Optimize the use of antibiotics in the neonatal intensive care unit: an interrupted time series study

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Abstract

Background: This study aims to monitor and evaluate the use of antibiotics in neonates over a 22-month period. The goal is to inform antibiotic stewardship strategies in level 3 neonatal intensive care units (NICU), identify scenarios where antibiotic use could be reduced, and implement interventions while ensuring safety.

Methods: Children admitted to NICU from January 1, 2020, to October 31, 2021, constituted the baseline group, while those admitted from November 1, 2021, to December 31, 2022, formed the intervention group. We employed an interrupted time series to analyze variables including the duration of antibiotic use, length of hospital stay, incidence of hospital-acquired infections, and antibiotic resistance in both groups.

Results: The study involved a total of 1678 infants, with 1138 in the baseline period and 540 in the intervention period. Analysis of antibiotic utilization in patients during the baseline period revealed statistically significant differences in factors such as positive maternal GBS colonization, mechanical ventilation, prematurity, asphyxia resuscitation, premature rupture of membranes at term exceeding 24 hours, elevated inflammatory markers exclusively, and amniotic fluid III° contamination. The rate of antibiotic use decreased from 182.2 days per 1000 patient days in the baseline period to 31.6 days per 1000 patient days in the intervention period. Additionally, the duration of hospitalization, occurrences of nosocomial infections, and the percentage of multidrug-resistant bacteria in blood cultures were significantly lower in the baseline period.

Conclusion: In cases of suspected EOS in children where clear evidence of infection is lacking, judicious administration of antibiotics is recommended. This is particularly important in situations involving pregnant mothers with positive GBS colonization, preterm delivery, contaminated amniotic fluid, elevated inflammatory markers exclusively, premature rupture of membranes in term infants exceeding 24 hours, resuscitation for asphyxia, and mechanical ventilation. Such careful use of antibiotics may lead to a reduction in the duration of antibiotic treatment, a decrease in the occurrence of nosocomial infections, and a lower prevalence of antibiotic-resistant organisms.

1 Introduction

Early-onset sepsis (EOS) remains a significant cause of neonatal infections and mortality, accounting for 10% of all neonatal deaths. While blood cultures serve as the gold standard for diagnosis, they are time-consuming and associated with a high false-negative rate. Current guidelines recommend early initiation of antibiotics for all suspected EOS cases, guided by risk factors, nonspecific indicators, and clinical manifestations. The lack of specificity in both clinical presentation and laboratory tests for EOS has led to an overuse of initial empiric antibiotics. In fact, 68.7% of non-infectious newborns and 88.4% of preterm infants born at less than 34 weeks of gestational age received antibiotics. Furthermore, antimicrobials were administered to 34.7% of children suspected of having EOS for more than 14 days.

This misuse of antibiotics not only disrupts the development of the intestinal microbiota but also increases the risk of wheezing, obesity, hypertension, diabetes, and antibiotic resistance . According to the World Health Organization, it is projected that 10 million lives will be lost globally by 2050 due to antibiotic-resistant infections. Therefore, there is an urgent need for clinicians to establish a standardized system for managing antibiotic use.

This study retrospectively analyzed antibiotic use in the NICU of our center, aiming to investigate the feasibility and safety of reducing initial empirical antimicrobial therapy. The goal is to implement an antimicrobial stewardship system in our center, ultimately reducing the incidence of nosocomial infections and drug-resistant bacteria. This endeavor also aims to provide valuable clinical insights for making informed decisions regarding antibiotic use in neonatal care.

2 Patients and Methods

2.1 Patients

Children admitted to our neonatal ward between January 1, 2020, and December 31, 2022, who met the inclusion and exclusion criteria, were selected for the study. Inclusion criteria necessitated both of the following: (1) admission within 72 hours after birth and (2) no antibiotic use before blood specimen collection. Exclusion criteria encompassed: (1) individuals with a hospital stay of less than 72 hours and incomplete clinical data; (2) those receiving prophylactic antibiotics outside of the hospital, and individuals with clear indications for antibiotic treatment or prophylaxis unrelated to EOS, such as congenital conditions carrying an infection risk or congenital anomalies requiring surgical intervention; (3) those with missing maternal pregnancy data. Electronic medical records were gathered, and analyzed for general information (gestational age, sex, birth weight, date of birth, total length of hospitalization), the child's condition (clinical symptoms, signs), test or imaging results, and antibiotic usage.

