7 (2-21)	8 (2-24)	0.18
Duration admission (days)	19 (9-44)	20 (9-42)	0.80
Onset of first infection (days)	7 (5-11)	8 (6-12)	0.07
Incidence (%)	191 (44.5)	99 (36.1)	0.03
Two or more infections (%)	38 (8.9)	12 (4.4)	0.02

Data are expressed as median (IQR) unless specified otherwise
CPAP = continuous positive airway pressure

showed an initially declined infection ratio, which still decreased over time (slope -1.25% per month, 95% CI -4.67, +2.44; $p = 0.50$). Our plotted ITS data show a high variability of nosocomial bloodstream infections per day-at-risk between the 2-month intervals (Fig. 2).

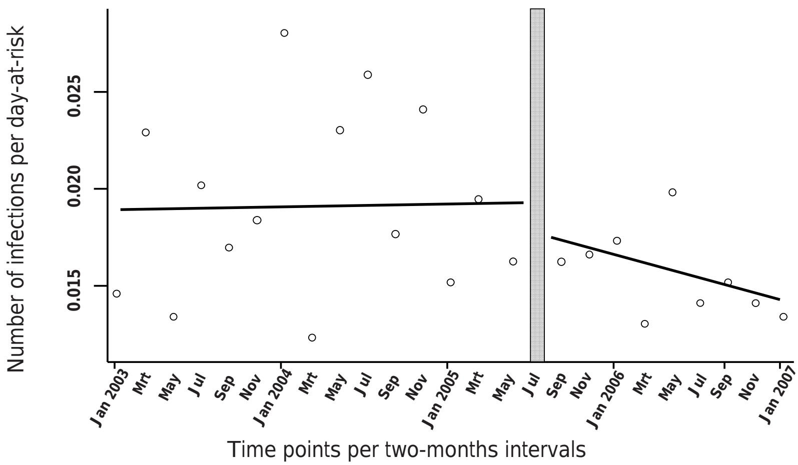


Figure 2. Time series of the infection rate per 2-months intervals. The trend lines show predicted volumes from the segmented loglinear regression analyses. The vertical line marks the period when the education program was given.

DISCUSSION

Adequate hand hygiene of healthcare professionals is the single most effective means of preventing nosocomial bloodstream infections. Hand hygiene compliance is based on disinfecting hands at appropriate moments, complete hand rubbing, and sufficient long drying time. Most earlier studies in this area reported only percentages of healthcare professionals applying hand disinfection or washing hands. This study explored the impact of a multifaceted intervention on hand hygiene practices in a neonatal intensive care setting. Separate aspects of hand hygiene compliance were studied.

Previous studies reported baseline compliance incidences from 28 to 44% (12, 24). In the present study the baseline compliance rate for disinfecting hands prior to patient contact was as high as 68.8%. This would suggest that there was already high awareness of the necessity of hand hygiene among the healthcare professionals studied. Nevertheless, the education program still resulted in a significant relative increase of 26.3% in hand disinfection compliance. This effect however, is probably not only based on the theoretical but also on the practical intervention. Infection prevention became a very important issue for all NICU healthcare professionals, due to the high rate of nosocomial bloodstream infections incidence, according to our observations. Their willingness to strive for a high standard of care resulted in an elevated and sustained performance feedback on hygienic behavior. So, the 30-min education program and the ongoing performance feedback reinforced each other.

Interestingly, improved hand hygiene practice was observed even before implementation of the education program. This phenomenon may be explained by the Hawthorne effect, which is the (usually positive) short lasting effect on the dependent variable caused by subjects' awareness that participants are under study (25). Our observation supports the need for multiple pretests in a non-controlled quasi-experimental designed study.

Despite the education program, we as well as others observed a washout effect in hand hygiene compliance afterwards (26-31). Repeated attention for appropriate hand hygiene is needed and different creative approaches are essential to renew this message among healthcare professionals. For one, multifaceted interventions seem to have a more prolonged effect (10, 27-28, 30-31). Grol and Grimshaw (10) assessed interventions aimed at promoting hand hygiene and classified these as to their effectiveness and sustained effect; regrettably they do not specify the duration of the sustained effect noted. Conly et al (27) observed a specified effect of a sequent intervention i.e. a decrease of nosocomial infections during five years. Pretest infection incidence was measured once during 2 months, so season influence or other bias is not accounted for. Two randomized studies measured the effectiveness of education programs term. Gould and Chamberlain (28) determined the effect of a hand hygiene education program after

3 months and found no effect of the program. Huang et al. (30) showed that 4 months after the program the intervention was still successful. Despite the promising results, it can be argued that the Hawthorne effect might have effected the hand hygiene compliance in these studies, seeing that characteristics of observed nurses were documented. In our study the compliance with hand hygiene for both high-risk procedures and low-risk procedures had improved significantly after the education program. Healthcare professionals seem to have followed the essential guidelines, and thus have contributed to nosocomial infection reduction. However, longitudinal measurement might detect a possible washout effect more precisely.

In contrast to NICU staff, hand hygiene compliance among visiting healthcare professionals was poor. Thus there is every reason to presume that they potentially may transmit pathogens between patients and wards. It would be advisable to give tailor-made hand hygiene feedback and instructions to visiting healthcare professionals.

Completeness of hand rubbing also appeared to have improved, notably with regard to the wrists, finger tops, thumbs, and between the fingers. Lam et al. (12) evaluated the hand washing technique with soap and also observed improvement after an intervention.

Sufficiently long drying time is needed for an optimal bactericidal effect. The education program significantly improved the observed median drying time from 4 to 10 s, comparable in magnitude to findings from some earlier studies in adult ICU settings (18, 32-33). Still, the median drying time was shorter than the manufacturer's recommended optimal drying time. Possible reasons are high workload, forgetfulness, and fear for skin irritation (10, 18). The need for availability of hand alcohol with a short application time of about 15 s has been recognized (34). A study reported on bactericidal activity of an ethanol-based gel in 15 s (35). The promising short application time should be tested in clinical settings. The consumption of hand alcohol in our study rose significantly after the education program. Brown et al. (24) made a similar observation. Hand alcohol consumption is related to the frequency of hand disinfection, and the increased use therefore substantiates our other observations.

Compliance with hand disinfection was lower with regard to infants nursed in a crib in comparison to those nursed in an incubator. Cribs lack a physical cover so there is easier access to the infant. This would result in more frequent patient contact without adequate hand hygiene. Surprisingly, directly after the education program compliance for crib-nursed infants improved and the significant difference in comparison with the incubator-nursed infants disappeared. Six months later, however, the earlier difference was again observed. This observation may be an exponent of a washout effect of educated knowledge that results in old habits of decreased hand hygiene with regard to infants nursed in cribs.

In the present study, the ITS analysis showed changes in slope and level, which were not significant. This may be caused by the high variability of the infection rate. Nevertheless, the incidence of nosocomial infections and number of infections per 1000 patient days had significant changed by 18.9% and 22.2%, respectively. The change in slope was not significant. It could be argued, however that a longer posttest period might have resulted in a significant change. On the other hand, repetition of an education campaign every 6 months could be necessary to reach significant differences in the time series.

In the present study the incidences of nosocomial bloodstream infections in VLBW infants were high (44.5% pretest and 36.0% posttest) in comparison with the 11 - 25% incidences reported in a review from the United States (36). However, in another study the infection incidence among VLBW infants was up to 53% (2). As a possible explanation, we transfer many VLBW infants to regional hospitals before the age of 3 days. Infants eligible for transfer weight more than 1000 g, may need continuous positive airway pressure but not ventilation support, and are relatively stable. Consequently the most vulnerable patients stay at our NICU. The education program in our unit was associated with an 18.9% decrease in the incidence of nosocomial bloodstream infections.

This study had several potential limitations. Firstly, the program offered may have overemphasized education, with too little attention to environmental changes as a means to facilitate appropriate hand hygiene behavior (10). Secondly, as explained above, the study was probably influenced by the Hawthorne effect (25). The hygienic behavior of the healthcare professionals could have been influenced by the two pretest and two posttest observations. Multiple repeated measurements or longitudinal study could offer more detailed information. Thirdly, we used the nosocomial bloodstream infection definition of Stoll et al. (3) developed for VLBW infants. Other authors have used the Centers for Disease Control and Prevention/ National Healthcare Safety Network definition for laboratory confirmed bloodstream infection. By this definition, patients up to 12 months must show one or more clinical signs of infection (hypothermia or hyperthermia, apnea, or bradycardia). Furthermore, two or more positive blood cultures must have been drawn on separate occasions in case common skin bacteria are cultured, i.e coagulase-negative staphylococci and bacillus (37). Our study showed that coagulase-negative staphylococci were responsible for most infections. Thus, at least two blood cultures should be drawn from infants suspected of bloodstream infections. Although, the latter definition better rules out false positive blood cultures caused by contamination we preferred the definition of Stoll and Hansen. We feel that the interpretation of clinical signs could be subjective and vary between healthcare professionals. As to this matter, note that body temperature, for example, could be influenced by changes in incubator temperature, incubator humidity, and during skin-to-skin care. In addition, drawing two blood cultures on separate occasions is not always possible due to the lack of venous access. Finally, we did not control confounders that may affect hand hygiene compliance, e.g. workload and healthcare professional/ patient ratio.

Based on the finding from this study we recommended future studies consider alternative techniques of data collection. For example, hand alcohol dispensers that record time, date and frequency of use of the device may provide data less influence by the Hawthorn effect. Such data could easily be collected over a longer period of time. Nevertheless, compliance, completeness of hand rubbing, and drying time then still need to be observed. Improving compliance with hand hygiene reflects healthcare professional's behavior. Jenner et al. (38) and Pessoa-Silva et al. (19) showed that social cognitive models may help to understand and influence human behavior. Behavioral science may inspire new research concepts aimed to improve hand hygiene compliance.

In conclusion, a multifaceted education program resulted in significantly improved hand hygiene compliance. The number of nosocomial bloodstream infections per day-at-risk decreased, although not significantly. Changing behavior so as to achieve sustained high compliance with hand hygiene is a continuing challenge. The effects of the education program fade away in time, so the program should be repeated at least every 6 months.

Acknowledgements
We wish to thank Marlous op de Weegh and Marcia Wouterson who participated in the data collection. We thank Ko Hagoort for text editing.

REFERENCES

1. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
2. Ng PC, Wong HL, Lyon DJ, et al. Combined use of alcohol hand rub and gloves reduces the incidence of late onset infection in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004;89(4):336-340.
3. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
4. Makhoul IR, Sujov P, Smolkin T, et al. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. Pediatrics 2002;109(1):34-39.
5. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
6. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.
7. Helder OK, Latour JM. Reduction of catheter related bloodstream infections in intensive care: one for all, all for one? Nurs Crit Care 2009;14(3):107-108.
8. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention, U.S. Pediatrics 2002;110(5):e1-24.
9. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clin Microbiol Rev 2004;17(4):863-893.
10. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
11. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356(9238):1307-1312.
12. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114(5):565-571.
13. Yildirim I, Ceyhan M, Cengiz AB, et al. A prospective comparative study of the relationship between different types of ring and microbial hand colonization among pediatric intensive care unit nurses. Int J Nurs Stud 2008;45(11):1572-1576.
14. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8(6):iii-iv, 1-72.
15. Gould DJ, Chudleigh JH, Moralejo D, et al. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev 2007(2):CD005186.
16. Grimshaw J, Eccles M, Tetroe J. Implementing clinical guidelines: current evidence and future implications. J Contin Educ Health Prof 2004;24 Suppl 1:S31-37.
17. Naikoba S, Hayward A. The effectiveness of interventions aimed at increasing handwashing in healthcare workers - a systematic review. J Hosp Infect 2001;47(3):173-180.

18. Boyce JM, Pittet D. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Am J Infect Control 2002;30(8):S1-46.
19. Pessoa-Silva CL, Posfay-Barbe K, Pfister R, et al. Attitudes and perceptions toward hand hygiene among healthcare workers caring for critically ill neonates. Infect Control Hosp Epidemiol 2005;26(3):305-311.
20. Pittet D. The Lowbury lecture: behaviour in infection control. J Hosp Infect 2004;58(1):1-13.
21. Cooper BS, Cookson BD, Davey PG, et al. Introducing the ORION Statement, a CONSORT equivalent for infection control studies. J Hosp Infect 2007;65 Suppl 2:85-87.
22. Perez A, Dennis RJ, Rodriguez B, et al. An interrupted time series analysis of parenteral antibiotic use in Colombia. J Clin Epidemiol 2003;56(10):1013-1020.
23. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27(4):299-309.
24. Brown SM, Lubimova AV, Khrustalyeva NM, et al. Use of an alcohol-based hand rub and quality improvement interventions to improve hand hygiene in a Russian neonatal intensive care unit. Infect Control Hosp Epidemiol 2003;24(3):172-179.
25. Polit B, editor. Nursing Research Principles and Methods. Eight editon ed: Lippincott Williams and Wilkins; 2007.
26. Bittner MJ, Rich EC, Turner PD, et al. Limited impact of sustained simple feedback based on soap and paper towel consumption on the frequency of hand washing in an adult intensive care unit. Infect Control Hosp Epidemiol 2002;23(3):120-126.
27. Conly JM, Hill S, Ross J, et al. Handwashing practices in an intensive care unit: the effects of an educational program and its relationship to infection rates. Am J Infect Control 1989;17(6):330-339.
28. Gould D, Chamberlain A. The use of a ward-based educational teaching package to enhance nurses' compliance with infection control procedures. J Clin Nurs 1997;6(1):55-67.
29. Helder OK, Latour JM. Undergraduate nurse students' education in infection prevention: is it effective to change the attitude and compliance with hand hygiene? Nurs Crit Care 2010;15(1):39-40.
30. Huang J, Jiang D, Wang X, et al. Changing knowledge, behavior, and practice related to universal precautions among hospital nurses in China. J Contin Educ Nurs 2002;33(5):217-224.
31. Salemi C, Canola MT, Eck EK. Hand washing and physicians: how to get them together. Infect Control Hosp Epidemiol 2002;23(1):32-35.
32. Karabay O, Sencan I, Sahin I, et al. Compliance and efficacy of hand rubbing during in-hospital practice. Med Princ Pract 2005;14(5):313-317.
33. Sickbert-Bennett EE, Weber DJ, Gergen-Teague MF, et al. Comparative efficacy of hand hygiene agents in the reduction of bacteria and viruses. Am J Infect Control 2005;33(2):67-77.
34. Dharan S, Hugonnet S, Sax H, et al. Comparison of waterless hand antisepsis agents at short application times: raising the flag of concern. Infect Control Hosp Epidemiol 2003;24(3):160-164.
35. Kampf G, Hollingsworth A. Comprehensive bactericidal activity of an ethanol-based hand gel in 15 seconds. Ann Clin Microbiol Antimicrob 2008;7:2.

36. Kilbride HW, Powers R, Wirtschafter DD, et al. Evaluation and development of potentially better practices to prevent neonatal nosocomial bacteremia. Pediatrics 2003;111(4 Pt 2):504-518.
37. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36(5):309-332.
38. Jenner EA, Jones F, Fletcher BC, et al. Hand hygiene posters: motivators or mixed messages? J Hosp Infect 2005;60(3):218-225.

Chapter 6

Hand disinfection in a neonatal intensive care unit: continuous electronic monitoring over a one-year period

Onno K. Helder, Johannes B. van Goudoever, Wim C.J. Hop, Johannes Brug, and René F. Kornelisse

BMC Infectious Diseases 2012;12:e248

ABSTRACT

Background: Good hand hygiene compliance is essential to prevent nosocomial infections in healthcare settings. Direct observation of hand hygiene compliance is the gold standard but is time consuming. An electronic dispenser with built-in wireless recording equipment allows continuous monitoring of its usage. The purpose of this study was to monitor the use of alcohol-based hand rub dispensers with a built-in electronic counter in a neonatal intensive care unit (NICU) setting and to determine compliance with hand hygiene protocols by direct observation.
Methods: A one-year observational study was conducted at a 27-bed level III NICU at a university hospital. All healthcare workers employed at the NICU participated in the study. The use of bedside dispensers was continuously monitored and compliance with hand hygiene was determined by random direct observations.
Results: A total of 258,436 hand disinfection events were recorded; i.e. a median (interquartile range) of 697 (559-840) per day. The median (interquartile range) number of hand disinfection events performed per healthcare worker during the day, evening, and night shifts was 13.5 (10.8 - 16.7), 19.8 (16.3 - 24.1), and 16.6 (14.2 - 19.3), respectively. In 65.8% of the 1,168 observations of patient contacts requiring hand hygiene, healthcare workers fully complied with the protocol.
Conclusions: We conclude that the electronic devices provide useful information on frequency, time, and location of its use, and also reveal trends in hand disinfection events over time. Direct observations offer essential data on compliance with the hand hygiene protocol. In future research, data generated by the electronic devices can be supplementary used to evaluate the effectiveness of hand hygiene promotion campaigns.

BACKGROUND

Staff compliance with hand hygiene protocols in neonatal intensive care units (NICUs) is highly important to limit the spread of pathogens by the hands of healthcare workers and thus to prevent nosocomial infections (1). Incidences of bloodstream infections in infants admitted to NICUs presently range from 12% to 53% (2). There is evidence that improved hand hygiene in NICU settings results in infection reduction (3). Hand hygiene performance used to be determined by direct observation, but electronic counting methods have been introduced as an alternative.

Three previous studies used bedside electronic counting devices designed to record hand rub dispenser lever-presses (4-6). Cheng et al. and Marra et al. concluded that unobtrusive measurement by electronic devices results in more objective data since direct observations might influence hand hygiene compliance behavior (4, 6). Boyce et al. found that hand disinfection was more frequent performed in the adult intensive care setting than in the general medical ward setting (5). However, these studies had some limitations: data were collected over a relatively short period and detailed information on hand hygiene events distribution over the day was not provided.

We present the results of a study whose objectives were: (1) to monitor the use of alcohol-based hand rub dispensers with a built-in electronic counter in our NICU over a one-year period; (2) to determine compliance with hand hygiene by direct observations; and (3) to compare numbers of hand disinfection events during different shifts and determine differences in distribution of these events over the day.

METHODS

Setting

This prospective observational study was performed from January 1st to December 31st of 2008 in a 27-bed level III NICU at a university hospital in the Netherlands. The NICU is organized into three identical sub-units with nine beds each.

Appropriate hand hygiene is considered an important safety issue which dealt with in education programs since June 2005 (2). The institutional hand hygiene protocol used during the study period dictated that hand hygiene had to be applied before patient and after patient contact as well as before and after invasive procedures. The presently used 'My five moments for hand hygiene' approach had not yet been published at the time (7). Hand alcohol is generally preferred to soap. The only exceptions are visible soiling of the hands, bathroom visits, and the presence of pathogens that are immune for hand alcohol, such as Clostridium and some gastroenteritis viruses. At least 3 ml of hand alcohol should be applied to rub hands for at least 30 seconds. Hand alcohol dispensers (Baktosept E, Bode Chemie GmbH, Hamburg, Germany) are available at each bedside. Furthermore, non-sterile gloves must be worn when there is a risk of exposure to a patient's body fluid. Then, hand disinfection is applied before and after glove use. In addition, two sinks with soap dispensers are located next to the nurses' station. One of these sinks also has a hand alcohol dispenser (Sterillium, Bode Chemie GmbH, Hamburg, Germany), which is exclusively used for surgical hand disinfection. However, Sterillium is approved for both hygienic and surgical hand disinfection. This dispenser is not provided with an electronic counting device.

Data collection

All 27 wall-mounted alcohol-based hand rub bedside dispensers have a concealed electronic counter and wireless transmitting equipment (ComSens NewCompliance, Delft, the Netherlands). The counter documents date and time of each individual use of the dispenser. The system does not allow distinguishing between categories of healthcare workers; data are collected anonymously. Each lever-press generates a click of the sensor; a click within a 2-second period of the previous click was considered as one hand disinfection event (5-6). All dispensers delivered 1.8 ml per full lever-press. Data collected from the dispensers were transmitted to a computer-linked receiver. The study population for which dispenser use was recorded consisted of healthcare workers only (nurses, nurse practitioners, nursing assistants, and physicians). Parents and visitors were strongly encouraged to wash their hands with soap only.

The frequency of hand disinfection events was expressed in two ways: the daily median [interquartile range (IQR)] number of hand disinfection events per bedside; and the daily median (IQR) number of hand disinfection events per healthcare worker. The day shift, evening shift and night shift extended from 8:00 AM to 4:00 PM; from 4:00 PM to 11:00 PM; and from 11:00 PM to 8:00 AM of the next day, respectively.

Additionally, we randomly observed healthcare workers' compliance with the hand hygiene protocol, using a tool described in a previous study (2). Failure to disinfect hands before or after patient contact, and before or after invasive tasks was recorded as noncompliance. Data were collected during thirty 60-minute observation sessions in each sub-unit, from 8:00 AM to 10:00 PM on weekdays. Hygienic performance starts at each new patient contact, so in theory a healthcare worker can perform more than one care sequence during an observation period. Observations were carried out from January to February 2008 and from May to June 2008, simultaneously with hand dispenser recordings. Immediate life-saving interventions were excluded from analysis (2). Three trained researchers and the prevention expert (OH) independently observed hand hygiene events. Interobserver reliability assessed by Cohen's Kappa was high ($\kappa > 0.70$).

The number of hand hygiene events for an ideal 100% compliance with hand hygiene was calculated (total sum of recorded hand disinfection events x 100/ compliance).

Statistical analysis

Data are expressed as the median (IQR). The sign test served to compare numbers of hand disinfection events among shifts for each day. SPSS version 17.0 (SPSS, Chicago, IL) was used for analysis, and $p < 0.05$ (two-sided) was considered as significant.

The Institutional Review Board of the University Medical Center Rotterdam approved this study at August 23, 2007.

RESULTS

During the one-year study period, a total of 717,445 lever-presses for all dispensers were recorded, equivalent to 258,436 hand disinfection events. The calculated median (IQR) number of hand disinfection events per day was 697 (559-840). The proportion

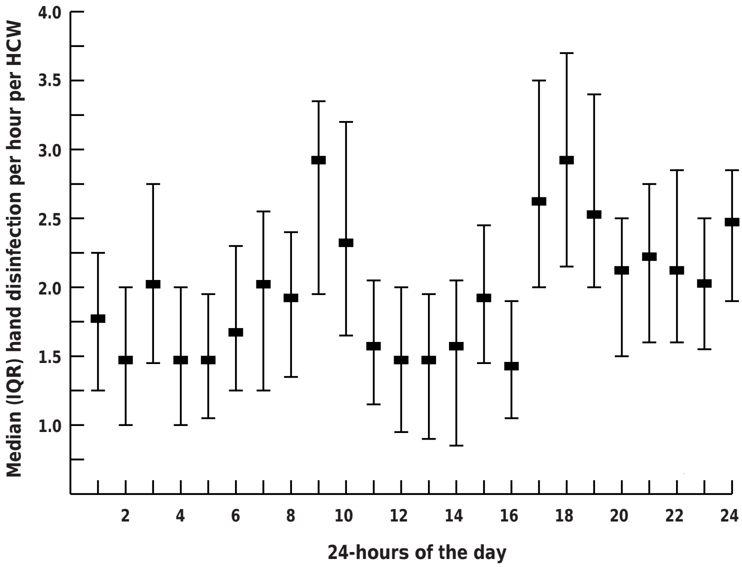


Figure 1. Median (IQR) number of hand disinfection events per healthcare worker plotted for each hour of the day, calculated over the one-year study period.
Analysis of hand disinfection events per healthcare worker by hour of the day revealed a significant increase in hand disinfection events from 8:00 AM to 10:00 AM, which coincides with the start of the dayshift and medical assessments. Another increase was found from 4:00 PM to 7:00 PM, which correspondents with elevated activities before dinnertime (p < 0.001 for both). The number of hand disinfection events was relatively low from 10:00 AM to 4:00 PM.

of hand disinfection events during day shifts was 41.0%, which is significantly higher than that during evening shifts (34.9%) and night shifts (24.1%).

The median (IQR) daily number of healthcare workers who provided patient care was 44 (42-45), i.e. 34 nurses and 10 physicians and nurse practitioners. The distribution of both disciplines (median) during day, evening and night shifts was 14 vs. 7; 10 vs. 2; and 9 vs. 1, respectively. The average number of lever-presses per hand disinfection events was 2.8, which equals 5 ml hand alcohol if all lever-presses were fully completed.

