Antimicrobial stewardship and infection prevention in the neonatal intensive care unit

Hoeven, A. van der

CHAPTER 8

Discussion

Discussion

The research described in this thesis aimed to evaluate various aspects of neonatal infections, including reducing antibiotic treatment duration, improving diagnostics, and the impact of ward design on colonization with and transmission of multidrug-resistant organisms.

Reducing antibiotic treatment duration

Antibiotic treatment is a critical component of neonatal care, it is used annually in at least 4000 infants in the Netherlands for treatment of suspicion of early and late onset neonatal sepsis. National and international guidelines are used, in combination with sepsis calculators to identify infants at risk based on clinical symptoms and risk factors.[1-3] However, these tools do not have optimal nor identical sensitivity and specificity and tend to err on the side of caution, given that failure to treat an infection promptly and adequately can lead to severe consequences.[4,5] This inevitably leads to overtreatment, given that only 1 out of 50 to 100 neonates treated with antibiotics eventually has a culture-proven early-onset sepsis, see **Figure 1**.[6,7]

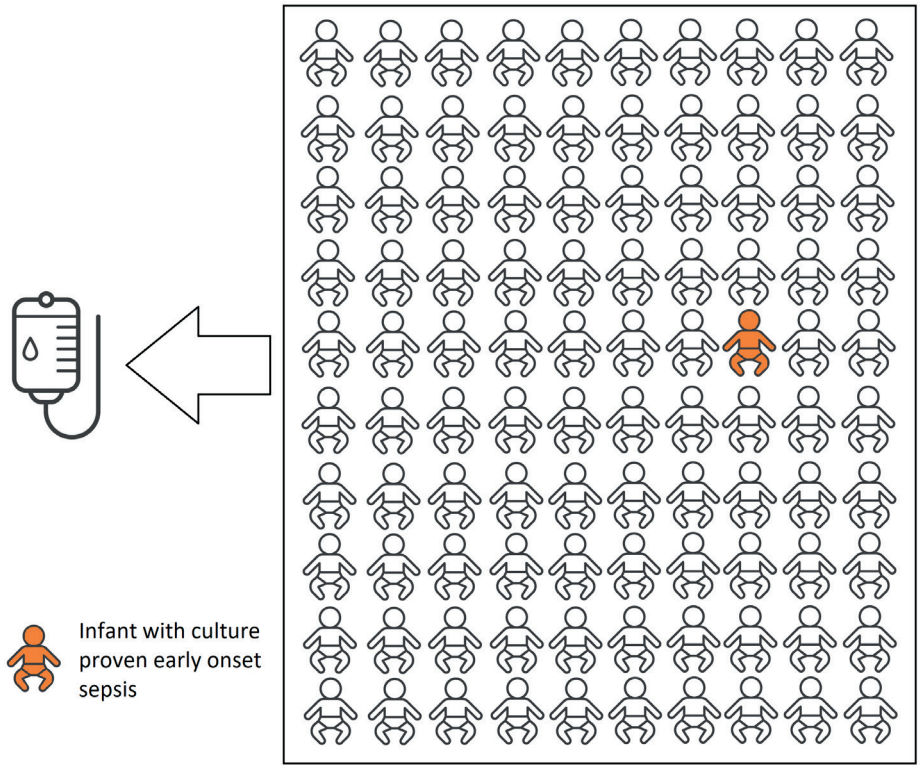

Figure 1. Overtreatment in infants with early onset sepsis. Adapted from Stocker et al.[6]

Given this scenario, once antibiotics are initiated, ongoing assessment is crucial to determine the necessity of continued treatment. The first chapters (**Chapters 2 and 3**) of this thesis presented findings regarding the evaluation timepoint of stopping antibiotics. At 24 hours after onset of a suspected infection, a combination of blood culture results, CRP and clinical signs of infection could safely rule out culture proven early onset neonatal sepsis, whereas a combination of blood culture results and CRP could rule out culture proven late onset neonatal sepsis.

Various studies employed different optimal timepoints at which the decision to discontinue antibiotic treatment can be made.[8,9] Whether this timepoint is at 24 or 36 hours after the suspicion of an infection, the crucial aspect is that this evaluation moment is consistently present at an early stage in every case where an infant is suspected of having an infection. Successful implementation of evaluation timepoints, ensuring ongoing assessment throughout the duration of antibiotic treatment, holds the potential not only to streamline antibiotic usage, but also to reduce hospitalization duration in a subset of infants. Additionally, there are new developments that enable children with neonatal infection to complete their antibiotic treatment at home, either intravenously or orally.[10]

Moreover, the impact of a shorter antibiotic duration extends beyond the immediate clinical realm. Evidence suggests that a briefer course of antibiotics results in less disruption to the newly developing microbiome in neonatal patients.[11,12] This reduction in microbial disturbance is vital for maintaining the delicate balance of the microbiota and may have long-term implications for the child's health. In addition, less antibiotic exposure for patients in the neonatal intensive care unit (NICU), might reduce the development of antibiotic resistance and outbreaks with drug resistant microbes. As we strive for a more judicious use of antibiotics, another crucial consideration is identifying the least harmful antibiotic options. Evaluating the safety profiles of different antibiotics in neonatal populations is essential to minimize adverse effects and long-term consequences. Future research should delve deeper into determining which antibiotics pose the least harm while maintaining efficacy.[13]