2.2 Methods

Using the timing of antibiotic stewardship as the focal intervention point, we identified patients admitted between January 1, 2020, and October 31, 2021, as the baseline group. Subsequently, we evaluated the actual antibiotic treatment administered to children in this baseline group. This assessment aimed to ascertain the degree to which antibiotic usage could be safely reduced and utilized as an intervention strategy. For the intervention group, we considered patients admitted from November 1, 2021, to December 31, 2022. Within this timeframe, our center's management team assessed study participants to confirm that antibiotics were not administered as part of the intervention. Then, we conducted an evaluation of the number of days of antibiotic use before and after the intervention using an interrupted time series approach.

Recommended compliance with guidelines for antibiotic therapy is defined as initiating antibiotic therapy in accordance with the guidelines if at least one red flag and/or two or more nonred flags are present. If these conditions are not met, the guidelines are not followed.

Antibiotic use was determined by multiplying the number of antibiotic doses by the dosing interval and dividing by 24 hours. In 'DOT/1000', DOT stands for the number of days of antibiotic use. If the child is admitted to the hospital and receives a single antibiotic, the DOT is the number of days of antibiotic treatment. However, if the child is admitted and receives two or more antibiotics, the DOT is the total of the days for each antibiotic treatment. In cases where a child is admitted and receives two or more antibiotics, the DOT is the sum of the number of days for each antibiotic treatment.

2.3 Statistical analysis

Statistical analysis was performed using SPSS statistical software, with normally distributed measures expressed as the mean ± standard deviation (SD ± S) and count data expressed as percentages (%), and the x^2 test was used for comparisons between two groups. $p < 0.05$ indicates statistical significance.

3 Results

3.1 Antibiotic use in the baseline group

A total of 1138 children were included in the baseline group, with antibiotic treatment recommended for 45.3% (514/1138) of the children according to Dutch guidelines. Among these, only 202 out of 514 (39.3%) received antibiotics in line with the recommended guidelines, while 14.7% of the children were administered antibiotics without adhering to the guidelines (see Table 1).

We conducted a comparison between the anti-infection group recommended by the Dutch guidelines and the actual clinical anti-infection group. We observed a statistically significant reduction in maternal GBS colonization positivity among maternal risk factors in the clinical anti-infection group. Additionally, in the clinical anti-infection group, we found a significant decrease in four out of the fifteen neonatal risk factors. These included mechanical ventilation, prematurity, asphyxia resuscitation, and premature rupture of membranes exceeding 24 hours at term (Figure A). Notably, some cases deviated from the guideline advice for antibiotic administration. These included elevated inflammatory markers exclusively, and amniotic fluid III° contamination. Consequently, our antibiotic management interventions encompassed positive maternal GBS colonization, mechanical ventilation, prematurity, asphyxia resuscitation, premature rupture of membranes exceeding 24 hours at term, elevated inflammatory markers exclusively, and amniotic fluid III° contamination.

3.2 Analysis of clinical data of children in the intervention and baseline groups

A total of 584 children were enrolled in the intervention group. Comparative analysis of clinical data between the intervention and baseline groups revealed no statistically significant differences in terms of sex, gestational age, birth weight, or mode of delivery ($P > 0.05$) (see Table 2). The primary indicators in both groups demonstrated that the DOT/1000 for antibiotic use was 182.2 and 31.6 in the baseline and intervention groups, respectively, with statistically significant disparities observed between the two groups

($P < 0.05$). Interrupted time series segmented regression analysis, as outlined in **Supplemental table 1** and illustrated in **Figure B**, further supported this finding.

