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# Reduced antibiotic use in extremely preterm infants with an antimicrobial stewardship intervention

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## ABSTRACT

**Introduction** Excessive administration of antibiotics to preterm infants is associated with increased rates of complications. The purpose of the study was to evaluate the effect of an antimicrobial stewardship intervention on antibiotic use in extremely preterm infants.

**Design, setting, patients and intervention** A before and after study of infants born at ≤28 weeks' gestational age was performed in the neonatal intensive care unit of Queen Silvia's Children's Hospital, Gothenburg, Sweden. Retrospective analysis of the baseline period (January–December 2014) guided the development of a limited antimicrobial stewardship intervention. The intervention consisted of updated local guidelines with a focus on shortened and standardised treatment duration plus increased access to infectious disease consultant advice. It was fully implemented during the intervention period (October 2017–September 2018).

**Objective** Primary aim was to compare antibiotic use, defined as antibiotic treatment days per 1000 patient-days, between the two periods, and the secondary aim was to evaluate the number of days with meropenem-based regimens before and after the intervention.

**Results** We included 145 infants with a median birth weight of 870 g and median gestational age of 26 weeks. The baseline period comprised 82 infants and 3478 patient-days, the intervention period comprised 63 infants and 2753 patient-days. Overall antibiotic use (treatment and prophylaxis) was 534 versus 466 days per 1000 patient-days during the baseline and intervention periods, respectively. Antibiotic treatment days decreased from 287 to 197 days per 1000 patient-days. The proportion of meropenem-based regimens was 69% versus 44%, respectively. No increases in mortality or reinitiation of antibiotics were seen.

**Conclusions** Implementation of a limited antimicrobial stewardship intervention anchored in analysis of previous prescription patterns can contribute to safe decreases in antibiotic use in extremely preterm infants.

### What is known about the subject?

- Antibiotics are indispensable in the care of newborn infants, but excessive use is associated with increased complications. Antimicrobial stewardship interventions can reduce inappropriate antibiotic treatment.

### What this study adds?

- A limited antimicrobial stewardship intervention contributed to reduced use of meropenem-based therapy in extremely preterm infants with a very high risk of neonatal sepsis.

## INTRODUCTION

Sepsis and other bacterial infections are frequent in neonatal intensive care of preterm infants. Babies that weigh <1500 g at birth (very low birth weight) have on average 1.2 episodes of suspected sepsis during their first months of life, and 15% suffer from confirmed late-onset sepsis.[1] The prevalence of infections is even higher in extremely low birthweight infants (birth weight <1000 g), with confirmed bloodstream infections occurring in around 40%.[2] Timely administration of antibiotics is important, but the symptoms and signs of infection in neonates are non-specific. This leads to high levels of antibiotic consumption in neonatal intensive care units,[3] associated with increased rates of complications[4–6] and a risk of emergence of multidrug-resistant organisms.[7–9] Antimicrobial stewardship programmes in neonatal units have been introduced around the world,[10–14] but published results of stewardship programmes for extremely preterm infants, where the complication and infection rates are highest, are scarce.

### Objectives

The primary aim was to determine the extent of antibiotic use and compare the number of treatment days during two study periods before and after implementation of an antimicrobial stewardship intervention for extremely preterm infants, born at ≤28 weeks' gestational age. The secondary aim was to evaluate the impact of the antimicrobial

stewardship intervention on the use of meropenem, a carbapenem-class antibiotic.

## METHODS

### Study design and participants

This was a before and after study of an antibiotic stewardship intervention for the treatment of systemic infections in extremely preterm infants, in a low-resistance setting. The antibiotic stewardship intervention was guided by a retrospective baseline surveillance of antibiotic use, which also served as historical control period. The outcome was evaluated by a repeated retrospective surveillance of antibiotic use in patients admitted during the first 12 months after the stewardship intervention was fully implemented. The retrospective baseline surveillance was conducted during 2016 with evaluation and guideline design during early 2017. The programme was implemented on 1 September 2017 after a due process of review and approval by neonatology staff and leadership. Retrospective surveillance of the intervention period was performed in the second half of 2018. During the time between the study periods, no systematical changes of clinical practice regarding treatment or infection control were performed.

The main outcome measure was total days with antibiotic treatment for infection. Secondary outcomes were adequate duration of treatment and number of days with meropenem-based antibiotic treatment.

Infants born at ≤28 weeks' gestational age, admitted to the study unit, were included. Exclusion criteria were: immediate transition to palliative care following initial resuscitation (to avoid random effects on mortality not related to treatment) and incomplete electronic medical records. The neonatal unit at Queen Silvia's Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden is a level III, 38-bed ward including a 14-bed intensive care unit. The unit provides level III care for Region Västra Götaland (population 1.7 million). Pregnant women with preterm labour at less than 28 weeks of gestational age are transferred to the adjoining delivery room prior to delivery if possible. Patients return to regional units when the clinical situation is stabilised and they have reached a corrected gestational age of >28 weeks.