Improving diagnostics

The landscape of diagnostic techniques has seen significant advancements with the integration of metagenomic next-generation sequencing (mNGS) in the modern micro-biological laboratory. In **Chapter 4** the advantage of a culture-free, broad-range 16S rRNA gene next-generation sequencing platform is shown in infants with suspicion of bacterial meningitis. The platform detected and identified bacteria present within cerebrospinal fluid (CSF) samples that were not always identified using conventional bacterial culture methods, supporting the clinical diagnosis of meningitis. Alternatively, the platform confirmed the absence of 16S rRNA gene copies in culture-negative samples, making the diagnosis of meningitis even less likely. This would facilitate the decision to discontinue antibiotics for a presumed case of meningitis.

Currently applied to CSF samples, this technology presents opportunities for expansion, including the potential analysis of blood samples and the exploration of viral pathogens in neonatal infections.[14]

mNGS has the potential advantage of enabling broad detection of all pathogens; identifying not only bacteria, but also viruses, fungi, and difficult-to-culture bacteria. Furthermore, it is not only possible to demonstrate the presence of bacteria, but it also provides insights into relevant properties, including the susceptibility of the identified bacteria to antibiotics, for instance, through the detection of resistance genes. However, one of the primary challenges for wider adoption of mNGS is the optimization of the turn-around time. Enhancing the efficiency of sample processing, sequencing, and data analysis is essential to make mNGS a more practical and more timely diagnostic tool, especially in acute clinical settings. The economic feasibility of implementing mNGS is a critical factor for its integration into routine diagnostics. Identifying ways to reduce costs associated with reagents, equipment, and data analysis will contribute to making mNGS more accessible and widely applicable.

Prevention of transmission

A detailed epidemiological overview of hospital acquired neonatal infections in our facility is provided in **Chapter 5**, revealing that nearly 1 out of 5 prematurely born infants acquires one or more episodes of nosocomial bloodstream infections during admission to the NICU. Benchmarking this data could facilitate the evaluation of potential interventions aimed at reducing the incidence of hospital-acquired infections, particularly line-associated infections. Among the infants in our NICU, a colonization rate of 3.2% with multidrug-resistant organisms (MDRO) has been observed. The transition from an open bay unit to single room units (SRU) did not yield a reduction in the prevalence of this colonization (**Chapter 6**). In addition, the transition to single room units did not reduce the number of cgMLST proven clusters of MDRO with an epidemiological link, suggesting that nursing infants in SRU is not protective against MDRO-acquisition (**Chapter 7**).

As ward design was not helping in minimizing the spread of MDRO in our study, other options are to be considered. While the prevalence of MDRO carriage in our NICU is relatively low, understanding the specific risks of acquiring MDRO are essential. Identifying these risk factors early on presents an opportunity to proactively manage potential challenges. Both the hospital environment (NICU) and healthcare workers contribute to the acquisition and subsequent transmission of MDROs. Furthermore, caregivers also constitute a source of MDRO carriage. Screening of mothers, fathers, and other caregivers with risk factors, such as a history of international travelling during or just before pregnancy, could provide valuable insights. This becomes especially pertinent in pregnancies where there is an increased likelihood of premature birth and thus admission to the NICU, as seen in multiples or infants with intrauterine

abnormalities. Awareness of parental MDRO carriage allows healthcare providers to tailor infection prevention strategies and provide timely and targeted interventions. This anticipatory approach ensures that, from the onset, infants born to parents with MDRO carriership receive optimal and tailored treatment in the event of an infection. While early identification of MDRO carriage in parents offers clinical advantages, it is imperative to acknowledge and address the potential psychosocial impact. Communicating such information to parents requires sensitivity, taking into account the psychological effects of knowing their carrier status and the subsequent management of their child. Balancing the clinical benefits with the emotional well-being of the parents is crucial in implementing effective and ethical screening strategies.

In the pursuit of innovative infection prevention strategies in the NICU, it is essential to consider alternative options. One promising option is the reinforcement of the neonatal microbiome as a preventive measure against MDRO. Administering probiotics, for instance, offers a means to bolster the microbiome, potentially creating an environment less conducive to MDRO colonization in the gastrointestinal tract.[15] This approach seeks to manipulate the microbial balance to limit opportunities for MDROs to establish residence in the neonatal gut. Probiotics contribute to a reduction in the incidence of necrotizing enterocolitis in neonates and may potentially decrease the occurrence of sepsis; however, they do not lead to a decrease in the number of line infections.[16-18] Further research is necessary to assess whether administration of probiotics may result in a reduction of sepsis caused by antibiotic-resistant bacteria.