In the study cohort, there were 6 and 2 neonatal fatalities in the baseline and intervention groups, respectively, all attributed to poor prognosis following parental abandonment. An analysis of the utilization of different classes of antibiotics indicated that the intervention group had a lower count and utilized fewer classes of antibiotics compared to the baseline group ($P > 0.05$) (see **Figure C**).

3. 3 Distribution of pathogenic bacteria in the baseline and intervention groups

Blood cultures were conducted for all children prior to administering antibiotics, and cerebrospinal fluid cultures were performed in one child based on clinical necessity. The positive blood culture rate was 1.14% (n = 13) in the baseline group and 0.68% (n = 4) in the intervention group. Among the positive blood culture samples, the most prevalent pathogens in the baseline group were *Escherichia coli* (n = 3) and *Staphylococcus epidermidis* (n = 3), followed by *human Staphylococcus subspecies* (n = 2), *Staphylococcus parapsilosis* (n = 1), *Sphingomonas oligosporus* (n = 1), *Streptococcus parapsilosis* (n = 1), *Enterococcus faecalis* (n = 1), and *Streptococcus retardans* (n = 1). In the intervention group, common pathogens included *Staphylococcus epidermidis* (n = 2), *Staphylococcus aureus* (n = 1), *Enterococcus aureus* (n = 1), *Enterococcus faecalis* (n = 1), and *Escherichia coli* (n = 1). Additionally, cerebrospinal fluid culture identified *Staphylococcus epidermidis* as the causative organism in one child from the baseline group.

The drug sensitivity results (**see Supplemental table 2**) indicated that in the baseline group, the majority of strains demonstrated resistance to penicillin and cephalosporins, except for sensitivity to imipenem. Conversely, in the intervention group, most strains exhibited sensitivity to penicillin and triple cephalosporins.

4 Discussion

This study has defined the parameters for the initial prudent empiric antimicrobial therapy within our NICU. It encompasses cases of maternal GBS positive colonization, mechanical ventilation, preterm labor, resuscitation for asphyxia, preterm rupture of membranes at 24 hours of full term, elevated inflammatory markers alone, and III° contamination of amniotic fluid. This approach has been proven to be an effective and secure strategy for antibiotic stewardship in our center.

The Dutch version of the 2021 guidelines for the management of neonatal sepsis based on risk factors and clinical presentation says that antibiotics should be given early to newborns with suspected EOS. This does not take into account things such as the protective effects of antibiotics given to the mother during pregnancy or the environment of the ward. Numerous studies indicate that using antibiotics during labor lessens the risk of early newborn sepsis [7−13]. One trial included 6872 women and babies, and the

risk of neonatal sepsis was considerably reduced in infants whose mothers received antibiotics prenatally (RR 0.67, 95% CI (0.52 to 0.85)) [7]. Furthermore, the ward environment is a major source of infection for patients, and a clean ward environment can lower the frequency of newborn sepsis infections, particularly multidrug-resistant bacteria [14].A study that used measures such as enhanced end-of-life disinfection and training to clean neonatal wards found that the incidence of sepsis infections in neonatal wards was 5.97% before the intervention and 3.44% after the intervention, with a significant decrease in the infection rate [15]. Our center's neonatal wards were designed with infection management in mind. For example, the distinction of dirt passage, visiting passage, medical staff passage, and so on; the setting of the isolation ward and rotation ward; the design of the baby washing room, milk dispensing room, liquid dispensing room, instrument decontamination room, doctor's office, duty room, and toilet; and so on; and strict attention was given to hand disinfection before and after contact with children, which is one of the major reasons for the lower rate of antibiotic use and the occurrence of nosocomial infection in this unit.