The median (IQR) number of hand disinfection events per healthcare worker per day was 15.9 (13.1-19.3). In Figure 1 the numbers of hand disinfection events per healthcare worker are plotted for each hour of the day, calculated over the one-year study period.

The distributions for day shift, evening shift, and night shift are presented in Table 1. Differences between shifts were all statistically significant ($p < 0.001$). The median (IQR) number of hand disinfection events per patient day was 27.6 (23.0-36.3).

In total 1,168 direct observations of events requiring hand hygiene were analyzed; in 65.8% of cases healthcare workers fully complied with the protocol. The interquartile range of compliance with hand hygiene determined at the separate observation days varied from 50% to 71.5%.

Table 1. Distribution of hand disinfection events per healthcare worker over the different shifts.

Shift	Median (IQR)[a] hand disinfection events per healthcare worker
Day shift	13.9 (10.8-16.7)
Evening shift	19.8 (16.3-24.1)
Night shift	16.6 (14.2-19.3)
Total day	15.9 (13.1-19.3)

[a] IQR: interquartile range

Adjusted for the 65.8% compliance rate, the counted number of hand disinfection events should increase by about 50% to approximately 375,000 hand hygiene disinfection events.

DISCUSSION

Electronic dispensers provided data trends on the frequency of hand disinfection events in a clinical setting over an extended period of time. The median number of 15.9 hand disinfection per healthcare worker per day in our study falls within the median 5.0-30.0 range reported by Boyce et al. (1).

Three studies measuring hand disinfection events by electronic dispensers expressed the outcome as hand disinfections per patient day (5-6, 8). For a pediatric intensive care unit, a surgical intensive care unit and a general medical ward, the mean number was 41.2, 48.7 and 12.2, respectively (6). Marra et al. reported a mean of 53.8 hand disinfections per patient day in an adult medical-surgical intensive care unit; (6). Another study performed in a general pediatric ward measured the amount of used hand alcohol and translated this into 47 hand rubs per patient day (9). McGluckin et al. reported a mean of 6.7 hand washings per patient day in an inpatient rehabilitation unit (10). We documented a median of 27.6 hand disinfection events per patient day at our NICU. This relatively low number as compared to two of the studies mentioned above likely reflects our policy to provide care on indication. This approach takes into account the infants' sleep-wake rhythm so that they can sleep longer, which improves recovery from previous interventions. This approach leads to fewer patient contacts.

Combining the electronically collected data and the observational data allows generating an additional tool to monitor hand hygiene practices. The calculated number of required hand disinfection events per day could be an incentive for healthcare workers to strive for and reach 100% compliance. However, this calculated number is ward-specific and may be only adhered to if conditions such as case mix, number of patient days, and patient-healthcare worker ratio, are comparable to conditions of the initial study period.

Additionally, we showed that hand hygiene performance followed a daily pattern: it was most intense after shift handover, and after dinnertime. The median number of hand disinfection events per healthcare worker during day shifts was lower than that during evening shifts. This is probably caused by the fact that the work floor during day shifts counts twice as many healthcare workers than during evening shifts; the number of patient contacts is likely not doubled. The slightly lower number of hand disinfection events per healthcare worker during night shifts in comparison to evening shifts might be explained by the fact that night shifts in general correlate negatively with hand hygiene compliance (11). Additionally, in the night shifts there are fewer hand disinfection opportunities as healthcare workers only perform routine care and unavoidable interventions.

Direct observation of hygienic behavior is a well-known method to document hand hygiene compliance in a clinical setting. Nevertheless, it is time consuming, and knowing that they are observed may influence the healthcare workers' behavior (4-6). In contrast, the described electronic device unobtrusively records all hand disinfection events over an extended period of time. Furthermore, senior staff can motivate members of the healthcare team to improve their hand hygiene practices by relating the recorded number of hand hygiene events to the calculated number required for 100% compliance. Nevertheless, this device is not able to record noncompliance and the quality of hand disinfection. Non-compliance can be defined as failure to disinfect hands, lack of completeness of hand rubbing, or insufficient drying time. Applying both methods together therefore provides a more complete representation of hand hygiene practices.

This study had several limitations. The used type of dispenser is unable to detect whether dispenser use correlates with a defined hand disinfection opportunity. Second, this study was designed and performed before the 'My five moments for hand hygiene' approach was published (7). Three of the five hand hygiene indications were measured: before patient contact, before invasive procedures, and after patient contact. The 'My five moments for hand hygiene' approach is nowadays considered the "gold standard" method to monitor hand hygiene compliance. We missed the 3rd and 5th moments: 'after touching patient surroundings' and after body fluid exposure risk. However, our hand hygiene protocol dictates that healthcare workers must wear gloves when at risk of exposure to a patient's body fluid. They are also required to disinfect hands before and after glove use. Third, the variance of hand disinfection practices by individual healthcare workers was not documented. Furthermore, we also cannot rule out the possibility that parents or family occasionally used alcohol dispensers, although all NICU professionals instructed parents to wash their hands with soap only. NICU professionals did not report the use of hand alcohol by parents. In addition, healthcare workers also might have used hand alcohol at moments that are not corresponding to any indication for hand hygiene. This possible unnoticed use could have resulted in overestimation of hand hygiene events by healthcare workers. Therefore, the calculated number of hand disinfection events needed for an ideal 100% compliance is of limited accurateness and need to be considered with caution.

CONCLUSIONS

We conclude that the tested type of dispenser provides useful trend data that can be evaluated supplementary to the data obtained form direct observations. Although not tested as such in this study, we believe that electronic devices could be useful to evaluate the long-term effect of hand hygiene promotion campaigns. Direct observations according to the 'My five moments for hand hygiene' approach still provide important additional information on non-compliance and quality of hand hygiene.

Acknowledgements
We thank Ko Hagoort for editorial advice.

REFERENCES

1. Boyce JM, Pittet D:.Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Am J Infect Control 2002;30:S1-46.
2. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47:1245-1252.
3. Helder O, van den Hoogen A, de Boer C, et al. Effectiveness of non-pharmacological interventions for the prevention of bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review. Int J Nurs Stud 2012, Feb 29.
4. Cheng VC, Tai JW, Ho SK, et al. Introduction of an electronic monitoring system for monitoring compliance with Moments 1 and 4 of the WHO "My 5 Moments for Hand Hygiene" methodology. BMC Infect Dis 2011;11:151.
5. Boyce JM, Cooper T, Dolan MJ: Evaluation of an electronic device for real-time measurement of alcohol-based hand rub use. Infect Control Hosp Epidemiol 2009;30:1090-1095.
6. Marra AR, Moura DF, Jr., Paes AT, et al. Measuring rates of hand hygiene adherence in the intensive care setting: a comparative study of direct observation, product usage, and electronic counting devices. Infect Control Hosp Epidemiol 2010;31:796-801.
7. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37:827-834.
8. Larson EL, Albrecht S, O'Keefe M: Hand hygiene behavior in a pediatric emergency department and a pediatric intensive care unit: comparison of use of 2 dispenser systems. Am J Crit Care 2005;14:304-311.
9. Scheithauer S, Oude-Aost J, Stollbrink-Peschgens C, et al. Suspicion of viral gastroenteritis does improve compliance with hand hygiene. Infection 2011;39(4):359-362.
10. McGuckin M, Taylor A, Martin V, Porten L, et al. Evaluation of a patient education model for increasing hand hygiene compliance in an inpatient rehabilitation unit. Am J Infect Control 2004;32:235-238.
11. Earl ML, Jackson MM, Rickman LS: Improved rates of compliance with hand antisepsis guidelines: a three-phase observational study. Am J Nurs 2001;101:26-33.

Chapter 7

Computer screen saver hand hygiene information curbs a negative trend in hand hygiene behavior

Onno K. Helder, Anne Marie Weggelaar, Daniël C.J. Waarsenburg, Caspar W.N. Looman, Johannes B. van Goudoever, Johannes Brug, and René F. Kornelisse

American Journal of Infection Control 2012;40(10):951-954

ABSTRACT

Background: Appropriate hand hygiene among healthcare workers is the most important infection prevention measure; however, compliance is generally low. Gain-framed messages (i.e. messages that emphasize the benefits of hand hygiene rather than the risks of noncompliance) may be most effective, but have not been tested.
Methods: The study was conducted in a 27-bed neonatal intensive care unit. We performed an interrupted time series analysis of objectively measured hand disinfection events. We used electronic devices in hand alcohol dispensers, which continuously documented the frequency of hand disinfection events. In addition, hand hygiene compliance before and after the intervention period were directly observed.
Results: The negative trend in hand hygiene events per patient day before the intervention (decrease by 2.3 [standard error, 0.5] per week) changed to a significant positive trend (increase of 1.5 [0.5] per week) after the intervention ($p < 0.001$). The direct observations confirmed these results, showing a significant improved in hand hygiene compliance from 193 of 303 (63.6%) observed hand hygiene events at pretest to 201 of 281 (71.5%) at posttest.
Conclusions: We conclude that gain-framed messages concerning hand hygiene presented on screen savers may improve hand hygiene practice.

INTRODUCTION

Hospital-acquired infections are associated with mortality and morbidity in neonatal intensive care unit (NICU) settings. The reported incidence of these infections varies between 11% and 53% (1-3). Research shows that increasing compliance of healthcare workers (HCWs) with hand hygiene protocols reduces these infections and limits the spread of pathogens (4). Overall compliance with hand hygiene protocols in hospitals is low, however.

It has been shown that hand hygiene can be improved by strategies such as education, audits and feedback, environmental improvements, multimodal interventions, and reminders (4,5). Improved hand hygiene compliance is known to reduce the rate of hospital-acquired bloodstream infections (1). However, over time, a washout effect can be observed, in which the new behavior is not internalized, and participants relapse and return to their former automatic behavior, which includes insufficient hand hygiene (6). Up to now, there has not been a proven optimal intervention that leads to lasting high compliance with hand hygiene measures. It is hypothesized that repeated attention is needed over a prolonged period to reduce the washout effect. Therefore, it is also important to address the subconscious, automatic behavior of HCWs to maintain a high level of compliance with hand hygiene protocols.

Grol and Grimshaw showed that multiple interventions lead to a more sustained implementation of protocols by HCWs (7). Pittet et al. used different interventions, including poster campaigns, to promote hand hygiene; however, they did not provide any theoretical rationale behind their poster design (8). Gain-framed messages not only provide recommendations, but also emphasize the advantages of hand hygiene, rather than the risk of noncompliance. A literature review suggested that posters with gain-framed messages are theoretically effective in motivating HCWs' hygienic behaviors (9). Therefore, gain-framed messages may help promote hand hygiene in daily practice. The use of such gain-framed messages for improving hand hygiene has not been tested on hand hygiene practices in a real-life clinical setting, however (9).

The purpose of this study was to test the impact of gain-framed messages on the frequency of hand disinfection events and compliance in the NICU. Hand disinfection events per complete day and shifts during the day, evening, and night shift were compared.

METHODS

Design and Setting

We used an interrupted time series (ITS) design with objective measures of hand disinfection events. Two segmented periods of 8 weeks before the intervention and 8 weeks during the intervention were compared by an ITS to detect changes in the longitudinal trend in hand hygiene events associated with the introduction of the intervention. In addition, observations of hand hygiene behavior were systematically performed by research associates before and after the intervention. The study was conducted in a 27-bed, level IIID (10) NICU at the Erasmus MC – Sophia Children's Hospital in Rotterdam, the Netherlands, between January 25, 2008 and May 25, 2008. A level IIID NICU center is equipped for all kinds of complex care for infants, including for example, care for extremely low birth weight infants (< 1000 g), extracorporal membrane oxygenation, and surgical repair of complex congenital cardiac malformations. The NICU is divided into 3 identical sub-units with 9 beds each. Approximately 750 newborns are admitted annually.

Study population

All NICU HCWs who had physical contact with infants were included in the study. The HCWs included 14 neonatologists, 8 residents, 105 nurses, 12 nursing assistants, and 4 nurse practitioners.

Intervention

As a substitute for static posters, we used a screen saver on computer displays placed in front of the desk as a communication vehicle. The computer screen saver is an efficient medium with which to communicate with employees and expose employees to hand hygiene promotion messages in a more dynamic way compared with the static medium of posters (11-13). A total 6 computer screens, 2 per unit, were involved. Computer screens were placed behind each desk of the 3 sub-units, which were used by all HCWs and were located in high traffic areas. The computers enter "sleep mode" 5 minutes after their last use, and the screen saver is automatically displayed on the monitor. The screen saver messages included a 2-screen series with different messages that completed a cycle every 10 seconds (12). The messages were replaced by a newly designed 2-screen series every 2 weeks, to maintain the attention of the staff and avoid desensitization to the messages (12,13).

The screen saver messages emphasized the need for improved adherence to hand hygiene protocols and were designed according to theoretical principles of message framing (9). Images of hands, germs, and disinfection methods were shown, and titles were designed to attract attention. We added gain-framed messages aimed at promoting hand hygiene, in which we focused on the benefits to the patients and on the responsibility of HCWs to their patients and appealed to their instinctive altruistic motivation to "take good care" (example messages: "By performing appropriate hand disinfection, you maintain good health for the infants you are caring for;" "Don't take it personally. Your hands look fantastic, but you should disinfect your hands to maintain good health for the patients and yourself"). We used images that were compatible with the message. No other interventions were performed to improve compliance with hand hygiene measures during the study period.

Five months before the initiation of the present study, a multidisciplinary infection prevention education program was organized at our NICU. This program reiterated general hygiene guidelines, encouraging HCWs to culture all types of surfaces in the NICU to improve the awareness of invisible microorganisms, and reinforced the importance of appropriate hand hygiene.

Data collection

Electronic devices were used to objectively document the frequency of hand disinfection events. Wall-mounted bedside hand alcohol dispensers were replaced by identical dispensers with a concealed electronic counter and wireless transmitting equipment (ComSens, NewCompliance, Delft, the Netherlands). These electronic dispenser devices provided continuous documentation of hand disinfection events, including documentation of date and time of the individual dispenser usage. Each press of the lever generated a click of the sensor, and an additional click occurring within 2 seconds of the previous click was considered a single hand disinfection event (15).

In addition, the compliance of HCWs with hand hygiene protocols was evaluated during the final 2 weeks of the observation period before and after the intervention using a guided observation tool. Data from observations of HCWs who performed rescue procedures or who were visiting from other units (and thus who could not be exposed to the screen savers during the intervention period) were excluded from the analyses of these observation data. Hand disinfection should be done before touching a patient, before sterile procedures, before and after the use of gloves, after contact with body fluids, and after touching a patient. Failure to disinfect hands during any of these events was recorded as noncompliance. Washing the hands with soap and water is appropriate when hands are visibly soiled or after bodily fluid contact (16). Two medical students performed observations; the HCWs were unaware of the reason for the observations. HCWs are frequently observed for training as well as research purposes, and thus are used to these practices, reducing the risk of the Hawthorne effect (a usually positive short-term effect on the dependent variable caused by subjects' awareness that they are under study). The observers were not blinded to the intervention.

Along with compliance with hand disinfection protocols, we also documented the nature of the procedure (elective or rescue). Before study commencement, interobserver reliability was assessed using Cohen's κ. The mean κ was > 0.8, indicating good agreement. The following potential confounding factors were documented: birth weight, gestational age, and Clinical Risk Index for Babies (CRIB) score (17).

For analysis, the day shift was defined as 8:00 AM to 4:00 PM, the evening shift as 4:00 PM to 11:00 PM, and the night shift as 11:00 PM to 8:00 AM.

Power analysis

We previously measured the mean (SD) number of hand disinfection events per week as 5750 ±450. A power analysis showed that an increase of 675 hand hygiene disinfection events per week can be significantly detected with 80% power and a 2-sided 5% significance level. We previously showed a baseline compliance with hand hygiene of 65%, which improved after intervention to 88%. Therefore, we considered a target compliance of 80% to be realistic (1). Given the target improvement in compliance rate from 65% to 80%, we found that 135 observations in each observation period were needed to detect a significant difference with 80% power and a 2-sided 5% significance level.

Statistical analysis

We evaluated the effect of the intervention on hand disinfection practices with a segmented linear regression analysis of interrupted time series data, dividing the time series into a pretest segment and a posttest segment. We aggregated hand disinfection events over a 1-week period to determine the longitudinal effects and avoid autocorrelation. Hand disinfection events are influenced predominantly by the number of patient days; thus, we adjusted the number of hand hygiene events by dividing by the number of patient days. The data are expressed as median and interquartile range (IQR) unless indicated otherwise.

For the additional observations, data on compliance with hand hygiene are expressed as a percentage of all events that necessitate hand hygiene procedures. Univariate analyses using the χ^2 test were performed for a simple pretest-posttest comparison. P values < 0.05 were considered statistically significant. SPSS version 17 (Chicago, IL, USA) was used for data analysis.

Ethical considerations

The Erasmus Medical Center's Institutional Review Board approved the study. Because of the study's observational nature, the need for informed consent from the parents was waived.

RESULTS

The patient characteristics during the pre-intervention period (n = 125) and post-intervention period (n = 144) were well balanced. The median (IQR) birth weight was 1980 g (1367-3170 g) vs. 1810 g (1177-2956 g) (*P* = 0.14); mean gestational age was 34 weeks (31-38 weeks) vs. 33 weeks (28-37 weeks) (*p* = 0.33); and mean CRIB score was 1 (0-2) vs. 1 (0-3) (*P* = 0.99).

The daily median number of hand hygiene events during the 4-month study period was 792 (705-930), with a pre-intervention value of 804 (686-940) and a post-intervention value of 783 (726-899). The plotted interrupted time series data showed a clear change from a negative trend towards fewer hand hygiene events before the intervention to a positive trend after the intervention was introduced (Fig. 1). Table 1 presents the separate analyses of all shifts combined and specific shifts, showing similar results for the different shifts separately and all shifts combined. The number of hand disinfection events per patient day before the intervention decreased by 2.4 (standard error [SE], 0.5) per week (*P* = 0.001) per patient day. The immediate effect of the screen saver after its introduction was not significant (-1.4 [3.3]; *p* = 0.681). The posttest trend showed a significant increase of 1.5 (0.5) hand disinfection events per week per patient day (*p* =0.001). The change in trend before and after the intervention was highly significant.

A total of 677 observations were performed before and after the intervention was started. After excluding 51 rescue HCWs and 46 visiting HCWs, 584 observations were

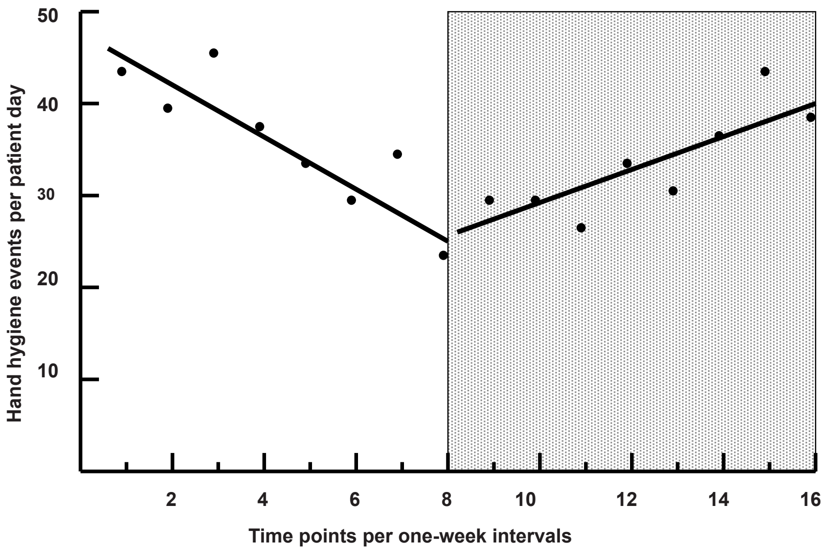


Figure 1. Time series of the aggregated hand hygiene events per patient day over 1-week intervals. The trend shows predicted volumes from the segmented linear regression analyses. The hatched area indicates the period from which the screen savers were introduced.

analyzed, including 303 observations before the intervention and 281 after starting the intervention. The compliance with hand hygiene protocols before patient contact showed a relative increase of 12.4%, from 63.6% (193 of 303 events for which the protocol required hand hygiene procedures) before the intervention to 71.5% (201 of 281) after the intervention ($p = 0.05$).

Table 1. Changes in number of hand hygiene events per patient day by shift.

Shift	Trend before intervention (SE)[a]	Immediate change (SE)[b]	Trend after intervention (SE)[a]	*p*-Value for change in trend
Day	-1.0 (0.2)	-1.7 (1.8)	0.8 (0.2)	0.001
Evening	-1.0 (0.1)	0.6 (0.8)	0.5 (0.1)	< 0.001
Night	-0.4 (0.2)	-1.0 (1.6)	0.4 (0.4)	0.057
All	-2.4 (0.5)	-1.4 (3.3)	1.5 (0.5)	< 0.001

[a] The baseline trend and intervention trend are expressed as hand disinfection events per patient day with a standard error (SE)
[b] The levels of change immediately after the start of the intervention are expressed as hand disinfection events per patient day with a standard error (SE)

DISCUSSION

The present study provides evidence, based on objectively measured hand hygiene events, that gain-framed screen saver messages designed to improve compliance with hand hygiene protocols may have beneficial effects on the frequency of hand hygiene events. The introduction of the screen saver messages was associated with a change from a negative to a positive trend. This change was observed for all shifts combined as well as for the day and evening shifts separately, but it was not significant for the night shift. Additional evidence indicating that the screen savers improved hand hygiene compliance was obtained from direct and systematic observations.

Before the screen savers were introduced, a negative trend toward fewer hand hygiene events was seen in our unit. Various interventions have been implemented in efforts to improve hand hygiene, and the negative trend may be due to a washout effect of such earlier interventions. This may indicate that hand hygiene promotion requires continuous efforts. The fact that health education intervention might not have long-lasting effects has been observed for a range of health behaviors (6,18).

During the intervention period, a clear shift in trend was observed, with an increased number of hand disinfection events per patient day. This positive trend was more pronounced for the day and evening shifts compared with the night shift. Earlier research has indicated that hand hygiene compliance is generally lower during night shift, possibly related to less peer pressure to perform appropriate hand hygiene (19).

The additional observations indicate that before the intervention, HCWs on the unit were compliant with hand hygiene procedures for 63.6% of the relevant events. Previous research reported compliance rates of 23%-44% by direct observations in NICU settings (20-22), but the relatively high compliance rate at baseline in the present study is in line with earlier observations in our NICU in 2005 (1). The observations after introduction of the screen savers indicated that hand hygiene compliance increased to 71.5%. These observational data support the time series results, but should be interpreted with more caution given the simple pretest-posttest comparison used. Although > 70% observed compliance is certainly high compared with other studies (20), it still represents an unacceptably high number of potentially dangerous opportunities for the spread of pathogens among patients during planned patient contacts (18).

Message framing for encouraging disease prevention behavior has been well studied. A meta-analytical review in 2007 found 93 studies and concluded that gain-framed messages are more persuasive in encouraging prevention behavior compared with loss-framed appeals (14). Because we did not compare gain-framed messages with other messages, we cannot conclude that gain-framed messages are superior in improving hand hygiene compliance. The electronic device could be used in a study comparing different message strategies.

To the best of our knowledge, 3 previous studies have used screen savers to change behavior or for educational purposes (11-13), but only 1 of these studies evaluated the effects (13). It is unclear how screen saver health education can best be applied in terms of, for example, exposure time, replacement schedule, and screen design (11,12). We chose to change the screen saver messages and pictures after 10 seconds, which appeared to be long enough for HCWs to read the message when they walked past the screen saver, but short enough to avoid boredom. New screen saver messages were introduced after 2 weeks, similar to the earlier examples (11,12). Further research could focus on varying exposure time, replacements and screen designs to inform further improvements of screen saver education.

This study had some potential limitations. The data collection period was relatively short, given that the linear trends both before and after the intervention must flatten or reverse at some point. We may overcome this problem in future studies by collecting data for a longer period until a reverse point is obtained. Another limitation was the interrupted time series design study without a control group, which precludes us from ruling out any effects of unknown confounding factors. However, a randomized controlled trial is not feasible for evaluation health education interventions via public announcements and messages. We considered a “community” intervention trial in which units were randomly allocated to receive the intervention or not, but there are insufficient units of similar size and focus in the Netherlands for conducting such a study. An interrupted time series design was our best option. We presume that the observed beneficial shift in trend of hand hygiene events might have been caused by the intervention with gain-framed messages.

