Variation in antibiotic use in neonatal intensive care units in the Netherlands

T. B. Yves Liem1*, Tannette G. Krediet2, André Fleer3, Toine C. G. Egberts1 and Carin M. A. Rademaker1

1Department of Clinical Pharmacy, Wilhelmina Children’s Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands; 2Department of Neonatology, Wilhelmina Children’s Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands; 3Eijkman-Winkler Centre of Microbiology, Infectious Diseases and Inflammation, University Medical Centre Utrecht, Utrecht, The Netherlands

*Corresponding author. Tel: +31-88-755-7218; Fax: +31-88-755-5316; E-mail: y.liem@umcutrecht.nl

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Objectives: To examine the variation in quantity and classes of antibiotics used in all 10 tertiary care neonatal intensive care units (NICUs) in the Netherlands during 2005.

Methods: We collected data from all tertiary care NICUs in the Netherlands on clinical and demographic characteristics and the type and quantity of systemic antibiotic use [expressed as defined daily doses (DDD)/100 admissions] in 2005. Antibiotics were ranked by volume of DDDs, and those antibiotics which accounted for 90% of the total volume of use [drug utilization (DU) 90%] were noted.

Results: Antibiotic consumption ranged from 130 to 360 DDD/100 admissions. In total, 9–24 different antibiotics were used, of which 3–10 were in the DU90% segment.

Conclusions: By comparing antibiotic use in Dutch NICUs we found a considerable variation in the number of different antibiotics used and in the total amount of antibiotic use. Further exploration of the opportunities to reach consensus in antibiotic policy, and to increase attention to antibiotic stewardship, is recommended.

Keywords: NICUs, neonates, antibiotic consumption

Introduction

Antibiotics are the most frequently used medicines in neonatal intensive care units (NICUs).1–6 High antibiotic exposure rates (75%–94%) have been reported; they are most probably based on the common practice of administering antibiotics, pending bacterial culture results, to sick neonates and to neonates with risk factors for developing infectious diseases.6

It is well recognized that the total amount of antibiotic use as well as the number of patients treated with antibiotics are risk factors for the selection of resistant bacteria. Detailed quantitative and qualitative knowledge of antibiotic use is essential in order to implement strategies for reducing the overuse and misuse of antibiotics and thereby address the threat posed by resistant microorganisms.7,8 Evaluation of antibiotic use is therefore important, since the prevalence of hospital-acquired antibiotic-resistant microorganisms is increasing in hospitalized infants.9

Previous studies have demonstrated a large variation in outpatient and inpatient antibiotic use among European countries.7,10 This variation is caused not only by differences in patient mix but also by differences in patterns of prescribing based on differences in physicians’ and patients’ attitudes to antibiotics, as well as cultural and social factors, and healthcare systems. This supports the belief that antibiotics could be used more effectively in many countries.7

In this national multicentre study, the aim was to examine the variation in quantity and classes of antibiotics used in all 10 tertiary care NICUs in the Netherlands during 2005.

Materials and methods

Setting

This study included all 10 tertiary care NICUs in the Netherlands. These NICUs are distributed geographically all over the Netherlands and are responsible for the treatment of the entire Dutch target population. The corresponding hospitals of the NICUs involved in this study were: Academic Medical Centre (AMC), Amsterdam; Free University Medical Centre (VUmc), Amsterdam; University Medical Centre Groningen (UMCG), Groningen; University Hospital Maastricht, Maastricht (azM); Leiden University Medical Centre (LUMC), Leiden; Erasmus University Medical Centre (Erasmus MC), Rotterdam; Maxima Medical Centre (MMC), Veldhoven; Isala Clinics, Zwolle; University Medical Centre St Radboud (UMCN), Nijmegen; and University Medical Centre Utrecht, Wilhelmina Children’s Hospital.
Variation in antibiotic use in NICUs

Data collection

Collection of clinical and demographic characteristics of NICUs

All data on the various clinical and demographic characteristics of NICUs were collected from the national neonatology registry. This registry belongs to the professional organization of paediatricians/neonatologists and is part of a larger network of medical registries owned by the Netherlands Perinatal Registry (PRN-foundation). The PRN-foundation is a joint effort of the four professional organizations that provide perinatal care in the Netherlands.

The numbers of admissions per NICU in 2005 were collected. Each NICU has its own patient mix which was characterized by the following patient characteristics: birth weight, length of stay and neonatal sepsis. The criteria for neonatal sepsis are identical for all NICUs in the Netherlands. Neonatal sepsis is defined by the occurrence of clinical signs of infection and a positive blood culture. Infants with clinical signs of sepsis including suggestive laboratory parameters, but without a positive blood culture, are not considered as having proven sepsis.