Conclusions

At present, too many infants are receiving prolonged courses of antibiotics. In the future, improvement is both possible and necessary. This can be accomplished by implementing evaluation timepoints at an early stage and discontinuing antibiotics where feasible. The discontinuation of antibiotics can be facilitated by the development and implementation of testing methods such as mNGS, which can provide increased certainty in detecting or ruling out an infection. Furthermore, the number of children with an MDRO infection must be further limited by continuous optimization of infection prevention measures. This thesis has contributed to the reduction of antibiotic treatment duration in infants suspected of neonatal sepsis in the NICU and has provided insight that physical barriers around a patient do not shield the patient from acquiring MDRO carriage.

Recommendations for future research:

1. **Reducing antibiotic treatment duration:**

    - Further investigation is needed to optimize and standardize the evaluation timepoints for discontinuing antibiotics in neonatal cases. This includes exploring alternative biomarkers and assessing the safety profiles of different antibiotics, aiming for a more judicious and effective use of antibiotics in neonatal populations.

2. **Improving diagnostics:**

    - Future research should focus on optimizing turn-around time for mNGS to make it a more practical and timely diagnostic tool in acute clinical settings. Additionally, economic feasibility should be addressed by identifying ways to reduce costs associated with reagents, equipment, and data analysis, making mNGS more accessible and applicable in routine diagnostics.

3. **Prevention of transmission:**

    - Given the limited impact of ward design on MDRO transmission, alternative strategies are needed. Screening parents and caregivers, particularly those with risk factors, should be considered to identify potential carriers and implement tailored infection prevention strategies.

References

1 Prevention and treatment of early onset sepsis. https://www.nvog.nl/wp-content/uploads/2018/02/Preventie-en-behandeling-van-early-onset-neonatale-infecties-1.0-07-06-2017.pdf (2017).

2 National Institute for Health and Care Excellence. Neonatal infection (early onset): antibiotics for prevention and treatment. (2012).

3 Infection Probability Calculator - Neonatal Sepsis Calculator, (https://neonatalsepsiscalculator.kaiserpermanente.org/).

4 Snoek L, van Kassel MN, Krommenhoek JF et al. Neonatal early-onset infections: Comparing the sensitivity of the neonatal early-onset sepsis calculator to the Dutch and the updated NICE guidelines in an observational cohort of culture-positive cases. EClinicalMedicine (2022).

5 Morris R, Jones S, Banerjee S et al. Comparison of the management recommendations of the Kaiser Permanente neonatal early-onset sepsis risk calculator (SRC) with NICE guideline CG149 in infants >/=34 weeks' gestation who developed early-onset sepsis. Arch Dis Child Fetal Neonatal Ed (2020).

6 Stocker M, Klingenberg C, Naver L et al. Less is more: Antibiotics at the beginning of life. Nat Commun (2023).

7 Giannoni E, Dimopoulou V, Klingenberg C et al. Analysis of Antibiotic Exposure and Early-Onset Neonatal Sepsis in Europe, North America, and Australia. JAMA Netw Open (2022).

8 Stocker M, van Herk W, El Helou S et al. C-Reactive Protein, Procalcitonin, and White Blood Count to Rule Out Neonatal Early-onset Sepsis Within 36 Hours: A Secondary Analysis of the Neonatal Procalcitonin Intervention Study. Clin Infect Dis (2020).

9 Stocker M, van Herk W, El Helou S et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet (2017).

10 Keij FM, Schouwenburg S, Kornelisse RF et al. Oral and Intravenous Amoxicillin Dosing Recommendations in Neonates: A Pooled Population Pharmacokinetic Study. Clin Infect Dis (2023).

11 Tamburini S, Shen N, Wu HC et al. The microbiome in early life: implications for health outcomes. Nat Med (2016).

12 Ni J, Friedman H, Boyd BC et al. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. BMC Pediatr (2019).

13 Reyman M, van Houten MA, Watson RL et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. Nat Commun (2022).

14 Agudelo-Perez S, Fernandez-Sarmiento J, Rivera Leon D et al. Metagenomics by next-generation sequencing (mNGS) in the etiological characterization of neonatal and pediatric sepsis: A systematic review. Front Pediatr (2023).

15 Wieers G, Verbelen V, Van Den Driessche M et al. Do Probiotics During In-Hospital Antibiotic Treatment Prevent Colonization of Gut Microbiota With Multi-Drug-Resistant Bacteria? A Randomized Placebo-Controlled Trial Comparing Saccharomyces to a Mixture of Lactobacillus, Bifidobacterium, and Saccharomyces. Front Public Health (2020).

16 Patel RM,Underwood MA. Probiotics and necrotizing enterocolitis. Semin Pediatr Surg (2018).

17 AlFaleh K,Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev (2014).

18 Dermyshi E, Wang Y, Yan C et al. The "Golden Age" of Probiotics: A Systematic Review and Meta-Analysis of Randomized and Observational Studies in Preterm Infants. Neonatology (2017).