The background antibiotic resistance is low in Sweden. Nationally, methicillin-resistant *Staphylococcus aureus* made up 1% of invasive *S. aureus* isolates during the study period, while 3%–8% of invasive *Escherichia coli* and *Klebsiella* isolates produced extended-spectrum beta-lactamases (ESBL).[15] Rates in paediatric patients were similar.[16]

### Data collection

We did a retrospective baseline surveillance of all antibiotics (prophylactic and treatment) that were administered to all infants born at ≤28 weeks' gestational age, who were admitted during 2014 (1 January–31 December), which constituted the control period. The retrospective surveillance process was then repeated after the antimicrobial stewardship intervention was fully implemented, including all infants born at ≤28 weeks' gestational age admitted between 1 September 2017 and 31 August 2018, which constituted the intervention period.

Each infant's electronic medical record was reviewed for details on intravenous antibiotic use; blood culture results; results of other relevant cultures; clinical symptoms at initiation and relevant blood chemistry results. At the time of the study, key parts of the medical records were recorded on paper and subsequently scanned to electronic format after patient discharge. Background information on infants was also registered. Respiratory distress syndrome (RDS) was defined as respiratory distress with typical radiological findings and bronchopulmonary dysplasia (BPD) as the need for supplemental oxygen at 36 weeks' corrected gestational age. Patent ductus arteriosus was defined as having received medical or surgical treatment of ductus, and necrotising enterocolitis (NEC) as NEC stage ≥2A based on the modified Bell NEC staging criteria.[17]

Antibiotic treatment episodes were classified as: (1) culture-positive sepsis, bacteraemia with a recognised pathogen and clinical symptoms; (2) sepsis with coagulase-negative *Staphylococcus* spp (CoNS), bacteraemia with CoNS and fulfilled Yale-criteria for CoNS infection[18]; (3) culture-negative infections, negative or absent blood cultures but fulfilled criteria for clinical sepsis according to Lindquist *et al* (signs of infection (apnoea, bradycardia, gastric retention or hypothermia) with ≥1 of the following: interleukin (IL)-6 ≥1000 mg/L in infants less than 3 days of age, IL-6 ≥100 mg/L in infants ≥3 days of age, C reactive protein ≥20 mg/L, white cell count $<5 \times 10^9$/L or $>30 \times 10^9$/L),[19] documented skin infection, thrombophlebitis, NEC or other confirmed diagnosis; (4) unconfirmed infection, not fulfilling any of the above criteria.

Early-onset infection was defined as treatment started <72 hours of birth and late-onset infection as treatment started >72 hours of birth.

Length of antibiotic treatment was counted in days. A date with any intravenous antibiotic was counted as 1 day, regardless of the number of different antibiotics used during that day. When the infant received only one dose of antibiotics on a specific date, it was counted as 1 day of antibiotic treatment. Any antibiotics provided after transfer out to a level II unit were not included in the study. Patient-days was calculated as the number of days from date of admission to the neonatal ward at the study unit, up to date of discharge or transfer to a level II unit. Total antibiotic exposure was then calculated as the total number of treatment days divided by the total number of patient-days for all included patients.

### Baseline procedures

Recommended first-line treatment for early-onset sepsis was penicillin G plus an aminoglycoside. For late-onset sepsis, the recommended first-line treatment was

cloxacillin plus an aminoglycoside, with vancomycin substituted for cloxacillin in extremely preterm infants. Escalation of therapy to meropenem-based regimens was performed at the discretion of the treating neonatologist. In cases with severe clinical presentation (hypotension with signs of insufficient organ perfusion or suspected NEC) and low gestational age (<28 weeks), first-line empirical treatment consisted of meropenem plus vancomycin. Fluconazole was added prophylactically to all patients born <27 weeks' gestational age who had central catheters or were treated with antibiotics. Cloxacillin prophylaxis (50 mg/kg administered two times per day) was recommended to all included patients with central catheters.

Blood cultures were compulsory before initiation of intravenous antibiotics. Lumbar puncture was performed if meningitis was suspected. Catheter removal was recommended in infections with *S. aureus*, *Candida* spp or gram-negative rods.

The indication for empirical antibiotics was clinical sepsis and defined symptoms of infection and ≥1 of the following: IL-6 ≥1000 mg/L in infants less than 3 days of age, IL-6 ≥100 or rising in infants ≥3 days of age or C reactive protein ≥20 mg/L.

There were no site-specific treatment protocols for confirmed, culture-positive sepsis or other defined clinical infections during the baseline period. Decisions on adjustments of antibiotics and treatment length were made at the discretion of the attending neonatologists.

