Strategies in the battle against neonatal nosocomial infections

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PART FIVE

Summary and Discussion

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

INTRODUCTION

Central-lines are indispensable in the provision of care to neonates admitted to the NICU, ensuring vascular access for the administration of medication, parenteral nutrition, as well as facilitating blood withdrawal and hemodynamic monitoring. The primary complication arising from the use of central-lines are CLABSIs, which are known to be major contributors to late-onset sepsis and thereby neonatal morbidity, mortality and significant economic burden.[1,2] Given that CLABSIs have become the poster child for 'preventable harm,' a great deal of attention has been placed on the reduction and prevention of CLABSI and other forms of nosocomial sepsis within the neonatal population. However, and despite the successes of several concerted efforts, the eradication of CLABSI has proven to be elusive for many institutions, including ours.

This Chapter will place the main findings and methodological challenges of the studies discussed earlier in this thesis in a broader scientific perspective. In addition, a number of unresolved issues in the battle against neonatal NI will be further explored as part of the continued work towards the discovery of better infection prevention practices. Finally, suggestions for future research will also be made.

SURVEILLANCE AND REPORTING OF NEONATAL NI

Importance of Consensus Definition

While it is recognized that the dynamic nature of infections within the framework of functional immaturity of the neonatal immune system has played a significant role in limiting the progress in eliminating neonatal NI, an appropriate consensus definition regarding the latter has likewise been shown to be one of the strongest contributors to the lack of improvement. Not only do case definitions form the basis for the establishment of sound epidemiological overviews, but they are also equally paramount for the selection of patients for clinical trials, benchmarking hospital outcomes and development, and implementation and evaluation of quality improvement strategies.

As discussed in **Chapter 1**, there is currently significant heterogeneity among studies regarding the definition of neonatal NI and CLABSI. This variability is not only present in the combination of laboratory tests incorporated in published definitions,[3-5] but also in laboratory results defined as normal as well as in integrated clinical signs and symptoms.[6,7] The presence of a positive blood culture is historically considered the "gold standard" for the confirmation of neonatal sepsis, yet many studies also include culture-negative or "clinical" sepsis.[8-10] Moreover, some reports base the diagnosis of sepsis on the duration of antibiotic treatment (i.e. 5 or more days) in addition to the presence of a positive blood culture.[11] A particular salient issue in CLABSI reporting is the variability (and even obscurity) in the method used to count central-line days, which may lead to an under- or overestimation of true CLABSI rates. A study conducted by Hazamy et al. (2015) in which the effect of a modified definition of CLABSI using calendar day units instead of hours to determine central-line dwell-time in relation to the onset of NI, showed a 16% reduction in CLABSI rates, suggesting that the manner in which central-line days are tallied may have a major impact on reported CLABSI rates.[12] Another important aspect to consider is how well the definition fits the clinical setting in which it is to be applied. Although many surveillance definitions, including those established by the Centers for Disease Control and Prevention (CDC) and European Center for Disease Control and Prevention (ECDC), recommend obtaining at least two blood cultures for the confirmation of Coagulase-negative Staphylococci (CoNS) sepsis,[13,14] neonatal data to support this premise is lacking, with usual practice encompassing a single-blood culture policy in many NICUs, including those in The Netherlands. With the aim of achieving nationwide surveillance of CLABSI rates in The Netherlands, objective and sustainable CLABSI

surveillance criteria with high construct validity were developed by the Working Group on Neonatal Infectious Diseases of the Section of Neonatology of the Dutch Pediatric Society for the neonatal population in 2021.[15] These criteria successfully allowed us to describe the epidemiology of neonatal CLABSI on both a local (**Chapter 2**) and national (**Chapter 8**) level, as well as assess the effect of numerous infection prevention interventions (**Chapters 4 and 6**) and the burden of infection in certain neonatal subpopulations (**Chapter 3**). However, it is important to remember that NI is a dynamic, complex and heterogeneous condition, signifying that any definition must undergo timely revision and refinement. Future steps to be taken include developing criteria for other NI subtypes and assessing how these criteria may be used as a framework for the development of an internationally recognized, overarching neonatal NI definition which maintains its clinical relevance while providing valid interpretation of progress.