Antibiotic resistance has emerged as one of the major public health threats of the 21st century [30, 31]. The most important reason for drug resistance is the misuse of antibiotics. *Escherichia coli*, Staphylococcus aureus, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* have been identified by the WHO as priority pathogens causing antibiotic resistance [31]. The etiology and drug resistance of neonatal sepsis vary from country to country. A multicenter retrospective study from seven low-income countries in Africa and South Asia evaluated clinical data from 1038 culture-positive neonatal sepsis cases, with gram-negative bacteria being the most common and 88% of them being multidrug resistant [32]. In another cohort study conducted over 20 years in China, 164,750 culture-positive sepsis cases were reported. Of these, 1 in 2 were caused by gram-negative bacilli, and 33% were multidrug resistant [33, 34]. There were 13 septic neonates in the baseline group of this study, with most isolates resistant to triple cephalosporins, penicillin, and ampicillin; there were 4 septic neonates in the intervention group, which is likely associated with better implementation of antibiotic stewardship controls. In addition, the intervention group had a significantly shorter length of stay than the baseline group, a lower incidence of nosocomial infections, and no significant increase in mortality, indicating that this intervention was safe and effective.

5 Conclusions

In conclusion, the establishment of defined parameters for initial empiric antimicrobial therapy represents a significant advancement in antibiotic stewardship within our NICU. This approach not only addresses the challenge of antibiotic overuse, but also enhances patient safety, optimizes resource utilization, and provides clear guidance for clinicians faced with complex clinical scenarios. The successful implementation of this strategy in our center serves as a model for other healthcare facilities aiming to improve antimicrobial prescribing practices in neonatal care. Further research and continuous monitoring of outcomes will be essential in refining and validating this approach over time.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Board of Fuzhou Dongfang Hospital and was performed in compliance with the Declaration of Helsinki and its later amendments. Parents gave informed consent to the processing of personal data at the time of the clinical evaluation.

Consent for publication

All parents provided written informed consent for infants to participate in the study.

Availability of data and materials

All data generated during this study are included in the published article.

Permission of data and materials

All materials, including graphics, images, and/or supplementary materials, in this article are original works and do not require permission.

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Authors' contributions

Writing-original draft: Y.Z. ; Data curation: L.C., P.X., Y.S., P.B., Y.Q. ; Methodology: Y.Z.,L. C; Writing-review & editing: G.M., X.J.

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Tables

Table 1. Adherence and non-Adherence with guidelines on antibiotic use in the baseline group.

	Dutch guidelines Recommendations (n=1138)	Clinical Implementation Recommendations		P
		Adherence adherence (n=734)	Non-adherence (n=404)	
Major criteria that indicated the need to start antibiotics				
Red flags:any maternal risk factors	60	19	41	0.384
Red flags:any infant clinical indicators	112	63	49	**0.008**
Red flags:any maternal risk factor and infant clinical indicators	11	1	10	0.123
Minorcriteria that indicated the need to start antibiotics				
Non-red flags:at least two maternal risk factors and no infant clinical indicators	13	5	8	0.967
Non-red flags:at least two infant clinical indicators and no maternal risk factors	119	31	88	**<0.001**
Non-red flags:at least one maternal risk factor and at least one clinical infant Indicator	199	83	116	0.559
Toal	514 45.3%	202 39.3%		
No recommendations to start antibiotics				
Red flags: none				
Non-red flags: one maternal risk factors and no infant clinical indicators	123	87	36	**<0.001**
Red flags: none				
Non-red flags: one infant clinical indicator and no maternal risk factors	126	108	18	**<0.001**
Red flags: none				

| Non-red flags: no maternal risk factors and no infant clinical indicators | 375 | 337 | 38 | **<0.001** |
| Toal | 624 | 532(85.3%) | 92(14.7%) | |

Note: Adherence: Clinical implementation is consistent with guideline recommendations; Non-adherence: clinical implementation is inconsistent with guideline recommendations

Table 2. Outcome data for study infants during baseline and intervention periods.