Acknowledgment
We thank Joyce van der Weijde for assisting with data collection and Janine Pijls for developing a data extraction program.

REFERENCES

1. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-52.
2. Ng PC, Wong HL, Lyon DJ, et al. Combined use of alcohol hand rub and gloves reduces the incidence of late onset infection in very low birthweight infants. Arch Dis Child 2004;89:336-340.
3. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatrics 2005;5:22.
4. Hautemaniere A, Cunat L, Diguio N, et al. Factors determining poor practice in alcoholic gel hand rub technique in hospital workers. J Infect Public Health 2010;3:25-34.
5. Raleigh VS, Hussey D, Seccombe I, Qi R. Do associations between staff and inpatient feedback have the potential for improving patient experience? An analysis of surveys in NHS acute trusts in England. Qual Saf Health Care 2009;18:347-54.
6. Salemi C, Canola MT, Eck EK. Hand washing and physicians: how to get them together. Infect Control Hosp Epidemiol 2002;23:32-5.
7. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362:1225-1230.
8. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356:1307-1312.
9. Jenner EA, Jones F, Fletcher BC, et al. Hand hygiene posters: motivators or mixed messages? J Hosp Infect 2005;60:218-225.
10. Stark AR, American Academy of Pediatrics Committee on Fetus and Newborn: Levels of neonatal care. Pediatrics 2004;114:1314-1347.
11. Anderson D, Dobson N, Lewandowski J. Using computer screen savers to enhance nurses learning in the intensive care environment. Dimens Crit Care Nurs 2007;26:160-2.
12. Steele AW, Barrow B, Veltri G, et al. Screen-saver technology: an easy way to enhance communication with employees. Jt Comm J Qual Patient Saf 2005;31:708-11.
13. Filoromo C, Macrina D, Pryor E, et al. An innovative approach to training hospital-based clinicians for bioterrorist attacks. Am J Infect Control 2003;31:511-4.
14. Boyce JM, Cooper T, Dolan MJ. Evaluation of an electronic device for real-time measurement of alcohol-based hand rub use. Infect Control Hosp Epidemiol 2009;30:1090-5.
15. Pittet D, Allegranzi B, Sax H, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. Lancet Infect Dis 2006;6:641-52.
16. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
17. Helder OK, Latour JM. Undergraduate nurse students' education in infection prevention: is it effective to change the attitude and compliance with hand hygiene? Nurs Crit Care 2010;15:39-40.
18. Earl ML, Jackson MM, Rickman LS. Improved rates of compliance with hand antisepsis guidelines: a three-phase observational study. Am J Nurs 2001;101:26-33.

19. van den Hoogen A, Brouwer AJ, Verboon-Maciolek MA, et al. Improvement of Adherence to Hand Hygiene Practice Using a Multimodal Intervention Program in a Neonatal Intensive Care. J Nurs Care Qual 2011;26(1)22-29.
20. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114:565-71.
21. Brown SM, Lubimova AV, Khrustalyeva NM, et al. Use of an alcohol-based hand rub and quality improvement interventions to improve hand hygiene in a Russian neonatal intensive care unit. Infect Control Hosp Epidemiol 2003;24:172-179.
22. O'Keefe DJ, Jensen JD. The relative persuasiveness of gain-framed and loss-framed messages for encouraging disease prevention behaviors: a meta-analytic review. J Health Commun 2007;12:623-644.

Chapter 8

Reduced nosocomial bloodstream infection rate among very low birth weight infants by sequential hand hygiene promotion: a ten-year experience

Onno Helder, Johannes Brug, Johannes van Goudoever, Caspar Looman, Irwin Reiss, and René Kornelisse

Submitted

ABSTRACT

Objective: To determine the long-term effect of sequential hand hygiene-promoting interventions on nosocomial bloodstream infection (BSI) rate and change in distribution of the most frequent causative pathogens over a decade.
Design: Observational study with an interrupted time series analysis.
Setting: 27-bed neonatal intensive care unit.
Patients: Very low birth weight (VLBW) infants (< 1500 g) admitted for more than 72 hours.
Interventions: Hand hygiene education program followed by a combination of gain-framed screen saver messages concerning hand hygiene and an infection prevention week with introduction of consistent glove use during dirty body site care.
Measurements and Main Results: Incidence of nosocomial BSIs; number of nosocomial BSIs per 1000 patient days; and inventory of causative pathogens for BSIs. 1964 VLBW infants admitted from January 1st 2002 to December 31st 2011 were studied. The proportion of infants with one or more BSI decreased from 40.5% to 24.3% ($p < 0.01$); the number of BSIs per 1000 patient days from 16.8 to 8.9 ($p < 0.01$). At baseline, without interventions, the number of nosocomial BSI per 1000 patient days significantly increased by +0.74 per quartile (95% CI +0.27, +1.22). The level of instant change after the first intervention was -4.5 (95% CI -9.84, +0.85, $p = 0.10$), followed by a significantly declined BSI trend change of -1.27 per quartile (95% CI -2.04, -0.49). The next interventions were followed by a direct drop in BSIs of -2.1 (95% CI -7.01, +2.88, $p = 0.41$) and next a neutral trend change of +0.54 (95% CI -0.17, +1.24) BSIs per 1000 patient days. The predominant causative pathogens were coagulase-negative staphylococci (67%) and S. aureus (14%). Their contributions relative to the other pathogens decreased significantly over time ($p < 0.01$).
Conclusions: Sequential hand hygiene promotion seems to contribute to maintenance of adequate compliance and a low nosocomial BSIs rate.

INTRODUCTION

Microorganisms carried by healthcare workers or present on surfaces and equipment around patients are a source of hospital-acquired infections (1-3). The Centers for Disease Control and Prevention (CDC) has singled out hand hygiene as the most effective measure to prevent the spread of pathogens (3). However, compliance with hand hygiene protocols is generally lower than 50% (4).

A vulnerable group of patients, very low birth weight (VLBW) infants (< 1500 g) receiving intensive care, are at high risk for hospital-acquired or nosocomial bloodstream infections (BSIs). They often need a central venous catheter inserted for the administration of medication and parenteral nutrition. These catheters form an entry for bacteria and thus raise the risk of BSIs (5). In this patient group the incidence of BSIs ranges from 13 to 53%; the number of BSIs per 1000 patient days from 6 to 15 (6-9). BSIs are associated with higher mortality and morbidity, prolonged hospitalization, and greater hospital costs (10-13).

Previously, we established the incidence of nosocomial BSIs among VLBW infants in our neonatal intensive care unit (NICU) at 44% (14). This high incidence prompted us to develop interventions to bring it down. The available evidence suggested that improved compliance with hand hygiene would be most effective (15-17). Implementation experts suggest that successful implementation of an intervention often requires a sequential approach which spotlights the challenge from different perspectives (18). Therefore, we introduced a multifaceted hand hygiene education program for the healthcare workers in our NICU, which reduced BSI rates on the long term.

The aim of this study is to evaluate the effects of different combined interventions aimed to improve hand hygiene on the occurrence of nosocomial BSIs and to determine a change in distribution of causative pathogens among VLBW infants over a ten-year period.

MATERIALS AND METHODS

Study design

This combined retrospective and prospective observational study had an interrupted time series design. Three time periods are distinguished: baseline prior any intervention from January 1, 2002 to July 1, 2005. Phase I, starting with a one-month multifaceted hand hygiene education program, lasted from July 1, 2005 to April 1, 2008. Phase II' interventions lasted from April 1, 2008 to September 30, 2008. 'Gain-framed' screen saver messages were introduced; an infection prevention week was held; and the consistent use of gloves during dirty body site care was promoted. The follow-up period ended December 31, 2011.

The Erasmus MC Institutional Review Board approved the individual studies.

Setting and patients

This study was conducted in a 27-bed level IIID NICU in a teaching hospital (19). This NICU has three identical sub-units with nine beds each.

All VLBW infants admitted > 72 hour to the NICU were included in the study. There were no exclusion criteria. These infants were divided into three cohorts, relating to the baseline, phase I, and phase II periods. Early onset sepsis and nosocomial infections were treated with penicillin plus gentamicin and flucloxacillin plus gentamicin, respectively. When appropriate, the choice of antibiotics was changed based on the culture results and antibiotic sensitivity. The antibiotic therapy protocol remained the same over the study period.

Interventions

During the baseline period no additional efforts were undertaken to influence compliance with hand hygiene and to reduce BSIs.

Phase I: Hand hygiene education program

In this first intervention phase a multifaceted education program was offered to all NICU staff who had patient contact, as described by Helder et al. (20). In brief, the education program was offered throughout June 2005 and was obligatory. Groups of three healthcare workers received information on the high BSI rate among VLBW infants, its co-morbidity, and mortality. In addition, they were told that the rate of non-compliance with hand hygiene was 40% at our NICU so as to create a sense of urgency for behavioral change towards improved compliance with to hand hygiene protocols. Performance feedback on personal hand hygiene practices was part of the program. Furthermore, senior nursing and medical staff were encouraged to serve as role models.

Phase II: Screen savers and infection prevention week including consistent glove use

Screen savers are used to disseminate motivational messages. As described by Helder et al., from April 2008 to May 2008 (21), screen saver messages presented on six computer screens used as workstations at the units showed so-called 'gain-framed' hand hygiene promoting messages. These have been shown to be effective to change behavior as they promote the desired behavior by showing the advantages of hand hygiene (21).

September 2008 an infection prevention week was held to keep attention focused on infection prevention aims. It was organized in collaboration with the institutional infection control practitioners (RdG, WvV). We first showed a self-produced movie featuring six common situations where infection prevention is an issue. Twenty hygienic errors were introduced for this purpose. Colleagues were asked to identify and document these errors which were used as contest. We also distributed mugs, toilet paper, and posters with poignant messages concerning hand hygiene (NewCompliance b.v., Delft, the Netherlands). Each of the five days had a special theme: general hygienic precautions, pathogens at the NICU, hand hygiene, invasive procedures, and recapitulation including an award ceremony for the best identified errors. In addition, during the first three days everybody was encouraged to culture surfaces at the NICU. The infection control practitioners commented on the findings from the cultures. Physicians were offered CVC insertion classes; nurse-assistants classes about hygienic handling of formula and mother milk.

Following the infection prevention week the consistent use of non-sterile gloves during dirty body site care was promoted (22). In combination with hand hygiene this has been proven effective in reducing infection rates in infants admitted at a NICU (7, 23). Wearing gloves is indicated when contact with infants' secretions is likely, e.g. when changing diapers, cleaning infants' mouth, introducing gastrointestinal tubes, inserting peripheral intravenous devices, and with endotracheal suctioning, blood sampling, and intubation (23-25). Wearing gloves during dirty body site care does not replace the need for appropriate hand hygiene since self-contamination could occur when gloves are taken off. Hand disinfection is still needed thereafter (25). A self-designed leaflet encouraging glove use was distributed throughout the NICU. They included photo portraits of key players' and catchy one-liners from these key players on the need to wear gloves. In this way, the key players were pushed to act as role models. Additionally, easy glove access was provided at each bedside.

Outcomes

The primary outcome was incidence of nosocomial BSI as defined below. The secondary outcomes were numbers of nosocomial BSIs per 1000 patient days and change in distribution of the most frequent causative pathogens. A nosocomial BSI was defined as an infection occurring later than 72 hours after admission with at least one positive blood culture and an elevated C-reactive protein concentration (> 10mg/l) (8, 26). Subsequent nosocomial BSIs in the same patient were defined as another infection when it was caused by another pathogen according to the antibiogram of the same microorganism in combination with a re-elevation of the C-reactive protein concentration (20).

Sample size

Based on the knowledge that approximately 45% of VLBW infants will develop a nosocomial BSI a sample size of approximately 180 per period would be required to detect a 30% reduction in the incidence of nosocomial BSIs (80% power with 5% two-sided significance).

Statistical methods

Effects of the interventions were analyzed according to the ORION statements (27). Longitudinal effects of the interventions were determined through an interrupted time series (ITS) with a segmented linear regression analysis of BSIs per 1000 patient days. Observations were based on large numbers; therefore we applied the rate as continuous outcome and used linear regression analysis. We aggregated number of nosocomial BSIs over three-month periods. The study period was divided into three different segments: baseline, phase I, and phase II. The slope of the segments indicates the rate of change in time of the interventions. A change in slope may indentify a gradual effect of the implementation. An abrupt change in level at the time of the implementation indicates an immediate effect (27). Data are expressed as median and interquartile range (IQR) unless indicated otherwise. SPSS version 17 (Chicago, IL, USA) was used for data analysis.

RESULTS

In total 1964 VLBW infants were included from January 1st 2002 up to and including December 31st 2011. Over this period, the annual number of admissions of VLBW infants increased by 40%; from 167 in 2002 to 234 in 2011. The infants' basic clinical characteristics did not significantly differ between the three phases (Table 1). The incidence of bloodstream infections decreased from 40.5% to 24.3% ($p < 0.01$); the number of BSI per 1000 patient days from 16.8 to 8.9 ($p < 0.01$).

Table 1. Clinical characteristics of the included infants.

	Baseline (n = 558)	Phase I (n = 541)	Phase II (n = 865)
GA (wk)	28.7 (27.3-30.1)	28.7 (26.8-30.1)	28.6 (26.7-30.3)
BW (g)	1050 (870-1265)	1030 (845-1230)	1060 (835-1265)
Admission (d)	20 (10-42)	18 (9.5-35)	17 (9-37)
Patient days (d)	16810	14083	22922
Infection rate (n)	40.5% (226)	30.7% (166)	24.3% (210)
BSI/ 1000 patient days	16.8	14.2	8.9
Onset first BSI (d)	8 (5-11)	9 (6-12)	9 (6-14)

Data are expressed as median (IQR) unless specified otherwise.
GA = gestational age; wk = week; BW = birth weight; g = gram; d = day; BSI = bloodstream infection.

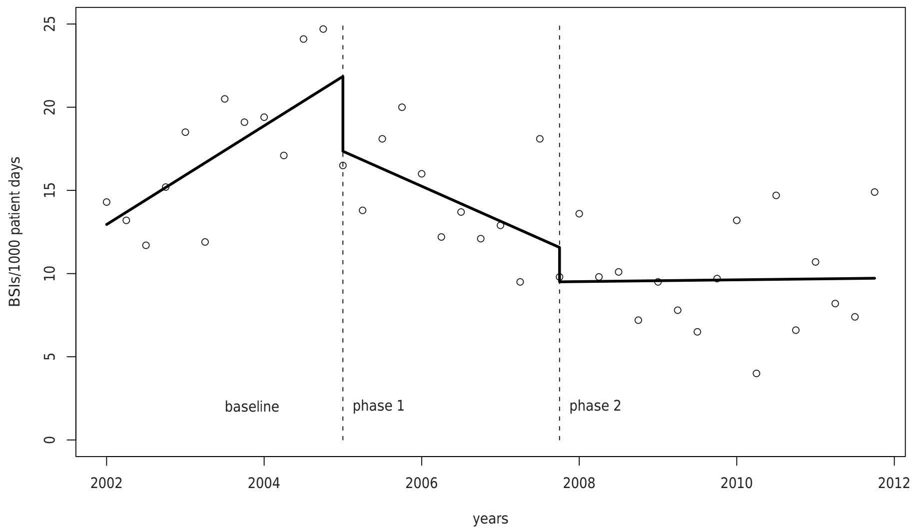


Figure 1. Three segments representing the baseline period without intervention, phase after hand hygiene promotion program, and phase after the combined interventions (screen saver, glove use and infection prevention week). The time series of the infection rate are aggregated per 3-month intervals. The trend lines show predicted volumes from the segmented linear regression analysis. The vertical dotted lines indicate the initiation of phase I and phase II.

The number of infants born with a gestational age less than 26 weeks increased in comparison with the first three and the last three years with 170% (41 vs. 111). While the BSI incidence in these high-risk infants was 36%, the number of BSIs per 1000 patient days was as low as 9.1 over the total study period. The BSI incidence of infants with a gestational age ≥ 26 weeks was 28.8% and number of BSIs per 1000 patient days was 12.4.

Time series analysis showed that the mean number of nosocomial BSIs per 1000 patient days significant increased by +0.74 per three months cohort (95% CI +0.27, +1.22, $p = 0.04$) in the baseline period. The level of instant change during phase I was -4.5 (95% CI -9.84, +0.85, $p = 0.47$), followed by a significant declining trend change in number of BSIs of -0.56 per quartile (95% CI -0.49, -2.04, $p < 0.01$) (Figure 1). In the second phase in the number of BSIs dropped directly after the intervention by -2.1 (95% CI -7.01, +2.88, $p = 0.41$) and thereafter a neutral trend change occurred of +0.2 (95% CI -0.17, +1.24, $p = 0.14$) BSIs per 1000 patient days per quartile.

The longitudinal infection data are shown in Table 2. The predominant causative pathogens were coagulase-negative staphylococcus (CoNS) (67%) and S. aureus (14%). The relative proportion of these skin bacteria in comparison to the other pathogens appeared to decrease significantly ($p < 0.01$) over time (Figure 2).

Table 2. Distribution of pathogens causing nosocomial bloodstream infections during 2002-2011, presented by one-year cohorts.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Gram-positive											
CoNS (%)	52 (72)	60 (65)	68 (72)	41 (59)	43 (64)	40 (65)	43 (69)	35 (70)	33 (63)	38 (68)	453 (66.8)
S. aureus	10	23	11	15	11	7	5	8	3	4	97 (14.3)
Other Gram-positive agents	3	5	4	4	3	0	2	0	1	0	22 (3.3)
Gram negative											
E. coli	2	2	3	4	3	4	6	1	6	4	35 (5.2)
Enterobacter	4	2	1	0	2	2	2	0	3	1	15 (2.2)
Klebsiella	0	0	1	2	0	1	0	4	0	2	10 (1.5)
Other Gram-negative agents	0	2	1	2	0	0	0	0	1	2	8 (1.2)
Yeasts											
Candida	0	0	2	1	2	1	0	1	1	1	9 (1.3)
Multiple pathogens	2	2	3	3	4	5	2	2	1	4	28 (4.1)
Total	72	92	94	70	67	62	62	50	52	56	678

CoNS = coagulase-negative staphylococci

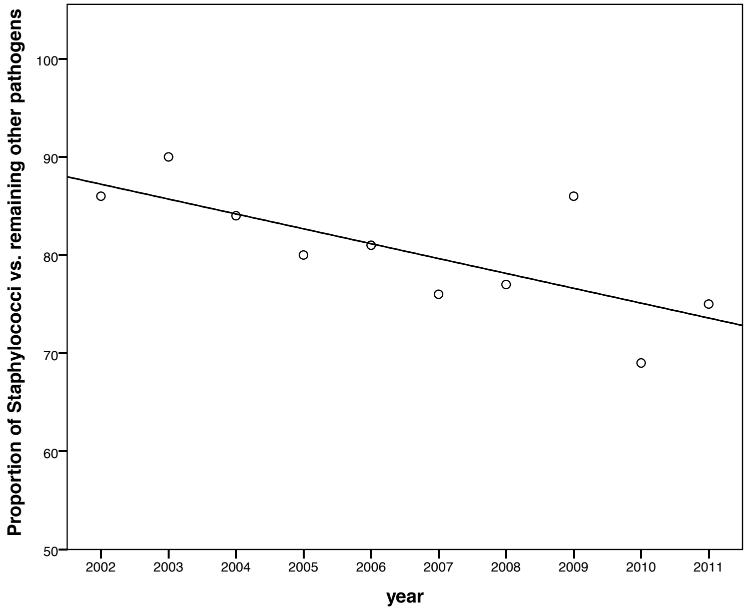


Figure 2. Percentage of Staphylococci infections (CoNS and S. aureus) in proportion to other remaining pathogens during ten year.

DISCUSSION

This study showed that sequential hand hygiene promoting interventions contributed to a significant long lasting reduction of nosocomial BSIs.

To our knowledge this is the first study that assessed sequential preventive interventions aimed to improve hand hygiene by an interrupted time series analysis in a long-term perspective at a NICU. Grol and colleagues already argued that implementation of improvement actions theoretically benefits from a sequential approach in which individual shortcomings could be challenged by appropriate interventions (18). Huang et al. and Payne et al. evaluated the effect of different sequential hand hygiene improvement actions in combination with appropriate CVC insertion and maintenance bundles, use of chlorhexedine for cleaning hubs, preparing and priming tubing for parenteral nutrition fluids under laminar flow hoods promotion (28-29). Both studies showed a significant reduction in BSIs in VLBW infants. Others reported short-term or medium-long term effectiveness of single hand hygiene promoting interventions (9, 30-31). In a study by Huang et al. single hand hygiene improvement strategy lowered the number of BSIs for only a few months (31). Won et al. used public praise and financial penalties or rewards as an ongoing intervention to improve hand hygiene among nurses

(9). However, this strategy is generally too time consuming to be feasible in NICUs. Furthermore, by focusing on nurses only, there is still a risk that other categories of HCWs will spread pathogens.

The relative proportion of CoNS and S. aureus as causative pathogen of BSIs significantly decreased over the ten–year study period. This is in line with the idea that improved hand hygiene in particular reduces the spread of these commensals or pathogens. Hira et al. found that antibiotic resistant and biofilm producing CoNS strains were significantly more prevalent among NICU personnel than in the general community (32). These CoNS strains are more virulent. NICU personnel are a likely cause for cross-contamination of virulent NICU-derived CoNS to patients (32). The bactericidal effect of hand alcohol combined with good compliance may well impede the spread of these pathogens.

Many confounders, but notably birth weight and gestational age, may influence incidence of nosocomial BSIs (13, 29). Data on birth weight and gestational age were available for all included infants. The median (IQR) birth weight and gestational age did not vary between the three segments. Nevertheless, disease severity seems to become higher during the study period. Higher disease severity is associated with a higher risk for nosocomial infections as more invasive procedures are performed and duration of parenteral feeding is longer (29, 33).

The higher disease severity can be explained by two developments. First, after the establishment of five regional high care centers in 2004 neonates who still required more care were transferred to one of these centers when they were relatively stable instead of staying at our NICU. Criteria for infants' transfer were weight > 1000 g, and need for continuous airway positive pressure or less respiratory support (34). Therefore, the most severely ill infants stayed in the NICU. A side effect of this policy was an increasing number of admissions with concomitant higher workload of the NICU team. A higher workload is associated with an increased infection rate (35). Second, active treatment of extremely premature infants (24 weeks gestational age) became current practice in the Netherlands in 2010. Nosocomial infections are relatively more frequent in these infants (35).

In the present study we found a 24.3% incidence of nosocomial BSIs among VLBW infants. Recent studies from the USA reported lower incidences of approximately 11% (13, 29). A careful evaluation of this difference is needed. Incidence of nosocomial BSI, a health care outcome, can only be compared when study populations or institutions are adjusted for a number of variables. Furthermore, similar definitions of nosocomial BSIs are required. Payne et al used the CDC/National Healthcare Safety Network laboratory confirmed nosocomial BSI definition. Two or more blood cultures drawn on separate occasions are needed when a common skin contaminant such as coagulase-negative staphylococci is cultured. This is important since most BSI in VLWB infants are caused by CoNS. Obtaining two blood cultures in VLBW infants is often difficult. Therefore, we as well as others use a definition that only requires one positive blood culture. This implicies that an overestimation of the number of nosocomial infections can occur.

In the present study the number of BSIs per 1000 patient days among infants with a gestational age < 26 weeks was lower than that in more mature born infants. By contrast, 36% of infants with a gestational age < 26 weeks had one or more BSIs, versus 28.8% of infants with higher gestational age. This supposed discrepancy illustrates the influence of different approaches regarding the choice of outcome measures and should therefore be judged with caution. However, the often-used outcome measurement of BSIs per 1000 catheter days has shortcomings in preterm infants. Both peripheral inserted CVCs and peripheral cannulae are a source of BSIs in preterm infants (6, 37-38). By expressing the BSIs solely in BSIs per 1000 catheter days there is a bias risk due to under registration of BSIs.