Exploiting the Potential of (Semi-) Automatic CLABSI Surveillance

Following the landmark publication on the efficacy of infection surveillance by Haley et al. (1985), surveillance of NI has become an indispensable component of successful infection prevention measures, allowing healthcare workers to identify areas for quality improvement and timely evaluate interventions.[16] The World Health Organization (WHO) recognizes surveillance of NI to be a key component of public health practice, having incorporated it as one of the eight core components for infection prevention and control.[17] Meanwhile, numerous studies and countries have successfully implemented large-scale surveillance approaches, including but not limited to the Dutch PREventie van ZIEkenhuisinfecties door Surveillance initiative (PREZIES), the American Vermont Oxford Network and the German Krankenhaus-Infektions-Surveillance-System.[18-20]

Conventionally, NI surveillance is performed by manually reviewing patient charts while applying standardized case definitions, a rather time-consuming and resource intensive process.[21,22] Likewise, given that traditional NI surveillance often relies on the knowledge and experience of infection adjudicators, it is prone to error and high interrater variability.[23] The aforementioned limitations of traditional NI surveillance methods have led to the development and implementation of semi- and fully-automatic surveillance systems for the identification of various types of NI, the most common ones being surgical site infections and CLABSI.[22,24,25] One of the first studies to describe successful automation of CLABSI surveillance using electronic data was conducted by Trick et al. (2004), suggesting that automated systems are a better alternative to manual surveillance.[26] By using (anonymized)

routine patient data stored in electronic medical records to identify patients who may have developed a NI, these systems ensure the delivery of large-scale data in a uniform, objective and efficient manner.[26]

Automated surveillance systems can be designed to either merely support (i.e. semi-automatic systems) or fully replace manual surveillance methods (i.e. fully-automatic systems).[25] While fully-automatic surveillance uses available electronic data and thereby require no manual assessment, semi-automatic surveillance in turn employs automation to derive a list of patients with a high probability of NI, after which manual chart review is performed to confirm their NI status.[25] Although the manual confirmation step in semi-automatic surveillance may still result in some degree of interrater variability, it does allow for a nuanced clinical interpretation of the patient's condition and the concomitant care processes that lead to infection, thus facilitating the diagnosis of neonatal sepsis given the ambiguity of clinical signs and symptoms in neonates.[25] Moreover, the manual review step has the potential to stimulate clinicians' acceptance of the surveillance result.[22]

For either of the above automation approaches to be successful, routine (clinical) data stored in electronic medical records must be available in an accurate, reliable and standardized format.[25] Unfortunately, limited access to clinical data and difficulties in processing data in computable and aggregated formats often complicate successful automation.[25,26] The availability of a large digital warehouse in which all routine patient data is stored, along with our well-defined national CLABSI surveillance criteria enabled us to establish our own, local semi-automatic CLABSI surveillance system, generating accurate and reliable results which laid the foundation for the epidemiological overviews and in-hospital quality improvement initiatives reported in **Chapters 2, 3 and 6**. Furthermore, in **Chapter 8** we present the first formal initiative of a nationwide collaboration to describe neonatal CLABSI data as a first step in determining the feasibility of a continued, prospective CLABSI surveillance in The Netherlands. An important finding and limitation of this study was the large heterogeneity in data formats, electronic medical records and thereby capacities for automatic extraction of routinely recorded patient data between the participating centers. As a result, conventional (manual) surveillance was performed, which may have introduced a degree of inter-rater variability. Therefore, an important next step in obtaining valid data for interfacility comparison in the Dutch NICU setting would be equipping centers with the needed digital infrastructure for clinical data warehousing, standardization of data elements and automation of data extraction to facilitate future benchmark initiatives.