Characteristics	Baseline (n=1138)	Intervention (n=584)	P
Maternal pregnancy status			
Prenatal antibiotic use	59	42	0.060
Neonatal status			
Gender n (%)			0.325
Male	615	301	/
Female	523	283	/
Gestational age	37.80±6.17	37.87±12.89	0225
Preterm birth less than 37wk (%)	337	162	/
≥34	239	118	/
29-33	89	42	/
≤28	9	2	/
Birth weight	3039 ± 1477	2985±959	0.377
easy childbirth	456	252	0.219
Length of hospitalization	**8.6**	**8.2**	**0.000**
Positive blood culture/cerebrospinal fluid culture	13	4	0.263
Gram-positive bacteria	10	2	/
Gram-negative bacteria	3	2	/
Antibiotic use (days of therapy per 1,000 patient-days)	182.2	**31.6**	**0.001**
Clinical regression			0.454
Improvement / cure	1132	582	/
Death	**6**	**2**	**/**
Nosocomial infections	**9**	**3**	**0.376**

Figures
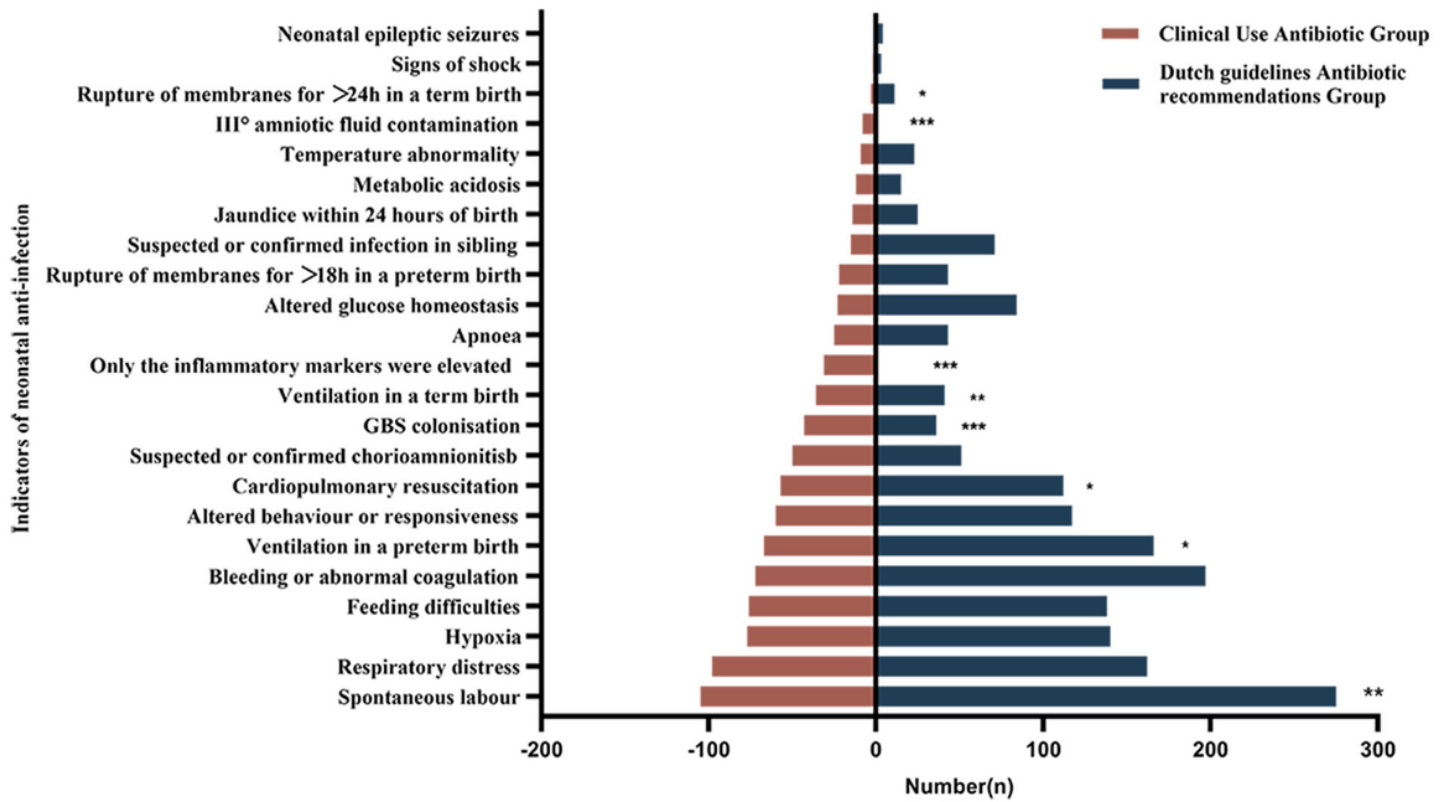
Figure 1

Figure A. Antibiotic use by indication during Clinical and Dutch guidelines recommendations.