### Antimicrobial stewardship intervention

The study team consisted of three of the authors, of whom one was a neonatologist (EH) and two were infectious disease specialists (MS, LG). Detailed guidelines outlining drug choice and duration of treatment were developed, informed by the retrospective surveillance data. We focused on key areas that we could align with national guidelines and evolving international management traditions.[20 21] The intervention-specific updated guidelines are presented in tables 1 and 2. The updated guidelines were implemented following approval from the department head and the medical staff of the unit. The intervention commenced at a specific date after thorough information to the staff. During the study period, the study team met regularly with a focus on surveillance of the need of further education of the staff. The attending neonatologists retained the right to choose empirical therapy and to escalate therapy to more broad-spectrum regimens at their discretion, throughout the study period.

### Statistical analysis

Continuous variables were compared with the Mann-Whitney U test and proportions with $X^2$ test (two-tailed). Univariate linear regression was used to analyse serial observations. We used a multivariable linear regression model to control for confounding. A p value of <0.05 was considered significant. IBM SPSS V.25 software and the OpenEpi online statistical calculator (www.OpenEpi.com) were used for the calculations.

### Patient and public involvement

No patient or public involvement was part of this study, which was initiated and led by the clinical research team.

## RESULTS

There were 1867 infants admitted to the neonatal unit during the two observation periods. Of these, 158 infants were born at 28 full weeks' gestation or less (n=87 during the baseline period, n=71 during the intervention period) and constituted the sample population (figure 1). The majority of the patients were born at the study unit, but a few were born at other hospitals and transferred into the study unit after birth. A number of patients were transferred out to a level II regional unit before discharge home, 44/82 (54%) during the baseline period and 32/63 (51%) during the intervention period. Any antibiotics provided after transfer out to a level II unit were not included in this study. In the baseline period, five infants were excluded from analysis (three because of immediate palliative care after initial resuscitation; two because medical records were partially unavailable due to a lack of scanned paper charts). In the intervention

**Table 1** Clinical practice and recommendations for extremely preterm infants (<28 weeks' gestational age)

| | Before intervention | After intervention |
|---|---|---|
| Treatment duration | No specified duration times | Clearly specified duration times for culture-positive sepsis and other clinical entities (see table 2)<br>Treatment for suspected sepsis with negative cultures limited to 5 days |
| Removal of central lines | Recommendation to remove central lines in infections with *Staphylococcus aureus, Candida* spp and gram-negative rods | Strong recommendation to remove central lines in all verified infections |
| Lumbar puncture | At the clinician's discretion | Compulsory lumbar puncture in all patients with severe septic symptoms and in all late-onset gram-negative infections |
| Infectious diseases consultant | No regular infectious disease consultant | Scheduled visits two times a week by a senior infectious disease consultant |

Table 2 Guidelines on antimicrobial choice and treatment duration for confirmed infections

| Microorganism | Antimicrobial choice and treatment length* (days) |
|---|---|
| Methicillin-sensitive *Staphylococcus aureus* | Cloxacillin (7–10) |
| Methicillin-resistant *S. aureus* | Vancomycin (7–10) |
| Coagulase-negative *Staphylococcus* spp | Cloxacillin/vancomycin (5–7) |
| Group B *Streptococcus* (*Streptococcus agalactiae*) | Penicillin G (7–10) |
| Group A *Streptococcus* (*S. pyogenes*) | Penicillin G (7–10) |
| *S. pneumoniae* | Penicillin G (7–10) |
| *Enterococcus faecalis* | Ampicillin—if sensitive, otherwise vancomycin or pip/taz (10–14) |
| *E. faecium* | Vancomycin (10–14) |
| α-*Streptococcus* ex. *S. anginosus, mitis, intermedius,* etc | Penicillin G (7–10) |
| Gram-negative rods ex. *Klebsiellae, Escherichia coli, Proteus, Enterobacteriacae, Pseudomonas, Serratia* spp, *Salmonella, Shigella*<br>Non-ESBL-producing gram-negative rods | Based on resistance patterns and infectious disease consultant (10–14) |
| ESBL-producing gram-negative rods | Meropenem/pip/taz—based on resistance patterns and infectious disease consultant (10–14) |
| ESBL carba-producing gram-negative rods | Based on resistance patterns and infectious disease consultant (10–14), combination therapy is required |
| *Listeria monocytogenes* | Ampicillin as first choice otherwise<br>penicillin G in high dose or meropenem<br>(14–21) |
| *Haemophilus influenzae* | Ampicillin if sensitive or based on resistance patterns (7–10) |
| *Candida albicans/parapsilosis* | Liposomal amphotericin B, consult the infectious disease consultant (14–21) |
| Herpes simplex | Aciclovir, contact the infectious disease consultant (14–21) |
| Enterovirus | Consult the infectious disease consultant (10–14) |
| Cytomegalovirus | Ganciclovir intravenously/valganciclvir orally<br>Congenital infection 6 weeks–6 months, symptomatic postnatal infection 2–6 weeks<br>Contact the infectious disease consultant |
| **Type of infection** | **Treatment length (days)** |
| Sepsis | See above |
| Necrotising enterocolitis | 10–14, consider longer treatment |
| Skin infection | 5–7, consider transition to oral therapy |
| Urinary tract infection | 10 |
| Septic arthritis | 14–21 |
| Osteomyelitis | 21–28 |
| Meningitis, gram-negative bacteria | 21 |
| Meningitis other | 14–21 |