Several potential limitations of our study need to be addressed. First, we were not able to evaluate the effect of each individual intervention since some interventions were performed together. Delaying potential effective strategies such as the consistent use of gloves and the infection prevention week was regarded as unethical. Secondly, the nature of the population of VLBW infants admitted to the NICU changed during the study period. The disease severity seemed to increase as described above. This might explain that there was no further decrease in nosocomial BSIs in the second phase while there were efforts to maintain or even to improve adequate hand hygiene. Third, compliance with hand hygiene protocols could not consistently be monitored because of budgetary and time constrains. Monitoring of hand hygiene could have given insight into the direct effect of each individual intervention. Finally, the occurrence of BSIs in this study is expressed as proportions and BSIs per 1000 patient days. Expressing BSIs per 1000 catheter days is preferable according the ORION statement (39). However, the number of CVC days was not available for this study. The expression of BSIs per 1000 patient days is subject to potential bias. A relatively long hospital stay with only high risk factors for a nosocomial BSI in the initial phase results in low BSI per 1000 patient days. This explains the relatively low BSI per 1000 patient days in extremely premature infants. However, the outcome measured as BSIs per 1000 catheter days was reported to have also shortcomings (37-38). Because, peripheral inserted CVCs as well as peripheral cannulae are a source of BSIs in preterm infants (37-38). By expressing the BSIs solely in BSIs per 1000 catheter days there is a bias risk due to under registration of BSIs by missing BSIs caused by peripheral cannulae. For future studies we should reach consensus on whether outcome in VLBW infants should be expressed as BSIs per 1000 intravenous device days.

We conclude that sequential hand hygiene promotion is required for a long-lasting reduction of nosocomial BSIs among VLBW infants. The contribution of CoNS and S.

aureus in comparison to the other pathogens decreased over time, which is suggestive for improved hand hygiene.

Acknowledgements:
We wish to thank Ron de Groot and Wim van Vianen for their collaboration during education lessons. We thank Ko Hagoort for editorial advice.

REFERENCES

1. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clin Microbiol Rev 2004;17(4):863-893.
2. Allegranzi B, Sax H, Bengaly L, et al. Successful implementation of the World Health Organization hand hygiene improvement strategy in a referral hospital in Mali, Africa. Infect Control Hosp Epidemiol 2010;31(2):133-141.
3. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37(10):827-834.
4. Erasmus V, Daha TJ, Brug H, et al. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol 2010;31(3):283-294.
5. Bizzarro MJ, Sabo B, Noonan M, et al. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31(3):241-248.
6. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
7. Ng PC, Wong HL, Lyon DJ, et al. Combined use of alcohol hand rub and gloves reduces the incidence of late onset infection in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004;89(4):336-340.
8. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
9. Won SP, Chou HC, Hsieh WS, et al. Handwashing program for the prevention of nosocomial infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2004;25(9):742-746.
10. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.
11. Makhoul IR, Sujov P, Smolkin T, et al. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. Pediatrics 2002;109(1):34-39.
12. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
13. Donovan EF, Sparling K, Lake MR, et al. The Investment Case for Preventing NICU-Associated Infections. Am J Perinatol 2012 Jul 26.
14. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban Neonatal Intensive Care Unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.
15. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
16. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet 2000;356(9238):1307-1312.

17. Boyce JM, Pittet D. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Am J Infect Control 2002;30(8):S1-46.
18. Grol RP, Bosch MC, Hulscher ME, et al. Planning and studying improvement in patient care: the use of theoretical perspectives. Milbank Q 2007;85(1):93-138.
19. Stark AR, American Academy of Pediatrics Committee on Fetus and N. Levels of neonatal care. Pediatrics 2004;114(5):1341-1347.
20. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.
21. Helder OK, Weggelaar AM, Waarsenburg DC, et al. Computer screen saver hand hygiene information curbs a negative trend in hand hygiene behavior. Am J Infect Control 2012;40:951-954..
22. Pittet D, Allegranzi B, Sax H, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. Lancet Infect Dis 2006;6(10):641-652.
23. Pessoa-Silva CL, Dharan S, Hugonnet S, et al. Dynamics of bacterial hand contamination during routine neonatal care. Infect Control Hosp Epidemiol 2004;25(3):192-197.
24. Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory C, et al. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 2002;51(RR-16):1-45.
25. Pittet D. Hand hygiene: improved standards and practice for hospital care. Curr Opin Infect Dis 2003;16(4):327-335.
26. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. Clin Microbiol Rev 2004;17(3):638-680.
27. Cooper BS, Cookson BD, Davey PG, et al. Introducing the ORION Statement, a CONSORT equivalent for infection control studies. J Hosp Infect 2007;65 Suppl 2:85-87.
28. Huang YC, Lien RI, Su LH, et al. Successful control of methicillin-resistant Staphylococcus aureus in endemic neonatal intensive care units - a 7-year campaign. PLoS One 2011;6(8):e23001.
29. Payne NR, Barry J, Berg W, et al. Sustained reduction in neonatal nosocomial infections through quality improvement efforts. Pediatrics 2012;129(1):e165-173.
30. Perlman SE, Saiman L, Larson EL. Risk factors for late-onset health care-associated bloodstream infections in patients in neonatal intensive care units. Am J Infect Control 2007;35(3):177-182.
31. Huang J, Jiang D, Wang X, et al. Changing knowledge, behavior, and practice related to universal precautions among hospital nurses in China. J Contin Educ Nurs 2002;33(5):217-224.
32. Hira V, Sluijter M, Goessens WH, et al. Coagulase-negative staphylococcal skin carriage among neonatal intensive care unit personnel: from population to infection. J Clin Microbiol 2010;48(11):3876-3881.

33. Suresh GK, Edwards WH. Central line-associated bloodstream infections in neonatal intensive care: changing the mental model from inevitability to preventability. Am J Perinatol 2012;29(1):57-64.
34. Helder OK, Verweij JC, van Staa A. Transition from neonatal intensive care unit to special care nurseries: experiences of parents and nurses. Pediatr Crit Care Med 2012;13(3):305-311.
35. Hugonnet S, Villaveces A, Pittet D. Nurse staffing level and nosocomial infections: empirical evaluation of the case-crossover and case-time-control designs. Am J Epidemiol 2007;165(11):1321-1327.
36. Pessoa-Silva CL, Hugonnet S, Pfister R, et al. Reduction of health care-associated infection risk in neonates by successful hand hygiene promotion. Pediatrics 2007;120(2):382-390.
37. Ainsworth SB, Clerihew L, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. Cochrane Database Syst Rev 2007(3):CD004219.
38. Barria RM, Lorca P, Munoz S. Randomized controlled trial of vascular access in newborns in the neonatal intensive care unit. J Obstet Gynecol Neonatal Nurs 2007;36(5):450-456.
39. Stone SP, Cooper BS, Kibbler CC, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. Lancet Infect Dis 2007;7(4):282-288.

Part III

DISCUSSION

Chapter 9

Implementation of a children's hospital-wide central venous catheter insertion and maintenance bundle

Onno Helder, René Kornelisse, Cynthia van der Starre, Dick Tibboel, Caspar Looman, René Wijnen, Marten Poley, and Erwin Ista

Submitted

ABSTRACT

Background: Catheter-associated bloodstream infections in children with central venous catheters are an increasingly recognized serious safety problem worldwide, but are often preventable. Central venous catheter bundles proved effective to prevent infections in studies performed in single or multiple units. Successful implementation requires changes in the hospital system as well as behavioral changes of healthcare professionals. The aim of the study is to evaluate the process and the outcome of the implementation of a state-of-the-art central venous catheter insertion and maintenance bundle throughout a large university children's hospital over an 18 month period.
Methods/ design: An interrupted time series design will be used; the study will encompass all children who need a central venous catheter. New state-of-the-art central venous catheter bundles will be developed. The Pronovost-model will guide the implementation process. We developed a tailored multifaceted implementation strategy consisting of reminders, feedback, management support, local opinion leaders, and education. Primary outcome measure is the number of catheter-associated infections per 1000 line days. The process outcome is degree of adherence to use of these central venous catheter bundles. A cost-effectiveness analysis is part of the study. Outcomes will be monitored during three periods: pre-intervention, intervention, and post-intervention for over 12, 3, and 18 months, respectively.
Discussion: By applying an implementation model we will explore the challenges of implementing a hospital-wide safety program. This work will add to the body of knowledge in the field of implementation. We postulate that healthcare workers' willingness to shift from providing habitual care to state-of-the-art care may reflect the need for consistent care improvement. Trial registration: Dutch trials registry, trial # 3635.

BACKGROUND

Catheter-associated bloodstream infections (CA-BSIs) in hospitals are a worldwide serious persistent problem. Although often preventable, they are a source of morbidity, mortality, prolonged hospital stay, and rising costs (1-4). CA-BSIs notably occur in units where many patients have central venous catheters (CVC); reported figures range from 1.2 to 23 CA-BSIs per 1000 line days in neonatal intensive care units and from 1.8 to 7.8 CA-BSIs per 1000 line days in pediatric intensive care units (3-8). The corresponding figures from a pilot study we performed in 2011 are 11.2 CA-BSIs and 7.9 CA-BSIs. Both unit types admit patients with compromised immune system and patients undergoing invasive procedures (9). High incidences in neonatal intensive care units may be due to an immature host defense in preterm infants (5, 10).

Pronovost et al. (11) showed that the introduction of improved CVC insertion techniques helped to bring down the incidence of CA-BSIs to nearly zero 16 to 18 months later. This study was mainly in adult intensive care units, but the successful outcome encouraged us to improve the CVC care for all children admitted to our children's hospital (11). A collaborative model developed by Pronovost and colleagues ("Pronovost-model") will guide the current study protocol (12).

There is growing evidence that a so-termed CVC insertion and maintenance bundle may be effective in preventing CA-BSIs in infants and children as well (9, 13-15). A bundle is a combination of interventions aimed to reduce CA-BSIs, such as ensuring maximum sterile barrier during CVC insertion and taking appropriate disinfection measures during intravenous medication administration. Regrettably, the evidence is limited by differences in the insertion bundle components in the various studies (13, 16).

Each ward in our children's hospital tends to have its own habits and protocols with regard to CVC insertion and maintenance care. These protocols are not all in line with the available evidence for optimal CVC care. In addition, the inconsistent policies may confuse patients and their parents upon transfer to another ward. It would be best, therefore, to implement a hospital-wide, state-of-the-art CVC insertion and maintenance bundle into a protocol for local use. Such implementation guided by the Pronovost-model has not yet been described. For that matter, little has been published on successful implementation of large scale innovations like this in a children's hospital. The proposed study presented here aims to obtain evidence for an effective implementation method. Furthermore, the cost-effectiveness of the implementation of a CVC bundle has hardly been studied before, so it can only be speculated upon whether it provides good value for money. CA-BSIs are known to be associated with high costs. A study in a neonatal intensive care unit in Belgium found that children with CA-BSIs stayed a mean 24 days longer in hospital at a mean extra charge of approximately €12,000 (2). In another study from a pediatric intensive care unit in the USA, the corresponding figures were 9 days and $33,000 (4). Concrete evidence about the (cost-) effectiveness of the implementation of CVC insertion and maintenance bundles is still lacking however. At the same time, this study may help enlarge the body of knowledge concerning implementation strategies.

The objectives are fourfold: (1) to assess the effects of hospital-wide implementation of a CVC insertion and maintenance protocol on the incidence of CA-BSIs per 1000 line days over 18 months; (2) to assess adherence to use of the CVC insertion protocol; (3) to assess adherence to use of the maintenance bundle; and (4) to explore the cost-effectiveness of implementing a CVC insertion and maintenance protocol.

Scientific hypothesis

We will test the following hypothesis: implementation of hospital-wide CVC insertion and maintenance bundles on the guidance of the Pronovost-model promotes adherence to its use and reduces the number of CA-BSIs.

METHODS

Study design

An interrupted times series (ITS) analysis covering three-month periods will be performed. Three subsequential phases are distinguished: pre-intervention, intervention, and post-intervention for over 12, 3, and 18 months, respectively. Figure 1 presents the study design. The Outbreak Reports and Intervention studies of Nosocomial infection

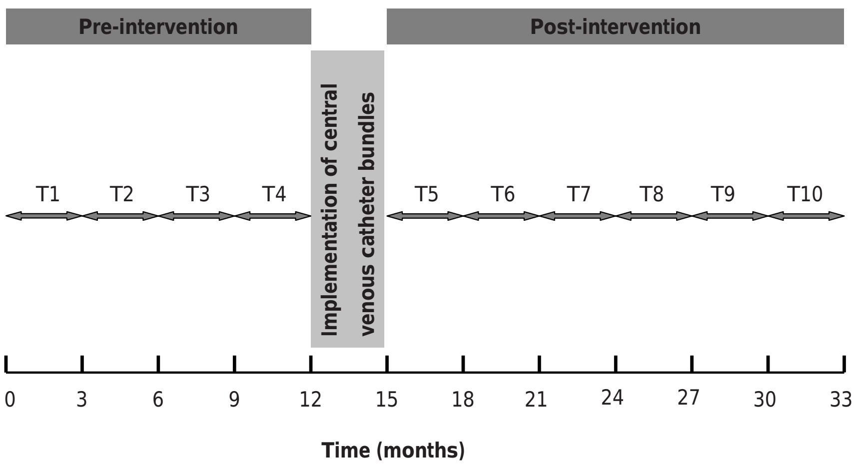


Figure 1. The interrupted time series study design of the CVC study.

(ORION) statement (17) will be applied to guarantee quality of reporting and the use of appropriate statistical techniques.

Setting and participants

The setting of this study is the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. In 2011 it counted 252 beds, 12,403 admissions, and 53,541 patient days. Distribution over the various wards was as follows: Neonatal intensive care unit: 27 beds, 775 admissions (8,447 patient days); pediatric intensive care unit: 34 beds (including 6 beds in high dependency transfer unit), 1504 admissions (10,070 patient days); medium care units: 96 beds, 4,536 admissions (29,436 patient days); day-care ward, 14 beds, 5,588 admissions (5,588 patient days); and operation room suite: 8 operation rooms, and 9,207 surgeries.

All wards except the day-care ward will be participating in this study.

Implementation model

Implementation will be guided by the Pronovost-model (12). The model gives priority to systems operation, centralised support, a collaborative culture, but also promotes local responsibility. Four stages are distinguished: (1) Collect evidence on interventions associated with improved outcomes and select the best feasible ones; (2) Identify possible barriers to implementation by monitoring the current practice and asking stakeholders why they would not comply with current protocols. On the other hand, identify intrinsic and extrinsic motivators that could help implementation; (3) Select process or outcome measures for adherence to the new protocols. Monitoring will encourage healthcare workers' desired behavior; (4) All local healthcare workers as much as possible provide care according to the new protocols. Striving to achieve an overall high adherence, implementation will be executed by means of the 'four Es': 'engage', 'educate', 'execute', and 'evaluate'.

Collecting evidence

A state-of-the-art CVC protocol should meet the Centers for Disease Control and Prevention (CDC) recommendations, be in line with leading studies (3, 13), and be acceptable for key players in all wards. It must ensure that children who are moved internally always receive the same CVC care. We will set up a working group and a steering committee for this purpose. The working group will first make an inventory of all CVC protocols including port catheters presently used in our children's hospital. Evidence for effective measures to prevent infections will be retrieved from relevant published studies (Table 1) and assessed on criteria established by the Dutch Institute for Healthcare Improvement CBO in collaboration with the Dutch Cochrane library (18). The most frequently mentioned measures in these studies are maximum sterile

Table 1. Overview of intervention and effectiveness of CVC bundles in neonatal intensive care unit and pediatric intensive care unit settings.

Author (year)	Setting	Design	Intervention	Reduction of CA-BSI	Level of evidence
Wirtschafter et al. (2010)	NICU	A	Proper CVC insertion, hand hygiene promotion, closed tubing system, improved hub care	From 4.32 to 3.22 per 1000 line days	2-
Sannoh et al. (2010)	NICU	B	Hand hygiene promotion, proper hub care using chloorhexedine with alcohol, glove use promotion, CVC documentation	From 23 to 12 per 1000 line days	2++
Bizzarro et al. (2010)	NICU	B	Proper CVC placement, promotion of hand hygiene, daily evaluation CVC need, infection surveillance, dressing replaced on indication	From 8.40 to 1.28 cases per 1000 line days	2+
Andersen et al. (2005)	NICU [a]	B	Hand hygiene promotion, maximum barrier during CVC insertion, daily evaluation need for CVC removal	From 21% to 9% (95% CI 0.19, 1.0, $p = 0.05$)	2+
Costello et al. (2008)	PICU	C	Hand hygiene promotion, daily evaluation need for CVC removal, CVC insertion kid	From 7.8 to 4.7 and to 2.3 per 1000 line days	2-
McKee et al. (2008)	PICU	D	Proper insertion and nursing care, empower nurses to stop the insertion procedure if guidelines were not followed, using a checklist to ensure adherence to the guidelines, providing weekly performance feedback, promotion of hand hygiene, chlorhexedine skin preparation,	From 5.2 to 3.0 per 1000 line days	2+
Jeffries et al. (2009)	PICU	E	Maximum sterile barrier during CVC insertion, hand hygiene promotion, apply transparent dressing, prepare skin with anti and/ or detergent chlorhexidine gluconate 2%,	From 6.3 to 4.3 per 1000 line days	2+
Miller et al. (2010)	PICU	F	Disinfect catheter site using chlorhexedine, maximum barrier, full barrier during pre-packages of the insertion tray, daily assess CVC need, gauze change every 2 days	From 5.4 to 3.1 per 1000 line days	2+
Wheeler et al. (2011)	Children's hospital-wide	D	Full barrier precautions, chlorhexedine skin preparation with 2 minutes scrub and 1 minute air dry, use of insertion checklist, staff empowerment to stop the insertion procedure, daily assess CVC need, promotion of hand hygiene, chlorhexidine-impregnated sponge placed at insertion site, glove use for all CVC manipulations, change dressing every 7 day or on indication earlier, replace tubing sets no more than 72 hour, cap change every 7 day	From 3 to < 1 per 1000 line days	2+
Chuengchitraks et al. (2010)	PICU	G	Promotion of hand hygiene, maximal barrier precautions, provide skin antiseptic, optimal catheter site selection	From 2.6 to 2.4 per 1000 line days	2-

[a] Premature born infants with a birth weight < 1500 g
Design: A: multi center prospective pre-test posttest study; B: single center prospective pretest and posttest study; C: single center retrospective pretest and prospective posttest group, interrupted time series design; D: single center retrospective pretest and prospective posttest group, time series design; E: multicenter, prospective pretest and posttest group, time series; F: multicenter retrospective pretest and posttest group, interrupted time series; G: single center cohort study; 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2++ High-quality systematic reviews of case-control or cohort studies, or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal; 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal; 2- Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant probability that the relationship is not causal; 3 Non-analytic studies; for example, case reports, case series; 4 Expert opinion
CA-BSI: catheter-associated bloodstream infection; CVC: central venous catheter; BSI: bloodstream infection; NICU: neonatal intensive care unit: PICU: pediatric critical care unit.

barrier during insertion procedure, site cleaning with chlorhexidine, maximum aseptic administration of intravenous medication, promotion of hand hygiene, and daily evaluation of CVC indication (14, 19-22)**.** Based on the flaws in current practice observed in a pilot study we selected 10 interventions that seemed most appropriate for our patients. The key features are listed in Box 1. In case the literature is inconclusive we will resolve the problem through discussion until consensus is reached.

The working group will prepare a draft protocol for approval by the steering group. This will encompass both the insertion bundle and the maintenance bundle, each with its sub themes. The insertion bundle consists of: preparing a CVC insertion cart and providing assistance to the physician or nurse practitioner during the CVC insertion procedure (e.g. PICC line, umbilical catheter, jugulars/ femoralis/ subclavia catheter). The maintenance bundle consists of: proper daily nursing care, preparation of intravenous medication, administration of intravenous medication, blood drawing from a CVC, administration of a bacterial-static solution to short bowel patients, removal procedure, port catheter (e.g. general port catheter care, administration of medication and removal of the port needle).

Finally, once accepted the protocol will be made easily accessible at our in-hospital Intranet through keywords enabling to navigate to all sub themes. In addition we will write a CVC infection prevention manual with special attention to infection prevention in sick children and the side effects of BSIs. It will also present evidence from the literature on the preventive interventions.

Barriers

We have already explored barriers to successful implementation of the selected interventions. In five in-depth semi structured interviews with physicians and nurses we

Box 1. Major components of the insertion bundle and maintenance bundle.

Insertion bundle
Strict hand hygiene according to "my 5 moments"[a]
Full sterile barrier
Hygienic precaution training for all healthcare workers who insert CVCs
Sterile gown, mask, hat, double sterile gloves worn by the healthcare worker who inserts the CVC
Use of pre-packaged CVC insertion kit
At least 80% sterile drape covering the patient
Alcohol 70% with chlorhexidine 0.5% for preparing insertion site (infants < 26 weeks gestational age use of chlorhexedine 0.2% in water)
Use of a timer displayed at the bedside's screen to secure a air dry time of at least 30 seconds
Use a new needle after each attempt to insert a CVC through the intact skin
Chlorhexedine impregnated sponge attached at insertion site (infants < 40 weeks gestational age did not use the impregnated sponge)
Physic barrier between the environment and the child, insertion cart, healthcare worker who inserts the CVC
Maintenance bundle
Strict hand hygiene according to "my 5 moments"[a]
Hand washing when entering the unit, after using the bathroom, and when visually soiled
Hand disinfection during all other occasions
Using gloves during intervention in which healthcare workers may have contact with body fluids
Catheter site care
Daily inspection of insertion site (e.g. redness, collection of fluids, swelling)
Change transparent semi permeable dressing on indication only (e.g. loosened, collection of fluids)
Hub/ cap/ tubing care
Replace continuous tubing sets every 96 hours, unless visually soiled of contaminated
Daily replace tube in case it contains lipids, medication, blood or blood products an
Intermitted administration sets are removed direct after the administration of the medication
Disinfection of the hub with alcohol 70% and air dry for at least 30 seconds
At timer will be used to secure the 30 seconds air dry time
Daily question whether CVC still needed

[a] My 5 moments adopted from the CDC (46)
CVC: central venous catheter

discussed the key elements of the CVC procedures that would have to be changed and at the same time elicited potential barriers. Nurses as well as physicians said that applying an air-dry time of 30 seconds after disinfection of the skin or needless connector was time-consuming. Physicians in addition doubted concerning the necessity to use a new needle after each attempt to insert a CVC through the intact skin in the knowledge that multiple efforts are usually needed.

Measuring

As outcome measure we selected the number of CA-BSIs per 1000 line days, which will be calculated by dividing the number of bloodstream infections by the risk-adjusted denominator 1000 line days. As a baseline measurement we prospectively collected data from 1st January 2011 to 1st January 2012. Over that period we established a number of 11.2 and 7.9 CA-BSIs per 1000 line days at the neonatal intensive care unit and pediatric intensive care unit, respectively.

As process outcome we selected adherence to safety procedures, e.g. maximum sterile barrier during the CVC insertion procedure and adherence to hygienic protocols during intravenous administration. Adherence will be documented with the use of two observation tools (Table 2a and 2b). Performance related to the insertion procedure will be measured with two tools: the time out procedure that is linked with the CVC

Table 2a. Process indicators CVC insertion monitoring form.

	Process indicator	Satisfied	
1	Prepare skin with alcohol 70% with chlorhexidine 0.2% or chlorhexidine 0,2% in water in infants with a gestational age < 26 weeks	Yes O	No O
2	Air-dry of at least 30 seconds after skin preparation prior to guide-wire insertion	Yes O	No O
3	Use a new needle after each attempt to insert a CVC through the intact skin	Yes O	No O
4	The patient is at least 80% covered by sterile drape	Yes O	No O
5	The provider inserting the CVC use maximum sterile barrier e.g. sterile gown, double sterile gloves, mask, and hat	Yes O	No O
6	The optimal CVC site is selected or another site was argued for	Yes O	No O
7	Echo use during insertion of jugularis and subclavia catheter	Yes O	No O
8	Chlorhexidine impregnated sponge used in infants < 40 weeks gestational age	Yes O	No O

CVC: central venous catheter

Table 2b. Process indicators CVC nursing care monitoring form.