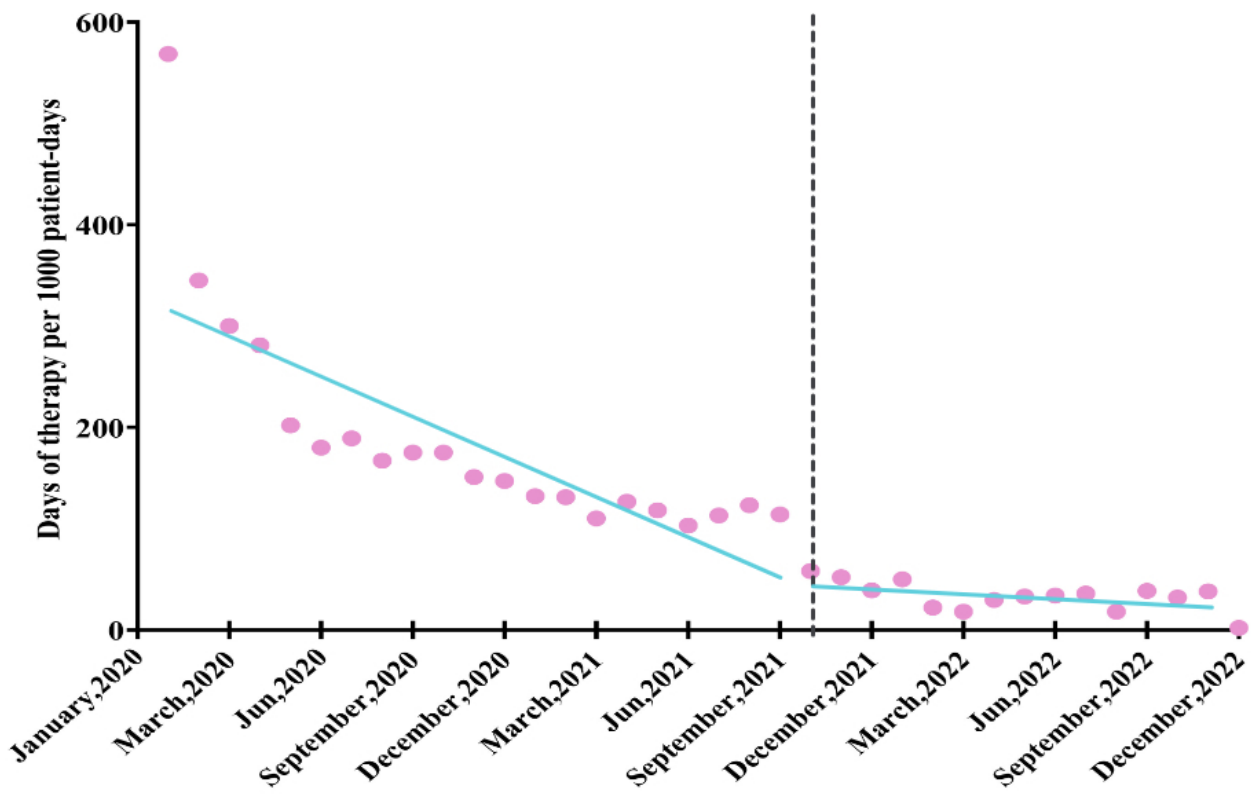Note:*P 0.05;**P 0.01;***P 0.001

Figure 2

Figure B. Run chart depicting the introduction of the antimicrobial stewardship program over time.
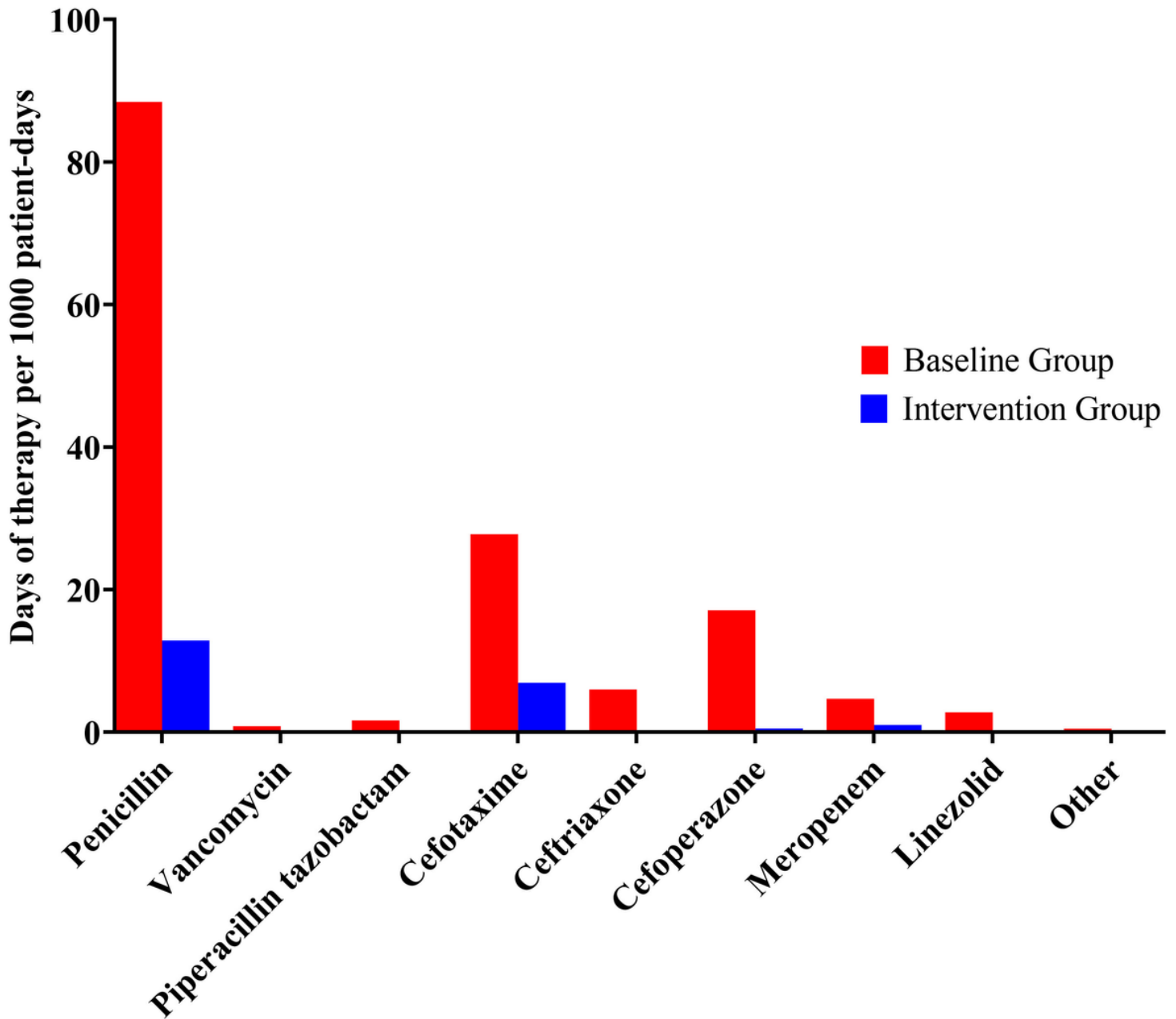
Figure 3

Figure C. Antibiotic use by drug during the baseline and intervention period.

Supplementary Files

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- Supplementaltable1.doc
- Supplementaltable2.docx