*For sepsis, unless stated otherwise.
ESBL, extended-spectrum beta-lactamases.

period, eight infants were excluded (three because of immediate palliative care after initial resuscitation, five because medical records were partially unavailable due to a lack of scanned paper charts). We were able to include 145 infants in the analysis and their characteristics are presented in table 3. There was an observation of more early deaths (within 24 hours) during the baseline period that did not reach statistical significance. Fewer infants had RDS during the intervention period. Fewer infants developed BPD, among those who could be evaluated (n=122; 23 patients were moved to level II units without electronic records before BPD could be diagnosed). No outbreaks or infections with multiresistant bacteria were noted during the baseline and intervention periods.

The outcome data are presented in table 4. The total antibiotic use decreased from 534 to 466 antibiotic

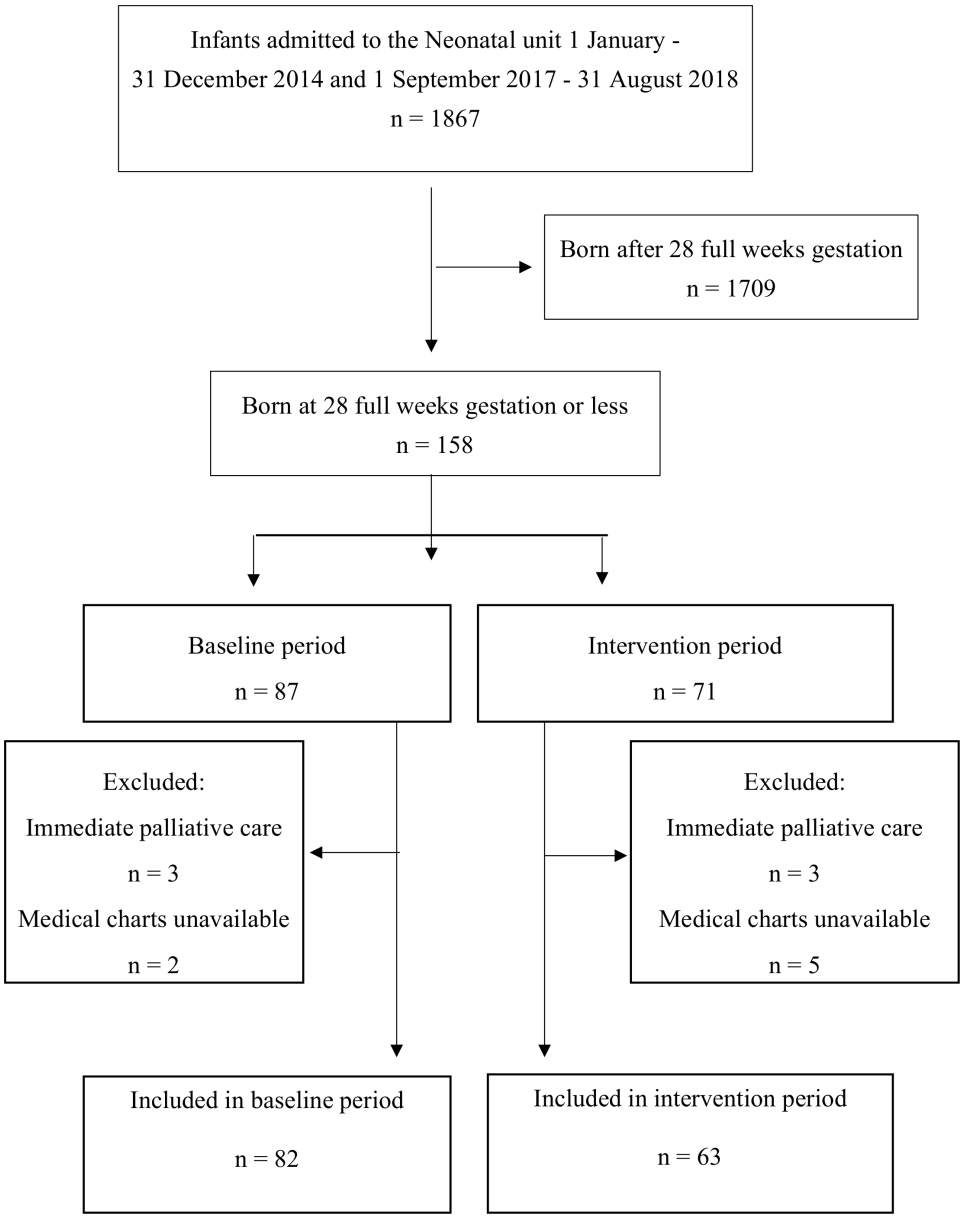


**Figure 1** Flow chart of included patients.

prophylaxis and treatment days per 1000 patient-days between the baseline and intervention periods. The intervention was targeted at antibiotic use for treatment, however, where we observed 90 treatment days less per 1000 patient-days, corresponding to a 31% decrease in antibiotic use. We found a statistically significant reduction in early reinitiations compared with the baseline period. The majority of treatment episodes were for late-onset neonatal infections (>72 hours after birth). Although the proportion of short treatments (<5 days) increased significantly, average treatment duration was similar in both periods for most infection types. Shorter treatment duration overall and for blood culture-negative infections were noted during the intervention period, but did not reach statistical significance (p=0.08 and 0.10, respectively). Antibiotic treatment days per patient-day fluctuated during the study periods, but without tendency to increase over time (figure 2). The number of lumbar punctures performed did not change between baseline and intervention periods (data not shown). Two infants had microbiologically confirmed meningitis, one during the baseline period (*Enterobacter cloacae*) and one during the intervention period (*Ureaplasma* spp).

To adjust for differences in severity of preterm complications, we performed a multivariable regression analysis that included variables with a univariate p value of <0.3 together with gestational age and duration of hospital stay (table 5). The intervention period remained independently associated with fewer days of antibiotic use in this model, with an adjusted estimate of 4.9 days less per infant. As expected, a higher gestational age at birth reduced the number of antibiotic days (around 3 days less per week) while a longer length of stay was associated with increases (1 more day with antibiotics per 4 days in hospital).

Table 3 Characteristics of patients in baseline and intervention periods

| | Baseline | Intervention | |
|---|---|---|---|
| | N=82 | N=63 | P value |
| Boys | 52 (63%)* | 39 (62%)* | 0.85 |
| Gestational age (weeks) | 26 (22–28)† | 26 (22–28)† | 0.37 |
| Birth weight (g) | 880 (440–2080) | 840 (395–1030) | 0.38 |
| <1500 | 80 (98%) | 63 (100%) | 0.51 |
| <1000 | 58 (71%) | 49 (78%) | 0.34 |
| Mortality within 24 hours | 5 (6%) | 1 (2%) | 0.23 |