Collection of data on antibiotic use

Data on the quantitative and qualitative use of antibiotics in 2005, in all 10 tertiary care NICUs, were collected by means of a survey distributed to the corresponding hospital pharmacies by the investigator. Data represented the dispensing of antibiotics from the hospital pharmacies to the NICUs. The hospital pharmacies were requested to report on the annual total volume of prescription of antibiotics for systemic use in the 2005 group J01 of the Anatomical Therapeutic Chemical Classification (ATC) system.

Total antibiotic use was expressed in defined daily doses (DDDs) per 100 admissions. The ATC/DDD classification from the WHO, version 2009, was used to calculate the number of DDDs of the various antibiotics. Neonatologists of all NICUs were asked for their local treatment guidelines on neonatal sepsis, meningitis and necrotizing enterocolitis (NEC).

Data analysis

We analysed the quantity of total antibiotic use for each NICU expressed in DDD per 100 admissions. Furthermore, for each NICU, antibiotics were ranked by volume of DDDs and the number of antibiotics that accounted for 90% and 100% of the total volume, i.e. the DU90% and DU100%, respectively (where DU stands for drug utilization). Finally, for each NICU we measured which part of the number and volume of antibiotic use included those antibiotics mentioned in the treatment guidelines in place at that specific NICU.

Results

Table 1 shows the clinical and demographic characteristics of each NICU in 2005. The number of admissions per NICU in 2005 ranged from 278 to 585. The proportion of infants with extremely low birth weight (ELBW) <1000 g varied between 6% and 15%. In all NICUs the highest percentage of infants were in the category of birth weight >1500 g (range 56%–72%). Furthermore, there was a substantial variation in the proportion of infants with sepsis (range 10%–24%).

Treatment guidelines for neonatal sepsis were in place at all NICUs (Table 1). Treatment guidelines for meningitis and NEC were in place at seven NICUs. All NICUs, except one, used amoxicillin, amoxicillin/clavulanic acid or benzylpenicillin in combination with gentamicin or amikacin for treatment of early-onset sepsis. For the treatment of late-onset sepsis, the NICUs used the following antibiotics: a penicillin derivative (benzylpenicillin, flucloxacillin, amoxicillin/clavulanic acid) in combination with gentamicin or ceftazidime, ceftazidime in combination with vancomycin, cefazolin in combination with gentamicin, or monotherapy with teicoplanin, vancomycin, cefazolin or flucloxacillin.

Table 2 shows the overall consumption of antibiotics; NICU G had the highest total antibiotic use (360.2 DDD/100 admissions), whereas NICU E had the lowest (129.9 DDD/100 admissions) (mean 222.1 DDD/100 admissions).

In total, 9–24 different antibiotics were used in the participating NICUs. In the DU90% segment a mean of 6.1 different antibiotics was found (range 3–10). Figure 1 shows the overall patterns of antibiotic use in the participating NICUs in 2005. All NICUs used penicillins (amoxicillin, amoxicillin/clavulanic acid, benzylpenicillin, ampicillin) in the DU90% segment. Additionally, the DU90% segment in 8 of 10 NICUs included aminoglycosides (mostly gentamicin). NICU I was the only NICU using a first-generation cephalosporin (cefarolin) in the DU90% segment, whereas 4 out of 10 NICUs used a third-generation cephalosporin (cefotaxime, ceftazidime) in their DU90% segment. Apart from one NICU, all other NICUs used a glycopeptide in their DU90% segment (seven NICUs used vancomycin, whereas two NICUs used vancomycin and teicoplanin). Finally, only three NICUs (B, C and J) used quinolones (ciprofloxacin).

Table 2 also shows the number of antibiotics that were mentioned in the treatment guidelines on neonatal sepsis, meningitis and NEC. In NICU J, 4 antibiotics (25%) were both used and mentioned in the treatment guidelines, whereas this number was 10 (77%) in NICU I. In the majority of the NICUs (6 out of 10), extended-spectrum penicillins (amoxicillin and amoxicillin/clavulanic acid), β-lactamase-resistant and -sensitive penicillins (flucloxacillin and benzylpenicillin, respectively), aminoglycosides (gentamicin and amikacin), cephalosporins (first- and third-generation) and glycopeptides (vancomycin and teicoplanin) were both used and mentioned in the relevant treatment guidelines.

In addition, the quantity of antibiotic use mentioned in the treatment guidelines in NICU D was 63.0 DDD/100 admissions (26% of total antibiotic use), whereas this was 127.3 DDD/100 admissions (98% of total antibiotic use) in NICU E.