	Process indicator	Satisfied	
1	Appropriate hand hygiene prior to preparation of intravenous medication	Yes O	No O
2	Disinfection of the cap or ampoule's surface using alcohol 70%	Yes O	No O
3	Applying 30 seconds air drying time after disinfection ampoule's surface	Yes O	No O
4a	Disinfection of connector with alcohol 70%	Yes O	No O
4b	Or disinfection of the stop cock in case intravenous medication is administered using an extension-line applying alcohol 70%	Yes O	No O
5	Applying 30 seconds air dry time for the stop cock of connector	Yes O	No O
6	Daily question whether the CVC is still needed in PDMS	Yes O	No O
7	Daily check of the insertion place for inflammation	Yes O	No O
8	Aspirated blood from the CVC will not be returned to the patient	Yes O	No O
9	The blue side of the Biopatch is visible	Yes O	No O

CVC: central venous catheter; PDMS: patient data management system

Table 3. Time out procedure performed prior to CVC insertion.

Time Out Pocedure
Insertion of CVC
ICK / ICN/ MC Unit:
Date:

Patient ID/ sticker

In case a 'NO": stop the procedure, Take care to change this into 'YES', Document in third column	YES	NO	Yes, was No
ID control of patient:			
Name, sex and birth date	O	O	O
Attendees:			
Attendees present themselves and appoint their function	O	O	O
Hand disinfection with hand alcohol	O	O	O
Physician or nurse practitioner applied maximal sterile barrier: (Sterile gown, sterile gloves, mask, and hat)	O	O	O
Insertion-cart including CVC is complete and covered with sterile drape according to the protocol	O	O	O
Correct size of CVC is present	O	O	O
Patient:			
Patient is sufficiently sedated on the guidance of the COMFORT behavior scale	O	O	O
Additional sedatives are available			
Analgesics are available	O	O	O
Age-appropriately monitored	O	O	O
The insertion area (insertion cart, patient, and place for MD or nurse practitioner) is lined with barrier tape	O	O	O
Patient is covered with sterile drape for at least 80%	O	O	O
Optimal insertion site selected by protocol	O	O	O
Skin disinfection by protocol	O	O	O
At least 30 seconds air dry time before introducing guidewire	O	O	O
A new needle at each attempt	O	O	O
CPR-form present (compulsory at ICUs)	O	O	O

Date: …-………-………
Name and initials of pediatrician / nurse practitioner:
Name and initials of attending nurse:

insertion protocol (Table 3) and a questionnaire will daily pop up in the patient's record in the electronic informing after signs of infection at insertion site as well as the need of having the CVC in place.

Implementation strategies

Engage. We will inform all stakeholders and senior management staff about the current high number of CA-BSIs per 1000 line days, the undesirability of having different CVC protocols in place, the need to reduce the numbers of CA-BSIs, implying we need to implement general preventive measures hospital-wide. Representative stakeholders from all wards will be invited to join the steering committee. Final approval of the CVC protocol by the steering committee is required and the members will support implementation in their respective wards and operation room suite.

Box 2 provides an overview of all proposed implementation strategies. Strategies for the dissemination of knowledge are based on the Pronovost-model and others (12, 23-24).

Engage & educate. To improve engagement and education level we will organise a hospital-wide theme week dedicated to CVC bloodstream infection reduction. Events are aimed at educating all staff involved on the new CVC protocol and CVC infection prevention manual and persuading them to change their usual care and comply with the new protocol. Two weeks prior, posters announcing the program will be spread, provided with supportive one-liners from senior management and senior clinical leaders including their portraits (25). The key players fully supporting the new protocol will act as role models for more junior colleagues. The key players' one-liners and pictures will be spread during the CVC week by flyers and the messages will be used as screen savers with throughout the children's hospital (26).

A tentative schedule for this theme week is the following:

Monday; flyer distribution, informative mini-symposium, marking of ten potential dirty surfaces at each ward, attaching a sticker on them and culturing the surfaces.

Tuesday; nurses visit bacterial laboratory and the new guidelines will be discussed;

Wednesday; physicians and nurse practitioners will receive clinical instructions; placemats with questions on appropriate CVC care are on the tables in the staff restaurant; lecture on reasons for non adherence to hand hygiene protocols.

Thursday; clinical instructions and lecture to promote high adherence to documenting CVC data in the patient data management system.

Friday, theme week wrap-up with musical act during lunch-time in the staff restaurant and a closing ceremony.

For educational purposes we will use several types of reminders, such as screen savers; stickers attached on disinfection solution bottles displaying the message: "apply 30 seconds air dry time"; infection prevention messages printed on toilet paper. Furthermore, if a CVC is in situ, a questionnaire will daily pop up in the patient's record in the electronic patient data management system. The questionnaire addresses the following items: "Is the transparent dressing in good order?"; "Is there any redness near the insertion place?"; and "Is the CVC still needed?". The response categories will be collected at nominal level e.g. yes or no.

Evaluate. Quarterly, the primary and process performance will be measured to evaluate whether the intervention is successful and to identify possible flaws. The information obtained may serve as input for additional improvements. Data will be compared to the baseline measurement data and data collected in the previous period, if applicable, by interrupted time series analysis. Findings will be reported to the directors of the children's hospital. Furthermore, findings on ward level will be presented to the management of the relevant ward. For steering purposes we will make use of insightful graphs and tables. Successful outcomes may be an incentive to continue on the road we have taken; negative outcomes may be an incentive to increase efforts.

Endure & extend. Pronovost and colleagues later added this idem to their model (12). We postulate that the daily questioning on the need to have the CVC in place, as sketched above, will create awareness of safety precautions. Furthermore, we presume that sharing of the quarterly performance outcomes will improve perceptions safe patient care. Finally, encouraging open discussion about possible procedure flaws and potential improvements will benefit the CVC process at large (24).

Primary outcome

The primary outcome will be the laboratory confirmed number of CA-BSIs per 1000 line days, following the CDC definition: (1) one or more positive blood culture(s) (not skin flora) and no other infection source; or (2) one positive blood culture and clinical signs and no other infection source (27). The diagnosis will be made by a member of the research team (OH, CvdS) and an infection control practitioner. Discrepancies between these persons will be resolved through discussion until consensus is reached; or will be solved by an independent physician using the institutional microbiological database and the patient file. The CDC defines CA-BSI as a primary BSI if a CVC was in place 48 hours before the development of the BSI and if it is not bloodstream related to an infection at another site (28). A CVC in situ is defined as a catheter introduced into a vein that terminates close to the heart or into one of the great vessels, and which is used for infusion, blood sampling or hemodynamic monitoring. It may be an umbilical venous catheter, a percutaneous CVC, a tunneled catheter, a port, or a peripherally inserted central catheter (PICC) (29).

Secondary outcomes

Adherence to the CVC insertion bundle and adherence to the maintenance bundle will serve as secondary outcomes.

The attending nurse will assess adherence to the CVC insertion bundle during the insertion procedure (Table 2a). To this aim we designed a digital tab with drop-down menu for the two different patient data management systems. The time out procedure prior to the CVC insertion is predominantly added for creating safety awareness during insertion (Table 3). Intravenous medication preparation and administration items will serve to measure adherence to the CVC maintenance bundle (Table 2b). Purpose-trained nurses will randomly assess these items during planned daily care.

Economic costs and benefits

Additionally, the cost-effectiveness of the implementation of the CVC bundle will serve as a secondary outcome measure, to be established through cost-effectiveness analysis. Taking a health care perspective, the cost-effectiveness analysis will make a comparison between the pre-intervention period ('usual care') and the post-intervention period regarding both the total costs and the number of CA-BSIs per 1000 line days.

Among the costs included will be the direct medical costs relating to CA-BSIs. These costs will be calculated by multiplying resource utilization with a unit cost price. As much as possible, real economic cost prices will be used rather than charges. Cost

Box 2. Selected implementation strategies.

Intervention types
Education program, theme week - Multidisciplinary seminar - Workshop physicians - Instruction lessons nurses - Instruction hygienic insertion and maintenance
Reminders - Leaflets - Screen savers - Daily questionnaire CVC need, pop-up in electronic patient management system - Sticker attached at disinfection solution: apply 30 seconds air dry time
Feedback (quarterly) - Reporting incidence of CA-BSI - Reporting adherence to insertion bundle - Reporting adherence to maintenance bundle
Engagement of the managing staff - One-liners combined with picture
Awareness - Time out procedure, and staff empowerment to stop in case of guideline violations occur - Daily goal sheet
Procedures - Revised protocols - CVC infection preventions manual.
Timers - 30 seconds air dry timer displayed on bedside screen

CA-BSI: catheter-associated bloodstream infection; CVC: central venous catheter prices will be calculated according to established methods (30). The time horizon will be from the patient's hospital admission until discharge.

Any possible savings on the costs of medical care need to be balanced against the costs of implementing the CVC bundle. All costs related to the implementation process will be taken into account. This implies that the study will take account of the costs for the implementation strategies (Box 2), as well as the changes in the care implicit to the implementation of the CVC bundle (Box 1) insofar as they result in additional costs compared to usual care. To arrive at total costs, we will include both personnel costs, material costs, and overhead costs.

The final end-point of the cost-effectiveness analysis will be incremental costs per case of CA-BSI (per 1000 line days) avoided. Sensitivity analysis is used to assess how sensitive the results are to any assumptions made.

Data collection

Four nurses trained in observation will unobtrusively observe staff when they apply the insertion and maintenance bundles. Observation will be guided by a self-designed structured observation form. The staff will be unaware of the reason for the observations; they are already frequently observed for training or research purposes. Data collection will be at random moments seven days a week and 24 hours a day. Data on sex, (birth) weight, and age of the patients involved will be retrieved from the patient data management system. Disease severity of infants admitted to the neonatal intensive care unit will be documented by the Clinical risk index for babies (CRIB) score (31); that of children admitted to the pediatric intensive care unit by the Pediatric Risk of Mortality III score (PRISM III) (32) or Pediatric Index of Mortality (PIM) score (33); that of children admitted to the oncology department by the Lansky score (children ≤ 9 year) (34) or Karnofsky score (children > 10 year) (34). There is no suitable disease severity score for patients admitted to the medium care ward, due to the diversity of diseases.

Sample size

A sample size of 12,840 line days, based on 4.2036 line days measured during the pre intervention period, would be required to detect a 30% reduction in the number of CA-BSIs per 1000 line days (80% power with 5% two-sided significance). The estimated rate of adherence to the insertion and maintenance bundles during the baseline period will be 60% and 20%, respectively; the post intervention rate aimed at will be 100% and 80%, respectively. Sample size calculation indicated that each sequential period requires 15 insertion observations and 16 maintenance observations to detect a relative difference of 37% and 300% alpha of 0.05 and a 1-beta of 0.8.

Statistical analysis

Data will be expressed as median and interquartile range (IQR), unless indicated otherwise. The baseline data showed that 69 children developed a CA-BSI. The effect of the intervention on rate reduction will be determined with a segmented loglinear regression analysis of interrupted time series, using a pre-intervention, intervention, and post-intervention segment. The slope or trend of the segments indicates the rate of change in time. An abrupt change at the time of the implementation indicates an immediate effect. Introducing slopes (percentual changes in time in infection rate before and after the implementation) corrects for unassociated background trends. A change in slope after the introduction of the intervention may identify a gradual effect of the implementation (17, 35). We aggregated CA-BSIs per 1000 line days over 3-month periods.

Ethical aspects

The Erasmus MC Institutional Review Board approved this study (MEC-2012-375).

DISCUSSION

The implementation strategy encompasses a multifaceted program which is tailor made for this specific hospital and ready for use. We hypothesize that implementation of this program will result in fewer CA-BSIs and improved adherence to CVC bundles (5, 22-23, 36). Tailored implementation strategies – i.e. based on content analysis of barriers and facilitators – seem to be more effective than non-tailored strategies (37-38). The Pronovost-model effectively helped to design strategies from the first to the last phase.

Various strategies will be employed. First, education by means of a mini-symposium, workshops, presentations, and so on. Second, improving staff intrinsic motivation, e.g. by audit, feedback, and reminders. Third, organisational change: preparing a shared protocol for all patients. Fourth, use of ICT: e.g. a timer on the computer screen at the bedside to clock the 30 seconds air drying time, online access to guidelines and the CVC infection prevention manual, use of screen savers, and daily reminder informing whether the CVC is still needed. Fifth, feedback: quarterly reporting of the CA-BSI incidence and the rates of adherence to the insertion and maintenance bundles. Sixth, awareness: time out procedure and daily goal sheet. Seventh, engagement of the managing staff: showing their commitment to the aim.

The Pronovost-model recommends enlisting all local stakeholders involved in patient care and discussing with them potential barriers and facilitators to adherence with the developed protocol. The Pronovost-model does not provide for eliciting support from senior management of the hospital. Nevertheless, they will be asked to demonstrate their commitment and assume ownership of the general aim to reduce CA-BSIs hospital-wide (24). We will explicitly designate senior management as ambassadors of the goals (39) by publishing their one-liners and portrait pictures. These ambassadors should convince all healthcare workers that safer CVC care is an important goal and make clear they support the campaign. The senior management is officially accountable for patient safety and even may act as role models.

Use of opinion leaders will be added to the implementation strategy. Clinical and senior management need to show their vision and clearly dissimilate this particular aspect of safety culture. Senior management of effective infection prevention programs dissimilated their success as improved clinical excellence and inspired their staff (25). Furthermore, the senior management will help resolve organizational and financial barriers and practically support initiatives (24-25).

The Pronovost-model describes the implementation process in broad terms; development of a fitting protocol or work-instruction is not included (12). However, an unambiguous protocol should guide any intervention in a univocal way. A comprehensive description how to develop a work-instruction will complete the Pronovost-model. Recently published studies should support the newly developed protocol and providing evidence will perfectly fit into phase 1 of the Pronovost-model; building evidence in favour for the chosen intervention.

Feedback is a powerful measure to increase adherence to infection prevention measures such as good hand hygiene and is therefore widely used (23, 40). However, once feedback is stopped any unwanted behavior could come up again (23, 41). On the other hand, providing continuous feedback is time consuming and therefore not realistic. Feedback should be used firstly to alter initial unwanted behavior and this should ideally move into desired behavior as an intrinsic driven and well-conditioned behavior.

Education is often used to support behavioral change, especially if flaws in knowledge are observed (5, 39, 42). A complicating factor is that level of knowledge varies among healthcare workers categories and within categories. This should be borne in mind when developing a hospital-wide education program. Physicians appreciate knowledge more than nurses and evidence-based education could be very useful to promote physicians' desired behavior (43). On the other hand, a washout effect is often observed (44-45). Knowledge previous received may recede to the background and will not always be ready to apply. Ideas on what is effective in infection prevention are developing over time, so regular updates are essential. In addition, repetition of education programs is necessary in a teaching hospital like ours; many healthcare workers are in training and leave the hospital after termination of their education program.

The Pronovost-model is merely medical oriented. Knowledge transfer is the main point of departure from the model, since it fits into physicians' learning style (43).

Goossens et al. found that strong scientific evidence was the strongest determinant that influenced physicians' behavior (43). However, regarding our goal, a clear healthcare team angle seems to be more appropriate for a broad dissimilation of improved hygienic behavior that has to be adapted by all members of the multidisciplinary team. Nurses have a more active learning style, for which the strongest determinant was found the fact whether the subject was 'interesting (…) or not' (43). This phenomenon affects whether a new procedure is potentially beneficial for patients or is gets embedded in the daily care.

We postulate that the proposed study has methodological strength because it is guided by a validated implementation model that has been translated into a hands-on program and is described in detail for implementation hospital-wide. Furthermore, regularly reporting the outcomes is in line with the ORION statement promoting transparent reporting on intervention studies aimed to reduce nosocomial infections. ORION recommended interrupted time series as preferable method for analysis that showed the change in results over time.

We anticipate several challenges in this study. (1) No randomisation to evaluate the effectiveness of the interventions. However, randomisation into an intervention and control group is inappropriate for our aim to implement an intervention hospital-wide, and the interrupted time series design is the second best solution and in line with the ORION guidelines. (2) The CVC bundle is adapted and tailor made for our hospital. Although this results in less generalizability, this naturalistic approach could help develop practical implementation strategies for other hospitals or other interventions. (3) The effective ingredient of the bundle is still unclear. However, as some interventions have been shown to be effective it would be unethical to test all separate interventions. (4) To control for confounders is a challenge due to the different safety climates in the different departments. By establishing a clear leadership we will try to show the benefits of a univocal approach towards infants' CVC care.

This detailed implementation strategy of the CVC bundle has a potential to effectively modify healthcare workers behavior and reduce the number of CA-BSIs hospital-wide.

Trial registration

Dutch trials registry (www.trialregister.nl), trial # 3635.

Acknowledgments

Jan Dekker is thanked for his contribution to identify potential barriers. Marian de Jong and Willemijn Corpeleijn are thanked for collection baseline data concerning bloodstream infections per 1000 CVC days. Oetze Vlasblom is thanked for providing support for this project at management and ICT level. We thank Ko Hagoort for text editing.

REFERENCES

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
2. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.
3. Costello JM, Morrow DF, Graham DA, et al. Systematic intervention to reduce central line-associated bloodstream infection rates in a pediatric cardiac intensive care unit. Pediatrics 2008;121(5):915-923.
4. Nowak JE, Brilli RJ, Lake MR, et al. Reducing catheter-associated bloodstream infections in the pediatric intensive care unit: Business case for quality improvement. Pediatr Crit Care Med 2010;11(5):579-587.
5. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.
6. Leboucher B, Leblanc M, Berlie I, et al. Effectiveness of an informative report on the prevention of nosocomial bloodstream infections in a neonatal intensive care unit. Arch Pediatr 2006;13(5):436-441.
7. Sannoh S, Clones B, Munoz J, et al. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. Am J Infect Control 2010;38(6):424-429.
8. Lam BC, Lee J, Lau YL: Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114(5):565-571.
9. Jeffries HE, Mason W, Brewer M, et al. Prevention of central venous catheter-associated bloodstream infections in pediatric intensive care units: a performance improvement collaborative. Infect Control Hosp Epidemiol 2009;30(7):645-651.
10. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
11. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355(26):2725-2732.
12. Pronovost PJ, Berenholtz SM, Needham DM: Translating evidence into practice: a model for large scale knowledge translation. BMJ 2008;337:963-965.
13. Bizzarro MJ, Sabo B, Noonan M, et al. Central Venous Catheter Initiative C: A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31(3):241-248.
14. Miller MR, Griswold M, Harris JM, 2nd, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. Pediatrics 2010;125(2):206-213.
15. Helder O, van den Hoogen A, de Boer C, et al. Effectiveness of non-pharmacological interventions for the prevention of bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review. Int J Nurs Stud 2012, Feb 29.

16. Aly H, Herson V, Duncan A, et al. Is bloodstream infection preventable among premature infants? A tale of two cities. Pediatrics 2005;115(6):1513-1518.
17. Cooper BS, Cookson BD, Davey PG, et al. Introducing the ORION Statement, a CONSORT equivalent for infection control studies. J Hosp Infect 2007;65 Suppl 2:85-87.
18. CBO: Evidence-based Guideline development. Manual for working group members of Dutch Institute for Healthcare Improvement (Kwaliteitsinstituut voor de Gezondheidszorg) Kwaliteitsinstituut voor de Gezondheidszorg CBO; 2007.
19. Andersen C, Hart J, Vemgal P, et al. Prospective evaluation of a multi-factorial prevention strategy on the impact of nosocomial infection in very-low-birthweight infants. J Hosp Infect 2005;61(2):162-167.
20. McKee C, Berkowitz I, Cosgrove SE, et al. Reduction of catheter-associated bloodstream infections in pediatric patients: experimentation and reality. Pediatr Crit Care Med 2008;9(1):40-46.
21. Chuengchitraks S, Sirithangkul S, Staworn D, et al. Impact of new practice guideline to prevent catheter-related blood stream infection (CRBSI): experience at the Pediatric Intensive Care Unit of Phramongkutklao Hospital. J Med Assoc Thai 2010;93 Suppl 6:S79-83.
22. Wheeler DS, Giaccone MJ, Hutchinson N, et al. A hospital-wide quality-improvement collaborative to reduce catheter-associated bloodstream infections. Pediatrics 2011;128(4):995-1004.
23. Grol R, Grimshaw J: From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
24. Zingg W, Walder B, Pittet D: Prevention of catheter-related infection: toward zero risk? Curr Opin Infect Dis 2011;24(4):377-384.
25. Saint S, Kowalski CP, Banaszak-Holl J, et al. The importance of leadership in preventing healthcare-associated infection: results of a multisite qualitative study. Infect Control Hosp Epidemiol 2010;31(9):901-907.
26. Helder OK, Weggelaar AM, Waarsenburg DC, et al. Computer screen saver hand hygiene information curbs a negative trend in hand hygiene behavior. Am J Infect Control 2012;40:951-954.
27. Edwards JR, Peterson KD, Andrus ML, et al. Facilities N: National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. Am J Infect Control 2007;35(5):290-301.
28. O'Grady NP, Lillian A. Burns, E. Patchen Dellinger, et al. Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011. CDC; 2011;1-83.
29. Wirtschafter DD, Pettit J, Kurtin P, et al. A statewide quality improvement collaborative to reduce neonatal central line-associated blood stream infections. J Perinatol 2010;30(3):170-181.
30. Hakkaart-van Roijen L TS, Bouwmans CAM Manual for costing research. Methods and guideline prices for economic evaluations of health care interventions (updated edition) [in Dutch]. Diemen: Health Care Insurance Board; 2010.
31. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342(8865):193-198.
32. Pollack MM, Patel KM, Ruttimann UE PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996;24(5):743-752.

33. Shann F, Pearson G, Slater A, et al. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med 1997;23(2):201-207.
34. Jacobsohn DA, Arora M, Klein JP, et al. Risk factors associated with increased nonrelapse mortality and with poor overall survival in children with chronic graft-versus-host disease. Blood 2011;118(16):4472-4479.
35. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27(4):299-309.
36. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8(6):iii-iv, 1-72.
37. Baker R, Camosso-Stefinovic J, Gillies C, et al. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2010(3);CD005470.
38. Bosch M, van der Weijden T, Wensing M, et al. Tailoring quality improvement interventions to identified barriers: a multiple case analysis. J Eval Clin Pract 2007;13(2):161-168.
39. Huis A, Schoonhoven L, Grol R, et al. Helping hands: A cluster randomised trial to evaluate the effectiveness of two different strategies for promoting hand hygiene in hospital nurses. Implement Sci 2011;6:101.
40. Boaz A, Baeza J, Fraser A, the European Implementation Score Collaborative G: Effective implementation of research into practice: an overview of systematic reviews of the health literature. BMC Res Notes 2011;4(1):212.
41. Naikoba S, Hayward A: The effectiveness of interventions aimed at increasing handwashing in healthcare workers - a systematic review. J Hosp Infect 2001;47(3):173-180.
42. Erasmus V, Huis A, Oenema A, et al. The ACCOMPLISH study. A cluster randomised trial on the cost-effectiveness of a multicomponent intervention to improve hand hygiene compliance and reduce healthcare associated infections. BMC Public Health 2011;11:721.
43. Goossens A, Bossuyt PM, de Haan RJ Physicians and nurses focus on different aspects of guidelines when deciding whether to adopt them: an application of conjoint analysis. Med Decis Making 2008;28(1):138-145.
44. Helder OK, Latour JM Undergraduate nurse students’ education in infection prevention: is it effective to change the attitude and compliance with hand hygiene? Nurs Crit Care 2010;15(1):39-40.
45. Salemi C, Canola MT, Eck EK: Hand washing and physicians: how to get them together. Infect Control Hosp Epidemiol 2002;23(1):32-35.
46. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37(10):827-834.

ADDITIONAL MATERIAL

Additional file 1: Detailed program of the CVC bloodstream infection reduction theme week.

Monday. Distribution of flyers including the theme week program in a glance, one-liners of senior management staff and leading clinicians, and the 10 key items that will be changed or that need extra attention. The senior management staff will visit all wards to inform the healthcare workers about the need for prevention and the aim of the theme week. Printed coffee cups with infection prevention messages will be spread. In addition, all healthcare workers receive a petit four depicting the icon of the CVC infection prevention theme week.

Healthcare workers will be asked to rank the most contaminated surface of their ward by attaching a red sticker. The infection control practitioner will culture these. Culture results will be presented at the theme week's closing day. The person who selected the most compromised surface will receive an award during the closing ceremony.