| Respiratory distress syndrome | 77 (94%) | 51 (81%) | 0.03 |
| Bronchopulmonary dysplasia (BPD) | 51 (72%)‡ | 27 (53%)§ | 0.03 |
| Patent ductus arteriosus | 48 (50%) | 29 (46%) | 0.10 |
| Intraventricular haemorrhage, grade 3–4 | 9 (11%) | 9 (15%) | 0.56 |
| Necrotising enterocolitis | 8 (10%) | 4 (7%) | 0.49 |
| Surgically treated | 3 (4%) | 3 (5%) | 1.0 |
| Length of stay at study unit (days) | 33 (1–127) | 23 (1–149) | 0.33 |
| Total hospital stay including level II¶ (days) | 78 (1–219) | 76 (1–149) | 0.73 |

*N (%).
†Median (range).
‡BPD development could be evaluated in 71 of 82 patients.
§BPD development could be evaluated in 51 of 63 patients.
¶The total number of days the infant was admitted to a neonatal unit, including the time after the infant was transferred out to a level II neonatal unit.

The results for different antibiotic types are presented in figure 3. There were significant decreases in the number of treatment days per 1000 patient-days for meropenem and vancomycin (figure 3A). The distribution of antibiotic types used for treatment was altered, with a lower proportion of meropenem-based regimens and increased proportions of aminoglycosides and other more narrow-spectrum antibiotic types (figure 3B). The proportion of regimens that included vancomycin did not change.

## DISCUSSION

We found that a limited but tailored antimicrobial stewardship intervention with updated management guidelines contributed to a 31% decrease in antibiotic treatment among extremely preterm infants. Furthermore, the proportion of meropenem-based regimens decreased significantly, from almost 70% of treatments given to less than 45%. These changes were achieved without significantly increased use of prophylactic antibiotics or increases in mortality, and with a lower frequency of early reinitiations of antibiotic therapy.

Although our intervention was less comprehensive, the results are similar to previous reports of the effects of antimicrobial stewardship programmes based on updated management guidelines that are tailored to individual neonatal intensive care centres.[10 12] Cantey *et al* reported a 27% overall decrease of antibiotic therapy following the introduction of treatment-duration guidelines.[10] However, less than 5% of the study population in that study was born at ≤28 weeks' gestational age. In another study from the USA, where the intervention was based on daily audits with feedback including treatment recommendations, overall antibiotic consumption was reduced moderately but the reductions in vancomycin and cephalosporins were in line with our figures.[13] That study included more extremely preterm infants, although no subgroup analysis for these patients was presented. The present study, which included 145 extremely premature infants, confirms the feasibility of a tailored guideline-based stewardship approach in these high-risk patients. In contrast, Ting *et al* reported equal or increased inappropriate antibiotic use in very low birthweight infants following an intervention based on daily audits with feedback.[22] The stewardship programme in their study used a different set-up and was aimed specifically at inappropriate antibiotic use, maybe explaining the contrasting results. There were still non-significant trends toward shorter average treatment duration and a decrease in the proportion of meropenem, in line with our findings.