MOVING FORWARD IN THE INFECTION PREVENTION REALM

Over the past decades, NI prevention has become an intricate web of technology and practice change in an ever more complex healthcare environment. Hospital wards are increasingly challenged with mounting evidence suggesting that change in clinical practice is the way to go when it comes to NI prevention. Prevention strategies for CLABSI have a particularly long-standing tradition. While most research in the past have focused on novel technologies such as antibiotic impregnated central-lines, antiseptic dressings and needleless connectors, more recent research has focused on prevention measures involving practice changes such as early removal of lines and improvement in post-insertion care.[27-29] These practice change approaches commonly encompass a comprehensive combination of straightforward and evidence-based measures at all levels of central-line insertion, including adequate hand hygiene, the use of maximal barrier precautions and implementation of checklists to ensure procedure standardization. Unfortunately, implementing practice changes has been found to be more difficult than introducing a new medical device, resulting in wide variation in the reported success rates of practice change strategies.[30]

In their pursuit of standardizing infection control methods and facilitating consistent and reliable performance of evidence-based practices, institutions worldwide increasingly make use of so-called 'care bundles,' defined by the Institute of Healthcare Improvement as a "small, straightforward set of evidence-based practices that, when performed collectively and reliably, have been proven to improve patient outcomes." [31,32] There are numerous conceptual advantages of care bundles including streamlining decisions, supporting goal-oriented care and reducing uncertainty by giving a practical but consistent solution to the delivery of care.[32] In response to the relatively high CLABSI rate of 14.3 per 1000 central-line days among preterm infants in our NICU reported in **Chapter 2**, we developed, implemented and evaluated the effect of a multi-modal CLABSI intervention program in **Chapter 6**. In contrast to what was hypothesized, our findings did not support the overall effectiveness of our multifaceted program, raising the question as to whether care bundles truly form the silver bullet in infection prevention, despite their growing popularity. Even though bundles offer a structured approach for improving the process of care, they may be inefficient by containing (too many) elements which may or may not be related to the bundle's purpose.[32] Reported bundles likely also suffer from positive publication bias and lack of external validity in real clinical practice which hinders the assessment

of their overall effectiveness.[32] The majority of individual components included in our care bundle were based on increasing awareness and training, the effect of which is likewise known to be transitory, thereby necessitating periodic, if not continuous reminding. Furthermore, the post-intervention period was short relative to the other study periods, indicating that a longer follow-up period may still result in a reduction in CoNS-related CLABSI. As such, more research will be needed to determine which bundle composition, specifically, has the strongest effect on infection prevention.

One of the most effective means of reducing NI is the performance of hand hygiene (HH). However, despite its importance, simplicity and thereby incorporation in the majority of infection prevention bundles, institutions' attempts at achieving high compliance rates continue to be a challenge. The relative lack of progress in the sustained improvement of HH compliance has a number of reasons. First, the majority of existing HH improvement strategies have largely focused on conventional measures, including training, educational campaigns and periodic reminders, which are known to have a limited and temporary effect.[33] Second, current HH guidelines are often incompatible with the already high workloads in clinical settings, especially in intensive-care settings where following HH guidelines compete with other clinical priorities. Finally, HH requires a conscious effort to remember and is often not regarded as an intuitive part the care process, even though remembrance may be enhanced through the installment of salient yet subtle event-based cues in the form of external stimuli. In **Chapter 7** of this thesis, we describe the development of a user-centered design concept in the form of 'Island-based nursing' as a means of facilitating and simplifying HH performance. By identifying behavior-, environmental- and process-related barriers to HH compliance, we were able to reduce the need for impractical HH indications. A unique aspect of our concept was the incorporation of a sensitizing environmental feature, or 'nudge,' in the form of an illuminated patient-zone demarcation to further increase the salience of the behavior and trigger the prospective task of HH in an intuitive and non-intrusive manner. A limitation of our concept however, was that it was merely designed to target the *quantity* of HH performance rather than its *quality*, while the latter has been shown to be an equally important aspect of optimizing HH behavior and reducing NI.[34,35] Although the effectiveness of the concept regarding improvement in HH compliance still awaits formal evaluation, our nudge nevertheless represents a promising new avenue in which long-lasting positive behavior and subsequent sustained reduction in NI may be achieved.