In the afternoon a mini-symposium will be held for all involved healthcare workers. It will start with a general introduction on the rationale of the CVC theme week, e.g. observed suboptimal hygienic performance and need for changing hygienic behavior, which will be supported by evidence from recently published studies. The advantages of the state-of-the-art CVC protocol will be presented, e.g. tailored to the needs of patients, as well as the process and outcome measurements, expected changes for physicians and nurses, and how the presence of the CVC will be documented in the patient data management systems.

Tuesday. The following educational activities are planned on Tuesday, Wednesday, and Thursday: daily tours at the bacteriological laboratory explaining the processing blood cultures and identification of pathogens.

During lunch time all healthcare workers will receive a placemat on which are printed 12 questions on CVC infection prevention and an open question: do you have a solution for the problem that healthcare workers fail to take 30 seconds air-dry time. Of all correctly completed questionnaires a winner is drawn who receives an award during the closing ceremony. In the afternoon nurses will be lectured on aspects of the CVC insertion and maintenance bundles that need extra attention.

Wednesday. Instruction lessons for physicians and nurse practitioners at different wards on improved hygienic procedures during CVC insertion. In the afternoon they are lectured measures to improve adherence to hand hygiene protocols.

Thursday. An afternoon lecture on technical aspects of the documentation and the need for accurate CVC registration.

Friday. Musical act during lunch-time in the staff restaurant. A cabaret group will compose a cheerful song for this occasion, entitled: 30 seconds are needed. During the closing ceremony this week's events were summarized, the results of the cultures were announced, and the questions on the placemats were discussed.

Chapter 10

General discussion and future perspectives

INTRODUCTION

The high number of hospital–acquired or nosocomial bloodstream infections (BSIs) at our neonatal intensive care unit (NICU) formed the rationale for this research project that aimed to reduce this number. Bloodstream infections are generally considered as unavoidable complications of hospital care. In this project, however, we emphasized that healthcare workers should be aware that they are the key to infection prevention. What's more, the entire healthcare team should feel accountable for these often avoidable infections. We put an emphasis on good hand hygiene as the cornerstone of infection prevention and took the standpoint that repeated interventions are needed to improve compliance with a hand hygiene protocol.

Papers presented in this thesis describe non-pharmaceutical preventive interventions with a focus on healthcare workers caring for very low birth weight (VLBW) infants.

MAIN FINDINGS

We addressed five main research questions. *First,* what are effective non-pharmacological preventive interventions to reduce nosocomial BSI in VLBW infants? Improved hand hygiene has been proven to be effective in reducing BSIs in adult settings. There is inconclusive evidence, however, that improved hand hygiene subsequently leads to infection reduction in infants. The same holds true for the use of different devices, and percutaneous inserted central catheter teams. More studies are needed to determine the benefits of these preventive measures in VLBW infants.

Second, how can we effectively implement preventive measures, in particular improved hand hygiene compliance in a NICU setting? A multifaceted education program performed in our NICU significantly improved hand hygiene compliance and reduced in nosocomial BSIs in VLBW infants. In this program we provided background information of infection prevention, reported current compliance with hand hygiene protocols and infection rate, gave instructions for optimal hand hygiene procedures, provided hand hygiene performance feedback, and encouraged senior healthcare workers to improve social norms regarding hand hygiene. In the direct period after the program, the proportion of infants with one or more BSIs decreased significantly from 44.5% to 36.1%. However, the effects of the education program faded away over time. This made us aware that we need to pay ongoing attention to appropriate hand hygiene behavior.

Third, can electronic devices that count hand hygiene events serve to monitor hand hygiene performance trends during a prolonged time? Hand hygiene behavior is generally monitored by direct observations. This method is time consuming and may influence hand hygiene behavior of the persons observed. Therefore, we tested unobtrusively the use of alcohol-based hand rub dispensers by new electronic devices (ComSens, NewCompliance, Delft, the Netherlands). These devices provide useful information of the use of the dispensers, and also reveal trends in hand disinfection events over time. Data generated by the electronic devices can be supplementary used to evaluate the effectiveness of hand hygiene promotion campaigns.

Fourth, do gain-framed screen saver messages change hand hygiene behavior? We successfully introduced gain-framed messages about hand hygiene presented on screen savers. The screen saver messages emphasized the need for improved compliance with hand hygiene protocols by focusing on the benefits to the patients. A negative trend in hand hygiene events per patient day changed to a significant positive trend during the intervention.

Fifth, what is the long-term effect of repeated interventions aimed to improve hand hygiene on the occurrence of BSIs in VLBW infants? Sequentially performed hand hygiene promoting interventions over a 10-year period resulted in a significant decrease in the nosocomial BSI rate from 40.5% to 24.3%. The interrupted time series analysis showed a significant declining trend in BSI per 1000 patient days after the first intervention. The second combined intervention showed a neutral trend change. Of Gram-positive BSIs, 67% were caused by coagulase-negative staphylococci and 14% by S. aureus. Their contributions relative to the other pathogens decreased significantly over time.

Finally, how to develop a children's hospital wide strategy for a CVC care bundle implementation? We described a research protocol aimed to improve hand hygiene combined with a bundle of measures to promote insertion and maintenance of CVC under maximal hygienic conditions. Therefore, a tailored multifaceted implementation strategy was developed consisting of reminders, feedback, management support, contributions by local opinion leaders, and education. Primary outcome measure is the number of catheter-associated infections per 1000 CVC day. The process outcome is degree of adherence to use of these central venous catheter bundles. A cost-effectiveness analysis is part of the study. This study is already ongoing.

METHODOLOGICAL CONSIDERATIONS

The studies presented in this thesis used different methodologies – from systematic review to quantitative quasi-experimental studies. These methodologies have recognized strength besides their limitations and the results should be interpreted in this perspective. Methodological considerations regarding the used study designs, definitions and measures are discussed below.

Review

The study reported in chapter three is a systematic review on potentially effective non-pharmacological measures to prevent BSIs in preterm infants. The strength of this review is that it was one of the first of its kind. However, the review had some limitations. Quantitative pooling of the results and a meta-analysis was not feasible due to the inconsistency in unambiguous description of the interventions and different definitions of BSIs. Furthermore, two articles were the author's own work. This potential limitation was solved by having the author replaced by a member of the advisory group. Finally, four studies did not report patient characteristics; therefore generalization to other patient populations was not possible.

Study design: interrupted time series analysis

Chapters five, six and seven used an interrupted time series (ITS) design to evaluate the effect of an intervention. Usually performed tests to evaluate the effect of a controlled intervention, such as a student T-test or χ^2 test, will generate cross sectional data; in contrast an ITS analysis will provide insight into the longitudinal effects of the intervention. The ORION statement (guidelines for transparent reporting of Outbreak Reports and Intervention studies Of Nosocomial infection) recommends the ITS design to report on evaluation of infection control interventions (1). An ITS study is one where multiple observations are recorded over time and are interrupted by one or more interventions. Its strength is that it estimates trends prior and after the intervention based on multiple observations. It also shows the direct effect, and represents data with an intuitive graph. The individual observations are collected at equally spaced intervals over a long period of time and can be applied to retrospective, prospective data and hybrid designed studies. An ITS analysis forms a strong alternative to randomized trials (1-2). One of the limitations is that there is no control group and randomization does not take place.

Observation of hand hygiene compliance

The strength of these observational studies was that hand hygiene behavior was observed using a guided, structured self-designed observation tool (3). Not only the nature of the procedure, but also completeness of hand rubbing and the applied drying time were observed. Hand hygiene before and after patient contact and before invasive procedures was recorded. Trained medical students performed the observations after their interobserver reliability had been assessed and found sufficient. On the other hand this method had some potential limitations. The direct observations data may have been influenced by the Hawthorne effect. Healthcare workers may adapt hygienic behavior when they are aware that they are observed. Therefore, we applied repeated observations at different times and used covert observation techniques to diminish this kind of bias. Nevertheless, the World Health Organization recommends that hand hygiene compliance should be determined by using their observation tool. However, the World Health Organization observation tool does not record the applied drying time or completeness of hand rubbing. (4). Recently, electronic counting methods to monitor the frequency of hand hygiene events have been introduced. Unobtrusive measurement by electronic devices yields more objective data (5-6). These devices can monitor hand disinfection events over a long time, 24 hours a day, seven days a week; which is nearly not feasible by direct observations. However, they do not allow for recording compliance with and quality of hand disinfection. Electronic devices provide useful trend data that can be evaluated supplementary to the data obtained from direct observations with the World Health Organization' hand hygiene observation tool (4).

Different BSI definitions

We defined a nosocomial BSI definition according to Stoll et al. as an infection occurring later than 72 hour after of birth, at least one positive blood culture, and an elevated C-reactive protein concentration (>10 mg/L) (7). Others studies reporting nosocomial BSIs in VLBW infants have used several other definitions (7-9). A leading definition is described by Disease Control and Prevention (CDC) has provided definitions for all kind of infections (8). The CDC defined a laboratory-confirmed BSI in infants ≤ 1 year as an infection with clinical signs [fever (> 38 ºC rectal), hypothermia (< 37 ºC rectal), apnea or bradycardia] AND signs and symptoms and positive laboratory results not related to an infection at another site AND a common skin contaminant cultured from two or more blood cultures drawn on separate occasions (8). BSIs in preterm infants are predominantly caused by coagulase-negative staphylococci and thus should require two blood cultures. In practice, it is quite a challenge to obtain two blood cultures on separate occasions in these very tiny infants. Therefore, the strength of the BSI definition of Stoll et al. is that it is not dependent on subjective clinical signs by using laboratory results indicative for an infection and only one blood culture (7). Other studies use slightly modified definitions for BSIs. van der Zwet et al. added more specific clinical signs to the CDC definition such as temperature instability, feeding problems, irritability, and apathy (9). According to the criteria of van der Zwet as well as the CDC, one positive culture of common skin bacteria does not prove a BSI. van der Zwet et al. report the inclusion of not unambiguously interpreted clinical signs as a potential weakness of the CDC definition (9). For example hypothermia and hyperthermia are defining CDC variables. Infants' temperature, however, is highly influenced by incubator settings (10). Thus, lack of hypothermia > 38 ºC or hypothermia < 37 ºC was often observed (9). They conclude that by strictly applying the CDC definitions only 75% of the BSIs would have been identified. We suppose that by applying the strict CDC definition of laboratory-confirmed BSI the number of identified BSIs in our studies would have been lower.

Different expressions of BSIs

BSIs are often expressed in terms of number of BSIs per 1000 CVC days (11-13). This is in line with the ORION statement (1). However, when applied in preterm infants this outcome measure has some shortcomings. Both CVCs and peripheral cannulae cause BSIs in preterm infants (14-15). Therefore, we suggest alternatively to express BSIs in preterm infants as BSIs per 1000 IV device days.

In contrast, we expressed nosocomial BSIs as BSIs per 1000 patient days. This has a potential limitation because the outcome is influenced by outliers in admission duration. It is also influenced by the discharge policy; due to the shortage of nursing staff, almost all infants on our unit are transferred to regional high care nurseries as soon as they no longer require ventilator support. Extremely preterm infants often need intensive care because of respiratory instability, while they have a low risk of nosocomial BSIs. These outliers may suppress the number of measured BSIs per 1000 patient days. Consequently, expressing BSIs per 1000 patient days is also of limited value.

PUTTING RESULTS IN BROADER PERSPECTIVE

Our findings

Promoting hygienic behavior resulted in an improved compliance with hand hygiene protocols from 65% to 88% in the present study. Campaigns such as screen saver messages improved compliance from 64% to 72%. In addition, the incidence of nosocomial BSIs decreased by 40% from 40.5% to 24.3% in VLBW infants. In other studies the prevalence of nosocomial BSIs in VLBW infants ranged from 9.1 to 44.0% (20-22). The achieved nosocomial infection reduction varied between 40 and 50% (22-23).

Since the interventions were relatively simple, similar results can probably be obtained at other NICUs. A comparison of our results with other studies is challenging due to numerous interfering variables. Other studies published after 2009 showed that hand hygiene compliance is about 50% (16-17). However, definitions of compliance with hand hygiene protocols, indications for hand hygiene, and measurement methods were different.

We could not retrieve studies which evaluated the effect of gain-framed message in infection control, except those which aimed to promote preventive health behavior such as prevention of sexual transmitted diseases, quit smoking, and skin protection by using sunscreen (18-19).

In sum, although different definitions and indications hamper comparisons between studies, compliance with hand hygiene in our studies is high in comparison with other studies. The prevalence we found falls within the range reported in other studies, and the reduction in infection rate is in line with other studies.

Other prevention measures

Striving to reduce the number of BSIs we selected hand hygiene as a focus for interventions, as recommended by several reviews (24-29). We did not study other interventions such as extensive hub care (13), intravenous bundles including proper CVC placement, daily evaluation of the need for CVC and improved hub care (12-13), or silver impregnated dressings (30). These alternative measures can also effectively reduce nosocomial infections as these are often the result of the presence of a CVC. Several studies tested the infection reduction effect of modified CVCs including coated (antibiotics, silver sulfadiazine, chlorhexidine, heparin) or impregnated catheters (antibiotics, silver, heparin (31-33). Meta-analyses in adults showed that heparin-coated and antibiotics-impregnated CVCs are most effective (33). Unfortunately, some of these catheters are still experimental while others have been tested in adults only (33).

Another strategy to prevent catheter colonization is the catheter lock technique. In this technique, the lumen is filled with a 100 to 1000 times higher dose of antibiotics than the systemic application of antibiotics while the catheter is not in use (34). Garland et al. showed that vancomycin-heparin locks reduced the incidence of CVC related BSIs in infants better than just heparin locks (34). Nevertheless, this method should not be used lightly as it can promote the emergence of vancomycin-resistant enterococcus (35). In vitro and animal studies showed that a low concentration of ethanol lock is more effective than a vancomycin lock (36-37). However, a study of Slobbe et al. in an adult setting showed that there is no evidence that ethanol locks significantly reduce BSIs (38). Despite the promising BSI reduction effect, the field of application for CVC locks is limited in the current NICU practice.

Inappropriate daily catheter hub care can also result in BSIs. These hubs are entered many times a day for the administration of medication and fluids. A pilot-study in our NICU and PICU showed that 24% of all hubs became contaminated (unpublished data). Garland et al. showed that contaminated hubs were the strongest predictor of subsequent catheter related BSIs, followed by exit site colonization. It was estimated that up to 67% of CVC related BSIs were acquired intraluminally rather than extraluminally (39). Appropriate hub and connector care is quite important, therefore. A recent study concludes that there is a strong association between the connector scrub time and pathogen growth status. A connector rubbing disinfection time from 10 to 15 seconds resulted in a decreased rate of bacterial growth (40).

Stasis of fluids inside the connector may promote fibrin as a building block for bacterial adhesion and biofilm formation (41-42). Coagulase-negative staphylococci and S. aureus have surface cell receptors on which fibrin acts. The attachment results in rapid colonization and the formation of more pathogen protecting biofilm (43). This biofilm makes successful elimination difficult. A connector with zero dead space could counter colonization with pathogens. A comparison between a split septum and zero fluid connector in immune-compromised cancer patients showed a significant reduction in catheter related BSIs in favor of the zero fluid connector (43). So, the use of zero fluid connectors could contribute to BSI reduction (43).

The optimal connector scrub time of 15 seconds followed by a drying time of at least 30 seconds is hard to achieve in a clinical setting. Next to repeated education programs one can alternatively choose to provide antiseptic barrier caps. The bactericidal effect of these antiseptic caps is promising but has not yet been tested in a NICU setting (40, 44-45).

Having a dedicated CVC insertion team could also help to reduce catheter related BSIs in preterm infants. Golombek et al. showed that a well-trained percutaneously inserted central catheter (PICC) insertion team could effectively reduce BSIs in extremely low birth weight infants (< 1000 g) (46). Catheters for the administration of total parental feeding in preterm infants are preferably inserted in the lower extremities as this strategy is associated with lower rates of BSI than insertion in the upper extremities (50% vs. 86%, $p < 0.05$) (47).

Cost reduction

Elimination of preventable nosocomial infections could definitely cut back healthcare cost seeing that treatment of these infections is very costly. The World Health Organization estimated the yearly costs in the United Kingdom, the United States, and Mexico at one billion pounds sterling, 4.5 - 5.7 billion US dollars, and 1.5 billion US dollars, respectively (48). Also, preterm infants with a BSI used more resources such as longer admission duration and additional clinical effort (21, 49). The directly measured additional average NICU costs of VLBW infants with a nosocomial BSI amount to 14,500 euro (21, 49-50). Fewer BSIs in preterm infants also reduces the associated long-term disabilities that are also a financial burden for the community (51-52). The 40% decrease in the incidence of BSIs over a 10-year period documented in this thesis implies that the yearly number of BSIs has decreased by about 45. Taking a conservative approach, this implies that we can save approximately 650,000 euro each year. Therefore, an investment in infection prevention is certainly cost-effective. It would be worth to perform more explicit cost-effectiveness studies and collect more detailed data.

Implications for practice

Hand hygiene is the cornerstone of infection prevention. Due to the washout effect, however, repeated attention is needed to maintain high compliance with hand hygiene protocols. Education, performance feedback, and reporting current BSI rate could help promote. All key players should strongly support a shift in mindset from the idea that nosocomial BSIs are inevitable to the awareness that they are preventable. We should continue to fine-tune initiatives to improve the maximum barrier technique during insertion of central venous catheters and peripheral intravenous catheters. Newly developed knowledge should be discussed, optionally tested and possibly incorporated into the insertion protocols.

Weak links in the process of preparing and administering IV medication and administration should be further assessed. For example hub disinfection and daily evaluation of CVC need require more attention. Hubs should be rigorously disinfected before use. A nurse friendly solution that prevents improper use should be explored. A daily recall of a patient data management system should facilitate effective evaluation during the daily patient round of a patient's CVC need. Manufacturers' initiatives to improve IV procedures should be carefully examined before adopting them.

RECOMMENDATIONS FOR FUTURE RESEARCH

Benchmarking

Outcome measurements should be standardized internationally so as to allow for meaningful comparison with findings from other research groups. Comparing experiences and learning from each other by benchmarking could give a new boost to infection prevention interventions (53). The aim of benchmarking is to identify best practices and improve outcome performance with the aid of another organization. Sharing data on infections per 1000 CVC days as well as surveillance data will be necessary to develop new preventive interventions. In practice, we need to compare data from neonatal intensive care units with comparable case mix, definition of sepsis, surveillance methods, staff size, and number of admissions. Furthermore, the hospital management should take an interest in infection prevention, be willing to share standard outcome measurements, have an open mind, and be willing to alter practices to achieve BSI reduction. Also, a national initiative could be considered in line with other benchmarking programs such as the German NEO Krankenhaus-Infektions-Surveillance-System (NEO-KISS); the USA National Healthcare Safety Network (NHSN); the UK Nosocomial Infection National Surveillance Scheme (NINSS); the international Vermont Oxford Network (VON) or the French Réseau d'Alerte, d'Investigation et de Surveillance des Infections Nosocomiales (RAISIN) (53). It is questionable whether this information should be made public or remain confidential by anonymous publishing. A comparison is only meaningful if data are adjusted for important patient characteristics such as gestational age, birth weight and severity of illness. A possible positive effect of public reporting could be the higher priority given to infection prevention (54). Hospitals are willing to improve procedures if positive publicity can be obtained. The positive effects could be even stronger if boards of directors should take the lead in infection prevention.

Collecting data

A large teaching hospital daily collects an enormous amount of data, mostly automatically. Besides, professionals at many levels enter additional data manually in electronic patient charts and patient data management systems. Regrettably, healthcare workers often receive too little feedback to guide patient safety or quality of care improvement. Hospital boards should take up this concept as a guiding principle and clearly facilitate this kind of monitoring aimed to improve quality of patient care. In our hospital the mainframe software is not designed to provide feedback. For instance, intelligent computer software is being developed to support surveillance of CVC related BSIs and to provide fast feedback on effects of interventions to reduce CVC related BSIs. A challenge is to standardize the required data sets, which still vary widely between departments. For example the description of CVCs and insertion location was not unequivocal in the data management system, which compromised precise calculation. Furthermore, information systems should be developed that enable institutional boards and national safety inspection boards to evaluate quality of the care provided.

Behavior change

Changing hygienic behavior of healthcare professionals is the cornerstone of infection prevention (35, 55). However, there is no single solution to alter the behavior of all different professionals. Physicians and nurses differ in learning styles; feedback from both strongly promotes infection prevention measures (56-57). Nurses, nurse practitioners and physicians are highly involved in patient care and their behavior can make the difference between putting an infant at greater or lower infection risk. In practice, carrying out care procedures in an unsafe manner will raise the risk; applying all prescribed hygienic precautions will lower it (58-59). NICUs often provide limited space between the incubators and cribs, which situation is associated with a higher rate of nosocomial infections (60). Single rooms or greater total area are preferable in the context of infection prevention.

Asking nurses, nurse practitioners and physicians to give mutual feedback on (in)correct hygienic behavior may improve safety of all kind of procedures such as insertion of peripheral or central venous catheters, preparation of intravenous medication, and its administration to the patient (56, 61). Nurse practitioners and physicians' feedback will be focused on the insertion procedure. Nurses are accountable for the administration of intravenous medication according the institutional guidelines. In rotation all involved nurses will be invited to provide at least five feedbacks on colleagues' hygienic behavior during the preparation and administration of intravenous medication. This may be a powerful tool due to its reciprocity. For example, after telling a colleague that he or she applied insufficient drying time after disinfection of a stopcock, this colleague's hygienic behavior will probably improve the next time you are nearby. So, you recollect your own feedback once given, and this will be a mutual function.

Partnerships within university hospitals

Partnerships on a national level, such as the Dutch quality of care consortium (*Consortium Kwaliteit van Zorg*) could contribute to knowledge building on infection prevention in infants and disseminate evidence based and best practice interventions among NICUs in the Netherlands. This consortium consists of experts from the eight university hospitals in the Netherlands and aims to improve quality of care by contributing to national discussions, initiating quality improvement processes, and improving daily patient care by applying scientific knowledge to practice. (www.nfu.nl/fileadmin/documents/12.5509_Samen_verantwoordelijk_Visie_NFU_2020.pdf).

CONCLUSIONS

We conclude that bloodstream infections affect a high proportion of VLBW infants admitted to a neonatal intensive care unit. Hand hygiene promotion programs and screen savers providing gain framed messages improved hand hygiene compliance – and this was associated with a significant reduction in the number of nosocomial bloodstream infections in these infants. Electronic counting devices are well suited to monitor hand hygiene. A further mindset change from inevitability to preventability of bloodstream infections is needed and other strategies can further decrease the rate of nosocomial bloodstream infections.

REFERENCES

1. Cooper BS, Cookson BD, Davey PG, et al. Introducing the ORION Statement, a CONSORT equivalent for infection control studies. J Hosp Infect 2007;65 Suppl 2:85-87.
2. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27(4):299-309.
3. Helder OK, Brug J, Looman CW, et al. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.
4. Sax H, Allegranzi B, Chraiti MN, et al. The World Health Organization hand hygiene observation method. Am J Infect Control 2009;37(10):827-834.
5. Cheng VC, Tai JW, Ho SK, et al. Introduction of an electronic monitoring system for monitoring compliance with Moments 1 and 4 of the WHO "My 5 Moments for Hand Hygiene" methodology. BMC Infect Dis 2011;11:151.
6. Marra AR, Moura DF, Jr., Paes AT, et al. Measuring rates of hand hygiene adherence in the intensive care setting: a comparative study of direct observation, product usage, and electronic counting devices. Infect Control Hosp Epidemiol 2010;31(8):796-801.
7. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110(2 Pt 1):285-291.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36(5):309-332.
9. van der Zwet WC, Kaiser AM, van Elburg RM, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infect 2005;61(4):300-311.
10. Helder OK, Mulder PG, van Goudoever JB. Computer-generated versus nurse-determined strategy for incubator humidity and time to regain birthweight. J Obstet Gynecol Neonatal Nurs 2008;37(3):255-261.
11. Larson EL, Cimiotti J, Haas J, et al. Effect of antiseptic handwashing vs alcohol sanitizer on health care-associated infections in neonatal intensive care units. Arch Pediatr Adolesc Med 2005;159(4):377-383.
12. Bizzarro MJ, Sabo B, Noonan M, et al. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31(3):241-248.
13. Sannoh S, Clones B, Munoz J, et al. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. Am J Infect Control 2010;38(6):424-429.
14. Ainsworth SB, Clerihew L, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. Cochrane Database Syst Rev 2007(3):CD004219.
15. Barria RM, Lorca P, Munoz S. Randomized controlled trial of vascular access in newborns in the neonatal intensive care unit. J Obstet Gynecol Neonatal Nurs 2007;36(5):450-456.
16. Rogers E, Alderdice F, McCall E, et al. Reducing nosocomial infections in neonatal intensive care. J Matern Fetal Neonatal Med 2010;23(9):1039-1046.