The baseline number of treatment days per 1000 patient-days in our study was similar to post-intervention figures in published stewardship studies (245–417 days of therapy per 1000 patient-days),[3 10 12 13] whereas we report a comparatively low figure for days of therapy after intervention, despite including only extremely preterm babies. The higher proportion of patients that avoided infection during the intervention period likely contributes to this observation. Other background factors such as antibiotic resistance or health system incentives can also influence

Table 4 Outcome data for baseline and intervention periods

| | Baseline | Intervention | |
|---|---|---|---|
| | N=82 | N=63 | |
| | 3478 patient-days | 2573 patient-days | P value |
| Antibiotic use, days per 1000 patient-days | 534 (517 to 551)* | 466 (447–485) | <0.001 |
| Treatment | 287 (272 to 302)* | 197 (182–213) | <0.001 |
| Prophylaxis | 247 (233 to 262)* | 269 (253–287) | 0.05 |
| Mortality | 7 (9%)† | 6 (10%) | 0.84 |
| Infection-related late deaths (>24-hour age) | 2 (2%)† | 1 (2%) | 0.60 |
| Reinitiation of antibiotics within 72 hours | 9 (11%)† | 1 (2%) | 0.04 |
| Did not receive antibiotic treatment | 17 (21%)† | 28 (44%) | 0.002 |
| Antibiotic treatment episodes, n | 99 | 49 | |
| Early-onset infection | 18 (18%)† | 7 (14%) | 0.55 |
| Treatment length (days) | 8 (1–61)‡ | 6 (1–39) | 0.08 |
| Treatment duration (≤5 days) | 22 (22%)† | 19 (39%) | 0.03 |
| Culture-positive sepsis | | | |
| No of episodes | 15 (15%)†§ | 4 (8%)¶ | |
| Treatment length (days) | 10 (2–17)‡ | 9 (1–10) | 0.36 |
| CoNS sepsis | | | |
| No of episodes | 9 (9%)† | 4 (8%) | |
| Treatment length (days) | 7 (4–8)‡ | 10.5 (5–23) | 0.18 |
| Culture-negative infection | | | |
| No of episodes | 62 (63%)† | 23 (47%) | |
| Treatment length (days) | 9 (1–61)‡ | 6 (1–39) | 0.10 |
| Without confirmed infection | | | |
| No of episodes | 13 (13%)† | 18 (37%) | |
| Treatment length (days) | 8 (3–20)‡ | 6 (2–19) | 0.49 |

*N (95% CI).
†N (%).
‡Median (range).
§*Serratia marcescens* (n=5), *Staphylococcus aureus* (n=5), *Enterococcus faecalis* (n=2), *Klebsiella oxytoca* (n=1), *Enterobacter cloacae* (n=1), Group B *Streptococcus* (n=1).
¶Group B *Streptococcus* (n=1), *S. aureus* (n=1), *Streptococcus anginosus* (n=1), *S. salivarius* (n=1).
CoNS, coagulase-negative *Staphylococcus* spp.

antibiotic use, and the different point estimates should be compared cautiously.

There are several reports of vancomycin-reducing guidelines in extremely preterm infants.[11 23] Although we did see a significant decrease in vancomycin treatment days (from 190 to 113 days per 1000 patient-days), our intervention was not directed specifically at vancomycin use. Swedish neonatal units have been spared of outbreaks with vancomycin-resistant bacteria, instead, there have been large outbreaks of ESBL-producing gram-negative rods.[24 25] Although multi-resistant gram-negatives are a dominant cause of resistance outbreaks in neonatal units globally,[26 27] there are still few reports of programmes aimed at reducing the use of antibiotics with gram-negative activity in neonates.[14 22]

The present study revealed a significant reduction of meropenem-based regimens following the intervention, partly explained by the lack of confirmed gram-negative bloodstream infections during the follow-up period. The proportion of meropenem-based treatment remained high after implementation of the updated guidelines, indicating a potential for further improvements in the rational use of antibiotics at our institution. In addition, the rate of lumbar punctures did not increase as expected and remains an obstacle to optimal treatment. To investigate this apparent lack of adherence to guidelines requires a qualitative approach that is beyond the scope of the present study.