THE CONCEPT OF "ZERO" NI IN THE NICU: HOW ATTAINABLE IS THIS CREDO?

Nosocomial infections represent a serious public health issue. A number of interventions reported in the literature have shown dramatic decreases in incidence rates, in particular CLABSI. However, the stark reduction in NI rates, sometimes down to near zero for brief periods as successfully demonstrated by Pronovost et al. (2006), has led to the flourishment of the so far elusive credo of 'zero risk.' [29,36,37] While our moral duty to avoid all forms of patient harm has led to an increase in the number of hospitals approaching this idealistic threshold, the question remains whether 'zero' NI is in fact a realistic goal to set, and indeed there are several reasons why the zero-risk concept is precarious. First, the zero-risk credo seems to be incongruent with the actual situation as defined by the patient-medical procedure-hospital environment interface. The risk of NI is multifactorial, comprising of a combination of the patient's underlying condition, disease severity and associated (invasive) medical procedures, as well as the length of hospital stay. Any performed procedure or stay in an intensive care unit will always be a cause of possible harm to a (high-risk) patient, as the simple reality of critical care medicine involves performing procedures within the milieu of a hospital ward teeming with pathogenic organisms and patients that are, themselves, not sterile. The mean infection rate in any intensive care unit, even when adjusted for the duration of risk exposure, will depend on the case-mix, being close to zero when the majority of patients receive low-risk care and higher, if care is more invasive. Moreover, smaller wards with fewer NICU beds and central-line days may more easily reach the zero-infection threshold, leading the incorrect perception that no opportunity for further improvement exists.[38] Thus, while it may be possible to report zero infections for a particular unit for a defined period of time, such an ideal situation is not likely to be sustainable, as the risk will remain in units that deal with the most critically-ill patients. A second reason for casting doubt on the zero NI credo is our still relatively limited understanding of the disease pathogenesis and routes of transmission. It remains difficult to decipher why certain patients do develop a NI while others do not, despite the deliverance of care according to good practice guidelines. It may well be rather naïve to believe that NIs are preventable through mere hand and skin antisepsis, especially in the NICU where certain infections such as CLABSIs may be caused by bacterial or fungal intestinal translocation. Moreover, the use of empiric antibiotic therapy and presence of immature host defenses are additional confounding factors in neonates admitted to the NICU. As such, and even though very low rates of CLABSI are not unachievable, we should be realistic about our ability to reach and sustain zero-risk periods and learn to adequately differentiate between risk reduction and zero risk.

FINAL CONCLUSIONS

This thesis provides a detailed overview of the current epidemiology of neonatal NI, including CLABSI. While highlighting the importance of this serious complication, it has laid the foundation for the development and evaluation of several novel prevention and reduction strategies. The incidence of sepsis among certain neonatal subpopulations such as neonates with hemolytic disease of the fetus and newborn remains high, illustrating the need to re-calibrate indications for central-line placement and overall CLABSI prevention measures. In contrast to what was hypothesized, a significant positive effect of several interventions and changes in clinical practice, including the implementation of single-room care and a comprehensive multi-modal strategy, could not be supported. On the other hand, support was found for behavioral change tools such as 'nudges' which seem to be a more promising avenue in the reduction of NI, providing such tools can be tailored to the clinical micro-system and context-specific needs of NICU healthcare workers. Furthermore, nationwide CLABSI surveillance provided a unique insight into the current (national) burden of neonatal CLABSI in The Netherlands, although the optimization of digital infrastructures, data availability and accessibility are urgently needed to reliably perform forthcoming benchmarking initiatives. Even though much progress has been made, we are far from done in the battle against neonatal NI.

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