17. van den Hoogen A, Brouwer AJ, Verboon-Maciolek MA, et al. Improvement of adherence to hand hygiene practice using a multimodal intervention program in a neonatal intensive care. J Nurs Care Qual 2011;26(1):22-29.
18. Latimer AE, Salovey P, Rothman AJ. The effectiveness of gain-framed messages for encouraging disease prevention behavior: is all hope lost? J Health Commun 2007;12(7):645-649.
19. Szklo AS, Coutinho ES. The influence of smokers' degree of dependence on the effectiveness of message framing for capturing smokers for a Quitline. Addict Behav 2010;35(6):620-624.
20. Grisaru-Soen G, Friedman T, Dollberg S, et al. Late-onset Bloodstream Infections in Preterm infants: a Two-Year Survey. Pediatr Int 2012;54:748-753..
21. Donovan EF, Sparling K, Lake MR, et al. The Investment Case for Preventing NICU-Associated Infections. Am J Perinatol 2012 Jul 26.
22. Payne NR, Barry J, Berg W, et al. Sustained reduction in neonatal nosocomial infections through quality improvement efforts. Pediatrics 2012;129(1):165-173.
23. Schulman J, Stricof R, Stevens TP, et al. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. Pediatrics 2011;127(3):436-444.
24. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect 2008;68(4):293-300.
25. Garland JS, Uhing MR. Strategies to prevent bacterial and fungal infection in the neonatal intensive care unit. Clin Perinatol 2009;36(1):1-13.
26. Kilbride HW, Wirtschafter DD, Powers RJ, et al. Implementation of evidence-based potentially better practices to decrease nosocomial infections. Pediatrics 2003;111(4 Pt 2):519-533.
27. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention, U.S. Pediatrics 2002;110(5):e1-24.
28. Toltzis P, Walsh M. Recently tested strategies to reduce nosocomial infections in the neonatal intensive care unit. Expert Rev Anti Infect Ther 2010;8(2):235-242.
29. Curtis C, Shetty N. Recent trends and prevention of infection in the neonatal intensive care unit. Curr Opin Infect Dis 2008;21(4):350-356.
30. Khattak AZ, Ross R, Ngo T, et al. A randomized controlled evaluation of absorption of silver with the use of silver alginate (Algidex) patches in very low birth weight (VLBW) infants with central lines. J Perinatol 2010;30(5):337-342.
31. Maki DG, Stolz SM, Wheeler S, et al. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. Ann Intern Med 1997;127(4):257-266.
32. Raad I, Darouiche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. Ann Intern Med 1997;127(4):267-274.
33. Gilbert RE, Harden M. Effectiveness of impregnated central venous catheters for catheter related blood stream infection: a systematic review. Curr Opin Infect Dis 2008;21(3):235-245.

34. Garland JS, Alex CP, Henrickson KJ, et al. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. Pediatrics 2005;116(2):198-205.
35. Suresh GK, Edwards WH. Central line-associated bloodstream infections in neonatal intensive care: changing the mental model from inevitability to preventability. Am J Perinatol 2012;29(1):57-64.
36. Qu Y, Istivan TS, Daley AJ, et al. Comparison of various antimicrobial agents as catheter lock solutions: preference for ethanol in eradication of coagulase-negative staphylococcal biofilms. J Med Microbiol 2009;58(Pt 4):442-450.
37. Chambers ST, Pithie A, Gallagher K, et al. Treatment of Staphylococcus epidermidis central vascular catheter infection with 70% ethanol locks: efficacy in a sheep model. J Antimicrob Chemother 2007;59(4):779-782.
38. Slobbe L, Doorduijn JK, Lugtenburg PJ, et al. Prevention of catheter-related bacteremia with a daily ethanol lock in patients with tunnelled catheters: a randomized, placebo-controlled trial. PLoS One 2010;5(5):e10840.
39. Garland JS, Alex CP, Sevallius JM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. Infect Control Hosp Epidemiol 2008;29(3):243-249.
40. Smith JS, Irwin G, Viney M, et al. Optimal disinfection times for needleless intravenous connectors. JAVA 2012;17(3):137-143.
41. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev 2002;15(2):167-193.
42. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2002;8(9):881-890.
43. Caillouet B. Protection of intraluminal pathway with zero fluid displacement connector reduces catheter-related bloodstream infections in a comprehensive cancer center. JAVA 2012;17(2):86-89.
44. Menyhay SZ, Maki DG. Disinfection of needleless catheter connectors and access ports with alcohol may not prevent microbial entry: the promise of a novel antiseptic-barrier cap. Infect Control Hosp Epidemiol 2006;27(1):23-27.
45. Oto J, Imanaka H, Konno M, et al. A prospective clinical trial on prevention of catheter contamination using the hub protection cap for needleless injection device. Am J Infect Control 2011;39(4):309-313.
46. Golombek SG, Rohan AJ, Parvez B, et al. "Proactive" management of percutaneously inserted central catheters results in decreased incidence of infection in the ELBW population. J Perinatol 2002;22(3):209-213.
47. Hoang V, Sills J, Chandler M, et al. Percutaneously inserted central catheter for total parenteral nutrition in neonates: complications rates related to upper versus lower extremity insertion. Pediatrics 2008;121(5):e1152-1159.
48. WHO. World Alliance for Patient Safety, Global Patient Safety Challenge 2005 - 2006: Clean Care is Safer Care. Geneva: World Health Organization; 2005.
49. Mahieu LM, Buitenweg N, Beutels P, et al. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47(3):223-229.
50. Payne NR, Carpenter JH, Badger GJ, et al. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. Pediatrics 2004;114(2):348-355.

51. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
52. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357-2365.
53. Haustein T, Gastmeier P, Holmes A, et al. Use of benchmarking and public reporting for infection control in four high-income countries. Lancet Infect Dis 2011;11(6):471-481.
54. Muller MP, Detsky AS. Public reporting of hospital hand hygiene compliance—helpful or harmful? JAMA 2010;304(10):1116-1117.
55. Pittet D. The Lowbury lecture: behaviour in infection control. J Hosp Infect 2004;58(1):1-13.
56. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230.
57. Goossens A, Bossuyt PM, de Haan RJ. Physicians and nurses focus on different aspects of guidelines when deciding whether to adopt them: an application of conjoint analysis. Med Decis Making 2008;28(1):138-145.
58. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355(26):2725-2732.
59. Miller MR, Griswold M, Harris JM, 2nd, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. Pediatrics 2010;125(2):206-213.
60. Brady MT. Health care-associated infections in the neonatal intensive care unit. Am J Infect Control 2005;33(5):268-275.
61. Grol RP, Bosch MC, Hulscher ME, et al. Planning and studying improvement in patient care: the use of theoretical perspectives. Milbank Q 2007;85(1):93-138.

Chapter 11

Summary

Many very low birth weight (VLBW) infants admitted at a neonatal intensive care unit (NICU) contract hospital-acquired or nosocomial infections. Improving hand hygiene might reduce the risk of these infections.

This thesis has three parts. *Part I, Challenges,* provides background information on strategies to improve hand hygiene compliance and presents the aims of the study. *Part II, Tools and interventions,* describes a newly designed tool and two interventions to improve hand hygiene. This part ends with an overview of ten years' experience with bloodstream infections (BSIs) in VLBW infants at the NICU of the Erasmus MC-Sophia Children's Hospital and the effect of hand hygiene promotion programs. *Part III, General discussion,* provides a protocol for future research and a general discussion including directions for future research.

Part I: Challenges

Chapter 1 provides an overview of the background and relevance of infection prevention in NICUs. Nosocomial BSIs among VLBW infants are placed in a worldwide perspective. Infection rates in infants in low and middle-income countries are three to 20 times higher than those in high income countries. Most nosocomial infections among adult intensive care unit (ICU) patients are device–related, like in the case of ventilator-associated pneumonia, and urinary or central venous catheter related infections. The incidence of nosocomial infection in adults receiving intensive care is lower than that in VLBW infants in NICUs. In NICUs BSIs are predominant causes of nosocomial infections. Nosocomial BSIs in preterm infants are associated with increased mortality, morbidity, duration of admission, treatment costs, and risk of long-term disabilities.

Preterm infants are highly at risk for nosocomial BSIs due to intrinsic and extrinsic factors. The most important of the intrinsic factors are the immature innate immune system, the diminished inflammatory response and immature humoral immunity including complement system and shortage of immunoglobulin. The major extrinsic factor is undergoing invasive procedures. Effective preventive measures are improved hand hygiene, better catheter care, and implementing bundles of preventive measures these combines the latter preventive interventions and add additional interventions such as improved hub care, dressing care and daily evaluation central venous catheter need. The Wold health Organization (WHO), and Centers for Disease Control and Prevention (CDC) regard hand hygiene as the cornerstone of infection prevention.

Chapter 2 highlights that healthcare professionals as a united team should take the lead in infection prevention. Healthcare professionals' disinterested attitude towards hand hygiene and meagre knowledge concerning infection prevention measures need to change.

In **chapter 3** we argue that once-only attention to hand hygiene and hand hygiene techniques during nursing students' education program is not enough to improve hand hygiene in daily practice. Only repeated hand hygiene education will raise staff awareness of the need of infection prevention. We must attempt to change healthcare professionals' attitude from a laissez-faire mind-set to one of team spirit reflecting accountability for each BSI.

Chapter 4 reviews the effectiveness of non-pharmacological interventions for nosocomial BSI prevention in infants admitted to a NICU. Five categories were identified: hand hygiene, intravenous (IV) bundles, closed IV sets/ patches/ filters, surveillance, and percutaneously inserted central catheter teams. IV bundles may decrease BSI rate in infants. There is little evidence that activities of special catheter care teams result in BSI reduction. Hand hygiene promotion leads to improved hand hygiene. However, there is inconclusive evidence that this results to BSI reduction in infants.

Part II: Tools and interventions

In **chapter 5** we report that a hand hygiene education program was effective in reducing the incidence of nosocomial BSIs in VLBW infants. The study includes two pretests and two posttests. In total 1201 hand hygiene observations showed significantly improved hand hygiene compliance. Furthermore, the proportion of infants with one or more BSIs significantly decreased from 44.5% to 36.1%; and the infection rate per 1000 patient days significantly decreased from 17.3 to 13.5.

Chapter 6 describes the application of a new device that electronically counts the use of bedside hand alcohol dispensers. With this device we monitored the use of hand alcohol dispensers in the neonatal intensice care unit (NICU) over one-year period. The median (interquartile range) number of hand disinfection events was 697 (559-840). The median (interquartile range) number of hand disinfection events performed per healthcare worker during the day, evening and nightshifts was 13.5 (10.8 - 16.7), 19.8 (16.3-24.1), and 16.6 (14.2-19.3), respectively. We concluded that the electronic device provides useful information on frequency, time, and location of its use and reveals trends in hand disinfection over time.

In **chapter 7** we determined the effect of hand hygiene screen saver messages on workstation screens throughout the NICU units. These messages were composed using the gain framed messages theory and emphasised the advantages of hand hygiene rather than the risks of noncompliance. For the purpose of this study altruism was added because improved compliance with hand hygiene is predominantly beneficial for patients and less for healthcare professionals themselves. The negative trend in hand hygiene events per patient day before the introduction of the screen savers (decrease by 2.3 per week) changed into a significant positive trend after the intervention (increase of 1.5 per week). Direct observation confirmed these results.

Chapter 8 describes the long-term control of nosocomial BSIs by sequential executed hand hygiene promotion programs and identified longitudinal trends in causative pathogens for BSI. In total 1964 VLBW infants were admitted to our NICU over a ten-year period. After the interventions the proportion of infants with one or more BSI had decreased by 40% from 40.5% to 24.3%; the BSI infection rate per 1000 patient days by 58.9% from 19.7 to 8.1. An interrupted time series analysis showed a significant increase of the BSI infection rate in the baseline period, upon which the first intervention was followed by a significantly declined BSI trend change. The second combined intervention resulted in a neutral trend change. BSIs were most often caused by Gram-positive coagulase-negative staphylococci (67%), followed by S. aureus with 14%. The proportion of BSIs caused by staphylococci significantly decreased over time suggesting improved hand hygiene compliance.

Part III: Discussion

Chapter 9 focuses on a study protocol in which we described a children's hospital wide CVC bundle infection prevention program encompassing a CVC insertion and a CVC maintenance bundle. The insertion bundle includes a time-out procedure, mobile screens to shield the covered patient and physician's space to maintain full barrier precautions during catheter insertion, and patient coverage for at least 80%. The maintenance bundle includes proper disinfection of the ampoule followed by 30 seconds drying time and disinfection of the connection followed by 30 seconds drying time. Pronovost's theory will be used to guide the implementation process. Compliance with insertion and maintenance protocols and BSIs per 1000 CVC days will serve as outcome measurements.

The general discussion, **chapter 10**, places our findings in a broader perspective. The main conclusions are:

- Improved hand hygiene lead to a significant reduction of the BSIs rate in VLBW infants.
- A multifaceted education program and screen savers messages improved hand hygiene
- Ongoing attention to this issue is needed.
- Electronic counting devices could be utilized to monitor hand hygiene
- The challenges presented by infection prevention should be taken up in a joined effort by all involved healthcare professionals in the division of Neonatology, department of Medical Microbiology & Infectious Diseases, and department of Pediatrics.

Chapter 10 ends with suggestions for (near) future research, including bench marking and ways to improve hub care.

Appendices

NEDERLANDSE SAMENVATTING

Zorggerelateerde bloedbaaninfecties komen regelmatig voor bij prematuur geboren kinderen met een geboortegewicht kleiner dan 1500 gram die op een neonatale intensive care zijn opgenomen. Goede handhygiëne kan het infectierisico verminderen.

Dit proefschrift bestaat uit drie delen. Deel I, *Uitdagingen*, geeft informatie over de achtergrond en de doelen van dit proefschrift. Deel II, *Instrumenten en interventies*, beschrijft een elektronisch systeem dat het handalcoholgebruik meet en twee interventies ter verbetering van handhygiëne. Het eindigt met het effect van handhygiëne stimulerende interventies bij 'very low birth weight' (VLBW) neonaten: pasgeborenen met een geboortegewicht kleiner dan 1500 gram. De onderzoeken zijn uitgevoerd op de afdeling neonatologie van het Erasmus MC-Sophia Kinderziekenhuis. Het hoofdstuk sluit af met een overzicht van de incidentie van bloedbaaninfecties. Deel III, *Algemene discussie*, bevat een onderzoeksprotocol dat beoogt om een 'Sophia-brede', uniforme inbrengtechniek voor centraal veneuze katheters (CVK) en uniforme verpleegkundige zorg voor de CVK te stimuleren en daarmee het aantal bloedbaaninfecties te verminderen. Dit wordt gevolgd door een algemene discussie. Aanvullend worden aanbevelingen gedaan voor toekomstig onderzoek en wordt afgesloten met een samenvatting van het proefschrift.

DEEL I: UITDAGINGEN

Hoofdstuk 1 geeft een overzicht van de achtergrond en relevantie van infectiepreventie op neonatale intensive care units (NICUs). Dit proefschrift gaat in op zorggerelateerde of nosocomiale bloedbaaninfecties. VLBW neonaten worden vergeleken met andere groepen patiënten. In 'rijke landen' doen nosocomiale infecties zich minder vaak voor dan in landen met lage en 'midden' inkomens. Op intensive care (IC) afdelingen voor volwassenen worden zorggerelateerde infecties meestal veroorzaakt door lichaamsvreemde materialen. Een longontsteking kan ontstaan door een beademingsbuis, urineweginfecties door blaaskatheters en bloedbaaninfecties door de centraal veneuze katheters (CVKs). Het aantal nosocomiale infecties bij volwassenen opgenomen op een IC afdeling is relatief laag in vergelijking met het aantal infecties bij neonaten die opgenomen zijn op een NICU. Daarnaast hebben neonaten die zijn opgenomen op een NICU in landen met lage en 'midden' inkomens een drie tot 20 keer zo grote kans op een infectie als neonaten in dezelfde doelgroep in 'rijke landen'. Op een NICU bestaat het grootste deel van de nosocomiale infecties uit bloedbaaninfecties. Deze bloedbaaninfecties komen verhoudingsgewijs veel vaker voor bij neonaten die op een NICU zijn opgenomen dan bij volwassen IC-patiënten. Nosocomiale bloedbaaninfecties bij prematuren zijn geassocieerd met een verhoogde kans op overlijden, bijkomende complicaties (zoals hersenbloeding, visusstoornis en chronische longaandoening), toegenomen opnameduur, hogere ziekenhuiskosten en blijvende handicaps.

Door intrinsieke en extrinsieke factoren hebben prematuren een verhoogd risico op het krijgen van nosocomiale bloedbaaninfecties. De belangrijkste intrinsieke factoren zijn de onrijpheid van een prematuur met een nog relatief onderontwikkeld afweersysteem, een beperkte inflammatoire respons en een tekort aan immunoglobulinen. Bij de extrinsieke factoren dragen de invasieve procedures het meest bij aan het verkrijgen van bloedbaaninfecties bij prematuren. Effectieve maatregelen zijn het toepassen van correcte handhygiëne, hygiënisch werken volgens richtlijnen bij het inbrengen van CVKs en optimaal hygiënische verpleegkundige zorg voor CVKs. De Wereldgezondheidsorganisatie en de Amerikaanse 'Centers for Disease Control and Prevention' beschouwen goede handhygiëne als de kern van preventieve maatregelen.

Hoofdstuk 2 benadrukt de noodzaak van leiderschap bij richting geven aan infectiepreventie waarbij alle professionals, die betrokken zijn bij patiëntenzorg, optreden als één team om infecties te verminderen. De soms slechte attitude ten opzichte van handhygiëne en de vaak beperkte kennis over infectiepreventieve maatregelen moeten verbeteren.

In **hoofdstuk 3** wordt gesteld dat het eenmalig aan de orde laten komen van handhygiënetechnieken, tijdens een opleiding tot verpleegkundige, niet toereikend is om dit vervolgens consequent toe te passen. Het niet naleven van de handhygiëneregels wordt namelijk niet alleen veroorzaakt door gebrek aan kennis, maar is ook zeker een kwestie van attitude. Om het bewustzijn en het belang van goede handhygiëne te verhogen is het herhalen van handhygiënescholing belangrijk. Het is een uitdaging om de houding van de gezondheidszorg professionals te veranderen van 'laissez-faire' naar een houding waaruit blijkt dat alle teamleden zich verantwoordelijk voelen voor elke bloedbaaninfectie en daarnaar handelen.

In **hoofdstuk 4** wordt een overzicht gegeven van mogelijk effectieve niet-farmacologische interventies die het aantal nosocomiale bloedbaaninfecties verminderen bij kinderen opgenomen op een NICU. Er blijken vijf interventiecategorieën te zijn: handhygiëne, infuusbundels (samengestelde interventies, met onder andere aseptisch inbrengen van CVK en optimale hygiënische zorg tijdens verblijf CVK), materialen (waaronder gesloten infuussysteem, afdekmateriaal, infuus filters), surveillance en katheter inbreng-teams die CVKs inbrengen. Er is bewijs dat infuusbundels kunnen bijdragen aan het verminderen van bloedbaaninfecties bij neonaten. Er is een beperkt bewijs dat door katheter inbreng-teams het aantal bloedbaaninfecties vermindert. De promotie van handhygiëne leidt weliswaar tot een verbeterde handhygiëne, maar er is vanuit de literatuur geen eenduidig bewijs dat dit leidt tot minder infecties bij neonaten opgenomen op een NICU.

DEEL II: INSTRUMENT EN INTERVENTIES

Hoofdstuk 5 beschrijft een handhygiëne-scholingsprogramma en de evaluatie van zowel de naleving van de handhygiëne richtlijnen als het effect hiervan op het aantal nosocomiale bloedbaaninfecties bij VLBW neonaten. Het onderzoek bevat twee voormetingen en twee nametingen. In totaal zijn er 1201 handhygiëne observaties uitgevoerd die aantonen dat de naleving van de handhygiëne richtlijnen significant is verbeterd. Het percentage kinderen met één of meer bloedbaaninfecties en het aantal bloedbaaninfecties per 1000 opnamedagen is significant afgenomen van respectievelijk 44,5% naar 36,1% en van 17,3 naar 13,5.

In **hoofdstuk 6** wordt een nieuw instrument geïntroduceerd, dat elektronisch het gebruik van de handalcoholdispenser bij elke NICU bedplaats registreert. In een studie is het gebruik van de dispensers gedurende een aaneengesloten periode van één jaar gemeten. De mediaan (interquartile range) van het aantal handdesinfectiemomenten per dag is 697 (559-840). De mediaan (interquartile range) van het aantal hand desinfectie momenten per afdelingsmedewerker gedurende de dag-, avond- en nachtdienst is respectievelijk 13,5 (10,8-16,7), 19,8 (16,3-24,1) en 16,6 (14,2-19,3). Er kan worden geconcludeerd dat de elektronische dispensers nuttige gebruikersinformatie geven. Deze informatie kan toegepast worden om trends over een langere periode te genereren.

Hoofdstuk 7 beschrijft een onderzoek naar het effect van berichten over handhygiëne die getoond worden als screensavers op werkstations op de NICU. Als theoretische achtergrond wordt 'gain-framed' berichten gebruikt. Bij deze theorie worden de voordelen van het gewenste gedrag, een goede handhygiëne, benadrukt en niet zozeer de risico's van het niet naleven van het gewenste gedrag. Een verbeterde handhygiëne komt vooral ten goede aan patiënten, eigenbelang speelt meestal geen rol. Daarom is als extra motivator altruïsme toegevoegd. De screensaver-berichten hebben geresulteerd in een toename van het aantal handhygiënemomenten. Directe observaties bevestigen deze resultaten. Kortom: het gebruik van screensaver-berichten lijkt een effectieve manier om de handhygiëne te verbeteren.

Hoofdstuk 8 beschrijft een studie over de lange termijn resultaten van opeenvolgende infectiepreventiemaatregelen op bloedbaaninfecties. Daarnaast wordt een overzicht gegeven van de verwekkers van bloedbaaninfecties gemeten over een periode van tien jaar van 2002 tot 2011. Gedurende deze periode zijn in totaal 1964 VLBW neonaten opgenomen geweest. De incidentie van nosocomiale bloedbaaninfecties is met 40% afgenomen van 40,5% naar 24,3%. Het aantal nosocomiale bloedbaaninfecties per 1000 opnamedagen is met 58,9% afgenomen van 19,7 tot 8,1. De bloedbaaninfecties worden grotendeels veroorzaakt door Gram-positieve micro-organismen, coagulase-negatieve stafylokokken (67%) en S. aureus (14%). Het aandeel bloedbaaninfecties veroorzaakt door stafylokokken verminderde significant gedurende de meetperiode, hetgeen een verbeterde handhygiëne suggereert.

DEEL III: ALGEMENE DISCUSSIE

In **hoofdstuk 9** wordt een ziekenhuisbreed CVK protocol voor een toekomstige studie beschreven voor het Erasmus MC-Sophia. Het protocol bevat zowel een bundel voor het inbrengen van een CVK als voor de verpleegkundige zorg. De inbreng-bundel omvat een time-out procedure, een scherm om patiënt en inbrenger te scheiden van de onsteriele omgeving en het voor tenminste 80% afdekken van de patiënt met steriel afdekmateriaal. De verpleegkundige zorgbundel bevat bijvoorbeeld het desinfecteren van de ampul of het septum. Het gedesinfecteerde oppervlak moet tenminste 30 seconden aan de lucht gedroogd worden. Na het desinfecteren van het aansluitpunt bij de patiënt dient men deze eveneens tenminste 30 seconden te laten drogen. Voor het implementatieproces van de protocollen zal gebruik gemaakt worden van Pronovost's implementatietheorie. De naleving van het protocol voor het inbrengen van de CVK en het CVK verpleegkundige zorg protocol, evenals het aantal bloedbaaninfecties per 1000 CVK dagen zullen gebruikt worden als uitkomstmaten.