The number of treatments was lower during the intervention period. A lower rate of early reinitiations of antibiotics contributed to this decrease. Although not a part of the stewardship intervention, this could still be related to the changes of management. Already during development, antibiotic stewardship programmes can

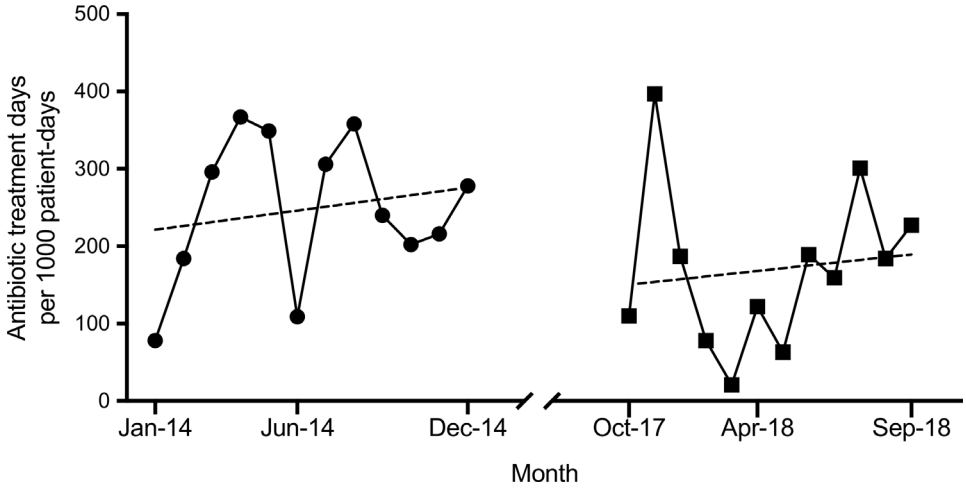


**Figure 2** Antibiotic use for treatment per month during the baseline period, January–December 2014 (left) and intervention period, October 2017–September 2018 (right). The slope is non-significant in both periods (p=0.56 and p=0.71, respectively).

affect the handling of infections.[18] In the study by Nzegwu *et al* most of the reduction occurred before the programme was implemented.[13] Clearly defined treatment duration may reduce the risk of unresolved infections.[28] Increased adherence to infection control procedures may also contribute to a lower frequency of late-onset sepsis.[29]

The effects of antimicrobial stewardship programmes tend to wear off over time.[30] To account for this, long observation periods are necessary. Zingg *et al* reported a yearly decrease of around 3% for a 7-year period.[31] Other studies report sustained effects for at least 4 years.[13] We did not have access to several years of data, but analysed monthly changes to identify trends. Although there were large fluctuations between months, they appeared to be random and there was no significant increase over time.

Fewer infants in the intervention group developed BPD. Even though this is consistent with earlier observations that prolonged use of antibiotics is associated with increased odds of BPD,[6] many other factors could have influenced the reduction of BPD. We used a pragmatic definition of BPD without oxygen reduction tests, as proposed by Walsh *et al*.[32] Less severe preterm complications might affect the threshold for antibiotic treatment,[33] and the importance of adjusting for confounders in stewardship evaluation studies has recently been stressed.[34] To adjust for differences in common complications and duration of stay, we included a multivariable regression model in the analysis. Admission during the intervention period remained independently associated with 5 days shorter total duration of antibiotic treatment. This estimate is not easily comparable to published reports that have not included such models.

There are limitations to the present study. The definitions of infection types and preterm complications were based on retrospective review of medical records and not on standardised prospective data collection. The limited sample size makes the data vulnerable to random changes in the incidence of infections. There were no confirmed gram-negative infections during the intervention period, which may affect the choice of therapy and treatment durations. The follow-up time was restricted to 1 year, which may be too short to evaluate the durability of the stewardship intervention. We used a metric (days with treatment) that does not account for changes in the spectrum of antimicrobial activity. The intervention was concentrated on a few key updates of management, and we did not include a standard-of-care neonatal unit as control. The overall results may represent a general effect of ongoing quality improvement rather than specific effects of the intervention. Improved diagnostics and reviewed indications for empirical antibiotics may be more effective approaches for reduced antibiotic use. Universally accepted definitions for culture-negative sepsis-like infections in neonates, especially for extremely preterm infants, are lacking.[35] This makes it difficult to evaluate and compare guideline changes for this common

**Table 5** Multivariable model for the number of antibiotic treatment days per patient

| | Change in treatment days | 95% CI | P value |
|---|---|---|---|
| Gestational age at birth (+1 week) | −3.3 | −4.8 to −1.9 | <0.001 |
| Length of stay (+1 day) | +0.24 | +0.2 to +0.3 | <0.001 |
| Respiratory distress syndrome | −2.5 | −9.8 to +4.7 | 0.49 |
| Patent ductus arteriosus | −0.7 | −5.5 to +4.1 | 0.78 |
| Treated during intervention period | −4.9 | −9.4 to −0.4 | 0.03 |