Discussion

This is the first study to analyse and compare quantitative and qualitative antibiotic use in all NICUs in a single country, in this case the Netherlands. We have demonstrated a considerable variation in the number of different antibiotics used in NICUs, as well as in the total antibiotic use expressed in DDD/100 admissions. In our study the number of antibiotics in the DU90% segment ranged from 3 to 10. It is remarkable that in a relatively small country such as the Netherlands, one NICU used only three antibiotics in the DU90% segment whereas another NICU used more than twice as many antibiotics in this segment.
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NEC, necrotizing enterocolitis; IQR, interquartile range; NA, not available.
*Two NICUs were part of a general hospital; the other eight NICUs were part of a university medical centre.
The DU90% has been proven to be an important tool to assess the quality of drug prescription. In addition to the number of drugs in the DU90% segment, the presence of, and adherence to, treatment guidelines may serve as general quality indicators. In our study we have demonstrated that each NICU had treatment guidelines on neonatal sepsis at least, and the majority had treatment guidelines on meningitis and NEC as well. Overall, the treatment guidelines on early-onset sepsis, meningitis and NEC were fairly similar, whereas those on late-onset sepsis varied widely. Although vancomycin is generally recommended, several NICUs used penicillin derivatives or first-generation cephalosporins. Fernando et al. found a fairly comparable pattern by comparing antimicrobial policies in 200 British and Irish neonatal units.

In comparison with other countries (e.g. the USA and UK), the recommended treatment guidelines for neonatal sepsis, meningitis and NEC in the participating NICUs in the Netherlands were more or less similar. It is difficult to explain why there is such a large variation between the number of different antibiotics used in each NICU as shown in Figure 1. One could hypothesize that this might be explained by the emergence of resistance in specific microorganisms in a particular NICU, resulting in usage of a wide range of different antibiotics. Although antibiotic resistance data for each individual NICU were not available at the time of our study, adjusting the treatment guidelines was not necessary according to antimicrobial resistance data from the Netherlands, as published in the annual report ‘Nethmap’ by the National Institute of Health (RIVM) and the Dutch Working Party on Antimicrobial Policy (SWAB). Another reason could be the presence and influence of antibiotic stewardship on the prescription of antibiotics in an NICU. Antibiotic stewardship has been shown to contribute positively to the accuracy of antibiotic therapy. In addition, stewardship of the empirical use of antibiotic regimens does matter in the control of antimicrobial resistance in an NICU.

As far as we know there have been very few studies comparing the differences in antibiotic use among NICUs. Nevertheless, several studies have recently compared and reported on antibiotic use in different paediatric intensive care units (PICUs).
in specific types of paediatric wards,26,27 in hospitalized paediatric inpatients28 and in numerous children's hospitals in one country.29–33 In comparison with a few of these previous studies, the mean number of antibiotics in the DU90% segment in NICUs in the Netherlands was relatively low, i.e. six. For example, in China this number varied between 16 and 20,30 in Russia it was 8 (out of a total of 22 antibiotics used) and in Croatia it was 11 (out of a total of 35).29

Our study had some limitations. First, we measured antibiotic use in the NICUs in adult DDDS. The recently proposed way to measure antibiotic use in children in ‘days of therapy’34 was not possible since data on antibiotic use of the participating NICUs on the patient level were not available. Since the range of body weight of the neonatal population did not vary that much, antibiotic dosages did not fluctuate. Moreover, we compared the differences in antibiotic use between different NICUs. Therefore, measuring antibiotic use in NICUs in DDD/100 admissions was legitimate. Secondly, data on antibiotic use were based on the purchase data of the hospital pharmacy. It only gives a rough estimate of antibiotic use, as it is not unusual in a neonatal population to use one vial of antibiotic for more than one infant. However, there is waste of unused antibiotics, which could be measured by collecting all discarded vials and aspirating the contents into syringes,35 a method not applied in the present study. Thirdly, our study period was just 1 year (i.e. 2005). Nevertheless, the antibiotic policies in the NICUs have not changed from 2005 to the present day. Therefore, data on antibiotic use investigating total antibiotic use in different NICUs over a period of 1 year were considered sufficiently reliable to make comparisons. It is very important to implement antibiotic stewardship across all NICUs in the Netherlands and to make an effort to harmonize antibiotic prescribing.

In conclusion, we found a considerable variation in the total amount of antibiotic use as well as in the number of antibiotics used in all NICUs in the Netherlands. We recommend further exploration of the opportunities to achieve uniformity in antibiotic policy for the treatment of infections in NICUs in the Netherlands. Moreover, antibiotic stewardship is recommended to improve the accuracy of antibiotic treatment and to limit the use of antibiotics beyond that determined by the protocol.

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Transparency declarations
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