In de Algemene discussie, **hoofdstuk 10**, worden de bevindingen in een breder perspectief geplaatst. De belangrijkste conclusies zijn:

- Infectiepreventieve maatregelen bij kinderen met een geboortegewicht kleiner dan 1500 gram leiden tot een significante vermindering van het aantal nosocomiale bloedbaaninfecties.
- Een samengesteld infectiepreventie programma en screensaver-berichten verbeteren de handhygiëne bij medewerkers.
- Terugkerende aandacht voor infectiepreventie is noodzakelijk.
- Handalcohol dispensers met een ingebouwde elektronische teller kunnen worden gebruikt voor het monitoren van handhygiëne.
- Toekomstige preventieve interventies en een continue samenwerking tussen medewerkers van de NICU, medewerkers van de afdeling Medische Microbiologie en Infectieziekten en de afdeling Kindergeneeskunde kunnen mogelijk bijdragen aan een lagere incidentie van bloedbaaninfecties.

Hoofdstuk 10 besluit met suggesties voor toekomstig onderzoek, inclusief benchmarking en verbeterende hygiënemaatregelen voor infuusbijspuitpunten.

LIST OF ABBREVIATIONS

BSI	Bloodstream infection
BW	Birth weight
CA-BSI	Catheter associated bloodstream infections
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CoNS	Coagulase-negative staphylococci
CPAP	Continuous positive airway pressure
CRBI	Catheter related bloodstream infections
CRIB	Clinical risk index for babies
CRP	C-reactive protein
CVC	Central venous catheter
D	Day
E. coli	Escherichia coli
ELBW	Extremely low birth weight
G	Gram
GA	Gestational age
H	Hours
HAI	Healthcare-associated infections
HC	High care
HCP	Healthcare professional
HCW	Healthcare worker
HH	Hand hygiene
IC	intensive care
IQR	Interquartile range
ITS	Interrupted time series
IV	Intra venous
MD	Medical doctor
MRSA	Methicillin-resistant Staphylococci Aureus
NA	Not available
NICU	Neonatal intensive care unit
NP	Nurse practitioner
Nurse ass	Nurse assistant
PDMS	Patient data management system
PICC	Percutaneously inserted central catheter
PICU	Pediatric intensive care unit
RCT	Randomized clinical trial
S. aureus	Staphylococcus aureus

SE	Standard error
SPSS	Statistical package for social science
VLBW	Very low birth weight
WK	Week

LIST OF PUBLICATIONS

Helder O, Boer de C. Preventie van bloedbaaninfecties bij pasgeborenen (submitted).

Helder O, van Goudoever J, Brug J, Looman C, Reiss I, Kornelisse R. Reduced nosocomial bloodstream infection rate among very low birth weight infants by sequential hand hygiene promotion: a ten-year experience (submitted).

Helder O, Kornelisse R, van der Starre C, Tibboel D, Looman C, Brug J, Poley M, Ista E. Implementation of a children's hospital-wide central venous catheter insertion and maintenance bundle (submitted).

Aufenacker-van Bethlehem S, Buijs V, Helder OK. Voorkomen van lijnsepsis. Tijdschr Kinderverpleegk 2012;(18)3:30-32.

Helder, OK, van Goudoever JB, Hop WCJ, Brug J, Kornelisse RF. Hand disinfection in a neonatal intensive care unit: continuous electronic monitoring over a one-year period. BMC Infect Dis 2012;12:248.

Corpeleijn WE, Kouwenhoven SM, Paap MC, van Vliet I, Scheerder I, Muizer Y, Helder OK, van Goudoever JB, Vermeulen MJ. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infantsduring the first 60 days of life. Neonatology 2012;102(4):276-281.

Helder OK, Weggelaar AM, Waarsenburg DC, Looman CW, van Goudoever JB, Brug J, Kornelisse RF. Computer screen saver hand hygiene information curbs negative trend in hand hygiene behavior. Am J Infect Control 2012;40(10):951-954.

Helder O, van den Hoogen A, de Boer C, van Goudoever J, Verboon-Maciolek M, Kornelisse R. Effectiveness of non-pharmacological interventions for the prevention of bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review. Int J Nurs Stud, 2012, Feb 29 [Epub ahead of print, doi 10.1016].

Helder, OK, Twisk JW, van Goudoever JB, van Elburg RM. Skin and rectal temperature in newborns. Acta Paediatr 2012;101(5):240-242.

Helder, OK, Verweij JC, van Staa A. Transition from neonatal intensive care unit to special care nurseries: experiences of parents and nurses. Pediatr Crit Care Med 2012;13(3):305-11.

Wielenga JM, Helder OK, Mansvelt P, van den Hoogen A. Is cranial molding preventable in preterm infants? A systematic review of the effectiveness of interventions. Pediatr Intensive Care Nurs 2011;12(1-2):3-10.

Helder OK, Brug J, Looman CW, van Goudoever JB, Kornelisse RF. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: an intervention study with before and after comparison. Int J Nurs Stud 2010;47(10):1245-1252.

Ista E, Helder O. Samenwerken aan een protocol. Hoe verpleegkundige intensive-carestudenten kunnen bijdragen aan het evidence-based maken van een protocol over endotracheaal uitzuigen van beademde kinderen. Ned Tijdschr Evid Based Pract 2010;1:20-23.

Helder OK, JM Latour. Undergraduate nurse students' education in infection prevention: is it effective to change the attitude and compliance with hand hygiene? Nurs Crit Care 2010;15(1):39-40.

van Brakel A, Bogers B, Helder OK. The efficacy of facilitated tucking of the neonate: a systematic review. Pediatr Intensive Care Nurs 2009;10:4-12.

Helder, OK, JM Latour. Reduction of catheter related bloodstream infections in intensive care: one for all, all for one? Nurs Crit Care 20009;14(3):107-108.

Helder, OK, Wielenga JM, Cranendonk A, Mansvent P, van de Hoogen A. Een literatuur studie naar interventies ter preventie van de vervorming van de schedel van prematuur pasgeborenen op de NICU. Verpleegkunde 2009;1:12-17.

Helder, OK, Latour JM. Endotracheal suctioning, there's more to it than just technical care. Pediatr Crit Care Med 2008;9(5):539-540.

Helder, OK, Mulder PG, van Goudoever JB. Computer-generated versus nurse-determined strategy for incubator humidity and time to regain birth weight. J Obstet Gynecol Neonatal Nurs 2008; 37(3):255- 261.

Helder, OK. Verbeteringen in de ketenzorg voor pasgeborenen, overplaatsen van IC naar HC-centra. Kind Ziekenh 2008; 31e jaargang, april:75-77.

Helder O, Wielenga J, Mansvelt P, Cranendonk A, van de Hoogen A. Evidence Based Nursing in de IC-Neonatologie en de rol van de Innovatie & Onderzoek werkgroep. Intensive Care Capita Selecta 2008;141-148.

Helder, OK, Hop CJ, van Goudoever JB. Vibration therapy reduces CPAP need in a prospective randomised controlled trial. Pediatr Intensive Care Nurs 2008;9(1):3-7.

Helder, OK, F Grootveld- Monteiro. Eerst verantwoordelijke verpleegkundige op een NICU, werkt dit? Tijdschr Kinderverpleegk 2005;5:11-12.

van Kilsdonk M, Flierman, M, Helder, OK. Wat te vroeg geborenen ons kunnen vertellen. Tijdschr Kinderverpleegk 2004;3:4-6.

Helder, OK, Peters, J. Evidence-based Nursing in de Neonatologie? Intensive Care Capita Selecta 2004;45-54.

Helder, OK, Franken, J. Samen werken aan scholing. Tijdschr Ziekenverpl 2003;113(10):44-47.

Hal van P, OK Helder. Infuuspompen en kwaliteit vanuit verpleegkundig perspectief, een multidisciplinaire aanpak. Technol Gezondheidsz 2001;5:16-18.

Helder, OK. In-wonen een zorg meer? Tijdschr Ziekenverpl 1988;3:88-89.

CURRICULUM VITAE

Onno Helder was born on the 6th of April 1964 in Hamilton, United Kingdom. In 1982 he graduated from secondary school 'HAVO' at the Eindhovens Protestants Lyceum, Eindhoven. He started his bachelors nursing training at the Hogeschool Eindhoven and received his degree in 1987. He joined the military service and worked as a nurse at the neurology department of the Dr Mathijsen Hospital in Utrecht from 1987 to 1989. Subsequently, he started his general pediatric nursing training at the Erasmus MC-Sophia Children's Hospital from 1989 to 1990. This general pediatric training was followed by a pediatric intensive care nursing training at the Erasmus MC-Sophia Children's Hospital from 1992 to 1993. He started his Master of Science in Nursing study in Cardiff/ Utrecht in 2000. In 2003 he obtained his MSc in nursing with a thesis entitled 'Barriers perceived by nurses to the implementation of the Newborn Individualized Developmental Care and Assessment Program for infants'.

In 2003 he started with nursing research projects at the Department of Neonatology. Thereafter dr. R.F. Kornelisse made him enthusiastic for infection prevention research. From 2005 he commenced his PhD studying infection prevention in preterm infants at the Department of Neonatology, Erasmus MC-Sophia Children's Hospital under supervision of prof. dr. van Goudoever, prof. dr. ir. Brug and dr. Kornelisse. He was awarded with the Evidence Based Care by Nurses grand in 2012. Since 1993 he is partial employed as a nurse in patient care at the Department of Neonatology, Erasmus MC-Sophia Children's Hospital.

Onno is married to Marion Taal and they have two children Lotte (1993) and Joep (1995).

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: O.K. Helder
Erasmus MC Department: Neonatology
Research School:

PhD period 2005-2013
Promotors: Prof.dr. J.B. van Goudoever
Prof.dr.ir. J. Brug
Copromotor: Dr. R.F. Kornelisse

1. PHD TRAINING

	Year	Workload (hours/ ECTS)
General courses		
- Scientific English Writing and Communication	2007	112/ 4
- Biostatistics for Clinicians	2009	28/ 1
- Certificate BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2009	8/ 0.3
Presentations (oral)		
- Catheter-hub cultures, indirect instrument for the measurement of hand hygienic practices in a NICU? ESPNIC London	2004	28/ 1
- Evaluation of compliance in hand hygiene practices in the NICU. ESNIC London	2004	28/ 1
- Infection control in the Neonatal Intensive Care Unit, 2nd International Military Nursing Congress, Istanbul	2005	28/ 1
- Research and Intensive Care: nosocomial infections in the NICU, 2nd Congress of the European federation of Critical Nursing associations, Amsterdam	2005	28/ 1
- Evaluatie van de handhygiëne op de Neonatale Intensive Care Unit, Vlaams Nederlands Wetenschappelijk Congres, Leuven	2005	28/ 1
- Efficacy of a multifaceted education program on hand hygiene, Europaediatrics, Barcelona	2006	28/ 1
- Impact of an education program on hand hygiene practices and nosocomial infection rate in a neonatal intensive care unit, World Congress on Paediatric intensive Care, Geneva	2007	28/ 1
- Effectieve maatregelen om infecties te voorkomen, Venticare, Utrecht	2010	28/ 1
- Infecties, het gevaar ervan en de preventie, Gouda	2010	20/ 0.7
- Measurement of hand disinfection events by using an electronic device, which determine the use of dispensers for a period of one year, 7th International Conference of Neonatal Nursing, Durban	2010	28/ 1
- Samenwerken aan infectiepreventie, Zorg rond de pasgeborene, Eden	2011	28/ 1

(International) conferences

- 4th ESPIC-Nursing Congress, Brussels	1993	14/ 0.5
- ESPIC-Nursing Congress, Zurich	1998	28/ 1
- 4th Wold Congress on Pediatric Intensive Care, Boston	2003	56/ 2
- PAOG-Heyendael symposium, Infectie en infectiepreventie op de verpleegafdeling en IC, Nijmegen	2006	8/ 0.3
- Catheter-related Bloodstream infections: prevention, outcome & treatment, Rotterdam	2008	8/ 0.3
- Boerhave Commissie, Richtlijnen. Nu de daad bij het woord, Leiden	2009	8/ 0.3

2. TEACHING

- Evidence-Based Nursing Courses at the Zorgacademie, Rotterdam	2006-2013	80/ 2.9
- Education infection prevention, Joint Commission International, Emma Children's Hospital Rotterdam	2011	16/ 0.6
- Grand round Infection prevention	2010	8/ 0.3
- Evidence-based Nursing Lunches	2004-2010	72/ 2.6
- NICU nurse education, Rotterdam	2004-2013	50/ 1.8
- Lecture TU Delft Medisign	2010	28/ 1

Seminars and workshops

- Infections for dummies, master class ESPNIC Nice	2008	32/ 1.1

Supervising Master and Bachelor's thesis

- iBMG - Framed messages ter bevordering van handhygiëne	2009	28/ 1
- Hogeschool Rotterdam - Nursing Bachelor project, 12 students: Transition from NICU to High care,	2005-2006	80/ 2.9

ECTS = European Credit Transfer and Accumulation System
1 ECTS credit represents 28 hours

DANKWOORD

De afgelopen jaren heb ik het voorrecht gehad om me te verdiepen in praktijkgericht onderzoek. Daarbij heb ik met veel mensen mogen samenwerken. Deze samenwerking heeft uiteindelijk tot dit proefschrift geleid. Bij het opzetten van het onderzoek heb ik veel vrijheid ervaren, dat maakte dat ik me zeer betrokken voelde bij de te maken keuzes. Mijn dank gaat uit naar iedereen die dit mogelijk heeft gemaakt.

Als eerste wil ik het voltallige team van de intensive care neonatologie bedanken. Collega verpleegkundigen, artsen, afdelingsmanagement, verpleegkundig specialisten, zorgassistenten, afdelingsassistenten en alle andere medewerkers van de intensive care neonatologie. Jullie hebben een hele grote klus geklaard met het drastisch verminderen van het aantal bloedbaaninfecties. Infectiepreventie staat op de kaart; een infectie overkomt een kind niet zomaar en jullie vervullen een actieve rol om dit te voorkomen. Een goede graadmeter zijn de ouders van kinderen op onze afdeling. Zij zeggen dat infectiepreventie een belangrijke plaats heeft op de afdeling. In het kinderziekenhuis maar ook daarbuiten, geniet onze afdeling bekendheid omdat er veel bereikt is op het gebied van infectiepreventie. Ik ben trots dat we dit hebben bereikt en hoop met jullie steun een nog veiligere zorg te bieden aan de kinderen die ons zijn toevertrouwd.

Prof. dr. J.B. van Goudoever, beste Hans, jij nam deel aan het gesprek met prof. dr. Luc Zimmermann waarin werd toegezegd dat ik als eerste verpleegkundige met een masters opleiding op de intensive care neonatologie een wetenschappelijke functie mocht vervullen. Het woord ‘promotie’ is tijdens dit eerste gesprek al gevallen. Hierop reageerde ik: “*Laat mij eerst maar eens een onderzoek doen en dit tot een goed eind brengen, dan zien we wel weer verder*”. En zo geschiedde, eerst twee kleinere studies en daarna volgde deze grotere studie. Ik ben je erg dankbaar dat je me de kans en de steun hebt gegeven om naast patiëntenzorg, een ander deel van het academisch kinderziekenhuis te ontdekken.

Prof. dr. ir. J. Brug, beste Hans, in de kliniek werken veel experts met kennis over de verpleegkundige en medische kant van de patiëntenzorg. Een deskundig op het gebied van implementatieprocessen ontbrak: iemand die weet hoe je verworven kennis over de meest effectieve interventie daadwerkelijk in de praktijk toepast. Om deze brug te kunnen slaan, had ik jouw expertise en steun nodig. Ondanks je werkzaamheden in het EMGO instituut van de VU Amsterdam, gaf je op de juiste tijd essentiële support. Hiervoor ben ik je zeer erkentelijk.

Dr. R.F. Kornelisse, beste René, jou ben ik veel dank verschuldigd. Jij hebt veel kennis over infecties/ infectiepreventie en het blijkt besmettelijk te zijn, want infectiepreventie heeft nu ook mijn grote belangstelling. Ik was jouw tweede promovendus en we hebben het tot een goed eind gebracht: het proefschrift is klaar! Er is hard en enthousiast gewerkt aan het verbeteren van de patiëntenzorg door het verminderen van het aantal bloedbaaninfecties. Het eerste artikel van de klinische studie kwam tot stand na een langdurig, herhaald en zorgvuldig slijp/ polijst/ politoer proces. Ik ben er trots op. Veel dank voor je niet aflatende optimisme, deskundige begeleiding en nauwgezet commentaar bij het schrijven van de manuscripten.

Prof. dr. I.K.M. Reiss, beste Irwin, bedankt, dat je als secretaris zitting wilde nemen in de kleine commissie. Als afdelingshoofd en stimulator van (zorg-) onderzoek op de afdeling intensive care neonatologie hoop ik in de nabije toekomst mede onder jouw leiding nog veel patiëntgerichte onderzoeken te kunnen verrichten.

Prof. dr. René Wijnen, beste René, dank dat je in de kleine commissie zitting wilde nemen. Elkaar steunen en aanspreken op (on-)veilig patiënten contact is voor jou vanzelf sprekend. De quote: *"Spreek mij aan op onhygiënisch gedrag"* die gebruikt is op posters ten behoeve van de Erasmus MC-Sophia-brede infectieweek: 'Schoner werken = infectie beperken', komt bij jou vandaan, een grote en goede steun.

Prof. dr. H. Verbrugh, beste Henri, hartelijk dank dat je in de kleine commissie zitting wilde nemen voor het beoordelen van het manuscript.

Prof. dr. A.J. van der Heijden, dr. N. Hartwig en dr. A. van den Hoogen bedank ik voor het plaatsnemen in de commissie. Heel bijzonder Agnes dat je, als collega verpleegkundig onderzoeker en expert op het gebied van infectiepreventie vandaag opponeert.

Masterstudenten: Daniël Waarsenburg, Marcha Wouterson, Marlou op de Weegh en Joyce van der Weijde, bedankt voor jullie bijdragen bij het verzamelen van de data voor de verschillende studies.

Yvonne Kant in het verleden werkzaam als unithoofd en nu als sectormanager, je hebt aan de wieg gestaan bij de ontwikkeling van zorgonderzoek. De noodzaak van onderzoek door verpleegkundigen vond je evident. Trots was je bij het bekend worden van de reductie van het aantal bloedbaaninfecties. Voor jou tastbare c.q. meetbare resultaten in de verbeterig van directe patiëntenzorg. Er zijn nog meer uitdagingen op het gebied van infectiepreventie, die wil ik graag met jouw steun aangaan.

Caspar Looman, dank voor alle weloverwogen statistische adviezen. Je steun bij de voor mij aanvankelijke complexe interrupted time series analyses was groot.

Ko Hagoort, dank voor je kritische blik en zeer waardevolle adviezen bij het 'editen' van manuscripten. Jouw manier van 'editen' gaat verder dan alleen het lekker laten lopen, je gaf vaak belangrijk inhoudelijke commentaar waarmee de artikelen verder verbeterd konden worden.

Zorgonderzoekers van het Erasmus MC-Sophia: Coby de Boer, Jos Latour, Erwin Ista, Monique van Dijk en Anneke Boerlage. Heel veel dank voor jullie betrokkenheid, inzet, samenwerking en gezelligheid tijdens mijn promotieproces. Sparren, advies of je frustratie delen is van groot belang geweest. Als zorgonderzoekersgroep hebben we ongelooflijk veel kennis en kunde in huis en dat werkt zeer stimulerend.

Kamergenoten Ellen van 't Verlaat en Annelies Bos, fijn dat jullie mijn kamergenoten zijn. Ik hoop dat we nog vaak lekkere koffie kunnen drinken.

Mijn paranimfen Hans Helder en Jan van Gorp wil ik wel heel bijzonder danken, jullie beiden stonden al vaker naast mij.

Hans, je doet onderzoek naar nematoden aan de Wageningen University, mede door jou heeft wetenschappelijk onderzoek mijn belangstelling gekregen. Een tijd terug was ik jouw paranimf en nu ben ik ben heel trots om je naast me te hebben, voorafgaand, tijdens en na de promotie. Veel steun heb ik van je gekregen tijdens mijn 'Master of Science in Nursing'. Hans door jou heb ik gemerkt dat wetenschap geen solitaire aangelegenheid is, samenwerken is noodzakelijk om in onderzoek je grenzen te verleggen.

Jan, we hebben gemeenschappelijke 'roots' en toch verschillende ontwikkelingen doorgemaakt. De belangen van de patiënt vooropzetten en verandermanagement zijn onderwerpen die ons beiden raken. Gedrag veranderen blijkt een lastige klus. Ondanks de drukke tijden vonden we tijd om samen fietstochten te maken zoals de pelgrimsvaart naar Santiago de Compostela, dat moeten we maar lang volhouden.

Ineke Breugem, tante en veel meer dan een lieve tante. Jij hebt me enthousiast gemaakt voor de kinderverpleegkunde. Toen al had je de ontegenzeggelijk vooruitziende blik, dat schrijven in (wetenschappelijke) vakbladen, mijn toekomst zou zijn. Je nodigde mij uit om in 'Tijdschrift voor de Ziekenverpleging' een artikel te schrijven over de voor- en nadelen van 'rooming in'; ouders die tijdens de ziekenhuisopname bij hun kind mogen slapen. 'Rooming in' was het onderwerp van mijn HBO-Verpleegkunde afstudeerscriptie en het artikel werd kort na mijn diplomering gepubliceerd. Ineke, je was aanwezig bij veel hoogtepunten en ik hoop dat we nog talrijke gezellige momenten met elkaar zullen hebben.

Lieve pa en ma dank voor de liefdevolle opvoeding die mij mede gevormd heeft. Gastvrijheid en zorgzaamheid voor de ander zijn bij jullie altijd belangrijke pijlers, die ik eveneens probeer uit te dragen. Ma in je werkzame leven was je niet alleen een verpleegkundige maar ook een mooi voorbeeld van betrokkenheid. Pa: *"Je moet niet verder willen springen dan dat je polsstok lang is",* met wilskracht en enthousiasme kan je best ver springen. Goed om jullie trotsheid te ervaren.

Lieve Lotte en Joep. Jullie zijn geweldige kinderen en ik ben er trots op om jullie vader te zijn. Afgelopen periode is er veel vrije tijd in het schrijven van dit proefschrift gaan zitten, maar gelukkig hebben we ook tijd gevonden om veel leuke dingen met elkaar te doen. Onvergetelijke reizen, ontmoetingen en zien hoe jullie je ontwikkelen, ik wil het allemaal graag blijven meemaken.

Lieve Marion, nu 22 jaar gelukkig samen. Jouw steun is voor mij erg belangrijk geweest en het is altijd heerlijk om thuis te zijn. Dit en echt belangrijke zaken van het leven, zoals vrienden, bergen, muziek, natuur en fietsen, ik hoop dat we dat nog lang samen mogen beleven.

Infecties

Beste mensen opgelet
een nieuw beleid wordt ingezet
de vorige vertoonde nog wat scheuren
Velen worden er gered
maar enkelen nog steeds besmet
dus staat er jullie heel wat te gebeuren….

Als het gaat om hygiëne
en wat er wordt verwacht
Dan zijn het serieuze zaken
neem de regels goed in acht

Jongens denk aan de infecties
neem je tijd voor je injecties
Hou de boel goed schoon
En vindt dit heel gewoon
Het is een helder verhaal

Jongens denk aan de infecties
neem je tijd voor je injecties
Hou de boel goed schoon
En vindt dit heel gewoon
Dat geldt voor ons allemaal

Zit niet aan je neus
krap niet aan je kont
blijf van je haren af
je handjes voor je mond

Kriebel in je oor
koffie in je snor
'tgaat allemaal vanzelf en
soms heb je 't niet door

Als het gaat om hygiëne
en wat er wordt verwacht
Dan zijn het serieuze zaken
neem de regels goed in acht

Denk niet bij het handen wassen
dit duurt een eeuwigheid
Je moet die tijd inlassen
dus doe wat nuttigs met die tijd

Doe gewoon een dansje neem een liedje in je hoofd
of denk maar aan iets stouts wat je je partner hebt beloofd
Droom maar even weg, ga lekker naar een warm land
zie jij jezelf al liggen met een biertje in je hand

Je voelt je echt gelukkiger het maakt je even blij
Ga dan weer vrolijk en schoon aan de slag
Dertig seconden zijn zo voorbij

Bron: Speelman en Speelman