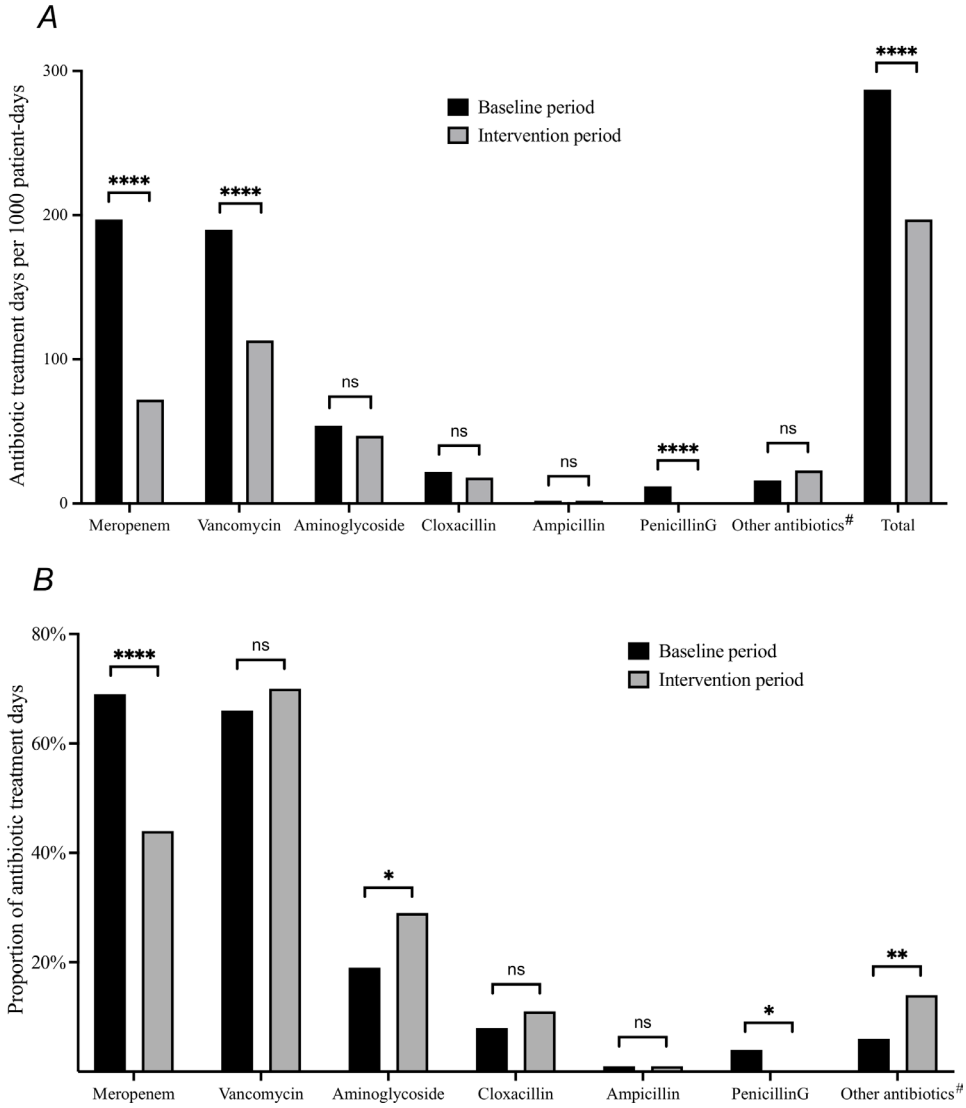


**Figure 3** Total use of different antibiotic types for treatment, presented as treatment days per 1000 patient-days. (A) Distribution of antibiotic types used for treatment, presented as the proportion of total treatment days that included each antibiotic type. (B) Note that combination therapy was common and the sum of proportions will be over 100%. #One treatment outlier (prolonged treatment for *Ureaplasma* meningitis) in the intervention group excluded from figure. ****p<0.0001; ***p<0.001; **p<0.01; *p<0.05; ns, p>0.05.

clinical entity. Roughly half the antibiotic consumption in this patient group at our unit was for prophylaxis. The intervention did not target this use, potentially reducing the effectiveness of the present stewardship initiative. Finally, even though tailored antibiotic stewardship programmes may be specific for each institution, the process of developing and implementing local stewardship initiatives has beneficial effects that are likely to appear in many different settings.

## CONCLUSION

We recorded a significant reduction of antibiotic treatment days following the implementation of a limited antimicrobial stewardship intervention for extremely preterm infants. The reduction was achieved without increases in adverse outcomes and appears safe, despite a majority of patients being very low birthweight infants with a high risk of prematurity complications. This study confirms the feasibility of antimicrobial stewardship interventions in high-risk populations. Further studies of targeted antimicrobial stewardship initiatives are needed to systematically address the practice of antibiotic prophylaxis, as well as high meropenem use in neonatal units.

**Contributors** LG collected and structured the data, performed initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. SL collected and supervised data, and reviewed the manuscript for important intellectual content. AE contributed to the study design, and critically reviewed and revised the manuscript for important intellectual content. EH and MS conceptualised and designed the study, supervised data collection and structure, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (no. 869-15).

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**Data availability statement** The datasets generated and/or analysed during the current study are not publicly available due to that the ethics committee specifically state that no data, which can identify a patient, can be publicly available.



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