

# Antimicrobial Stewardship in a Tertiary Neonatal Intensive Care Unit with Limited Resources

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**Abstract:** *Background:* Antimicrobial stewardship programs (ASP) have been recognized nationally as an effective way to combat antimicrobial resistance. Using data from the Pediatric Health Information System (PHIS) database, we noticed high utilization of antimicrobials in our hospital particularly in our tertiary level neonatal intensive care unit (NICU). This prompted focused efforts in the NICU consisting of development of management guidelines and prospective audit with intervention and feedback. *Method:* Using the PHIS database, we retrospectively measured days of therapy per 1000 patient days (DOT/1000 PD) in the NICU during the pre-implementation, implementation and post-implementation phases to determine the change in antimicrobial utilization. All antimicrobials administered between 01/01/14 to 12/31/19 were included in this review. Secondary outcomes including late-onset sepsis (LOS), necrotizing enterocolitis (NEC), mortality rates and hospital-wide antimicrobial utilization were also evaluated. Comparison of means among groups was performed by analysis of variance (ANOVA). *Results:* Overall, mean DOT/1000 PD for the NICU decreased 32% from the pre-implementation to the post-implementation phase (656.86 vs 480.81 vs 431.90 DOT/1000 PD,  $P < 0.01$ ). NICU LOS rates decreased from 2.4% to 1.5%. NEC and mortality rates remained unchanged from 4.2% to 4.9% and 3.4% to 4.4%, respectively. Mean DOT/1000 PD for the entire hospital decreased 22% overall (857.09 vs 739.71 vs 667.76 DOT/1000 PD,  $P < 0.01$ ). *Conclusions:* Implementation of a NICU ASP helped reduce antimicrobial utilization in the NICU without increasing morbidity and mortality. Hospitals with limited resources may consider targeted unit-based stewardship to help reduce antimicrobial utilization.

**Keywords:** Antimicrobial Stewardship, NICU, DOT, Early Onset Sepsis, Late Onset Sepsis, NEC, Antibiotics

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## 1. Introduction

Antibiotics are one of the most commonly prescribed medication in a Neonatal Intensive Care Unit (NICU) internationally. [1, 2]. The California Children's Services and California Perinatal Quality Care Collaborative (CPQCC) reported a 40-fold variation in antibiotic use rates (AURs). It ranging from 2.4% to 97% of patient days, in a combined data set from 2013. [3] This variability was not related to proven infection, surgical volume in the NICU, or mortality. While empiric antibiotic therapy is often unavoidable, clear evidence shows imprudent and prolonged course of

antibiotics can lead to morbidities including necrotizing enterocolitis (NEC), increased opportunistic infections, increased hospital length of stay, bacterial resistance and even mortality [4-7]. Studies have shown that change in gut microbiome persists for at least 4 weeks after antibiotic treatment which has been implicated in adverse neurodevelopmental outcomes in infants 18-24 months corrected age. [8, 9] Antimicrobial management is difficult in preterm and critically ill neonates as their response to infection is difficult to differentiate from other pathologic processes. However, the Centers for Disease Control and Prevention (CDC) estimates half of all antibiotic

prescriptions are either unnecessary or inappropriate. [10] Thus, it seems prudent to evaluate utilization rates in this patient population. The Infectious Disease Society of America and Society and Healthcare Epidemiology of America have published guidelines aimed at improving antibiotic prescription practices of healthcare providers and through their guidance many children's hospitals have established successful antimicrobial stewardship programs (ASP). [7, 11, 12]

The antimicrobial stewardship program in our facility was established in 2008 but due to limited resources the main focus of the program was on broad spectrum antimicrobials. Using the Pediatric Health Information System (PHIS) database in 2014, we identified high antimicrobial utilization overall in our hospital. Upon further evaluation, the NICU alone accounted for 20% of institutional antibiotic usage. Based on this data, we decided to focus our stewardship efforts in the NICU to see if it would decrease our NICU and overall hospital-wide AUR. The purpose of this study was to decrease antibiotic days of therapy (DOT) per 1000 patient days (PD) by focusing on the NICU without increasing morbidity or mortality.

## 2. Material and Methods

This study was conducted at Valley Children's Hospital; a 358-bed tertiary center serving 12 counties in central California. The hospital is a nonprofit, freestanding pediatric hospital with an 88-bed level IV NICU including three neonatal satellite locations. Approximately 1100 neonates are admitted annually, including both surgical and non-surgical patients.

After the NICU was identified as the highest antibiotic utilizer, the ASP focused their efforts in this unit. The ASP team consisted of one Infectious Disease (ID) physician (dedicated 0.25 full-time equivalent), a neonatologist and the NICU unit pharmacist (dedicated 0.5 full time equivalent). The pre-implementation period included January 1, 2014 to December 31, 2015. During this time, there was no NICU specific stewardship program established and ASP focused on broad spectrum antibiotic use for the entire hospital. The implementation period included January 1, 2016 through December 31, 2016. During this time, the stewardship team focused on education and established guidelines for early onset sepsis (EOS), late-onset sepsis (LOS) and NEC in collaboration with the neonatologists. Additionally, an EOS risk calculator was introduced to all neonatologists and neonatal nurse practitioners. [13] Early onset sepsis was defined as the onset of symptoms within 72 hours of life and LOS as the onset of symptoms at or greater than 7 days of age. Necrotizing enterocolitis was defined as the development of intestinal disease in the neonate with stage II or above on the modified Bell's staging criteria. During the implementation phase, the ASP team began performing prospective audits with feedback Monday through Friday. The ID physician and NICU based pharmacist reviewed all patients receiving antibiotics, identified interventions and

then met in person with the neonatologists. Interventions included defined duration, discontinuation, therapy optimization, and narrowing or broadening therapy. Additionally, an ID consult was recommended when appropriate. The unit based pharmacist continued this review and made recommendations as needed over the weekend.

The post-implementation period included January 1, 2017 through December 31, 2019. During this period, daily rounds ensured compliance to the processes set in place during the implementation period.

### 2.1. Outcomes

The primary outcome measure was antibiotic DOT per 1000 PD defined as the sum of the DOT accounting for each antibiotic over 1000 PD. Data for DOT for antimicrobials administered intravenously, intramuscularly, and orally was obtained from the PHIS database. Secondary outcomes were reported as a percentage of neonates with LOS, NEC (Bell stage  $\geq 2$ ) and mortality. This data was obtained from the California Perinatal Quality Care Collaborative (CPQCC) database with the exception of NEC which was obtained from the Vermont Oxford Network (VON) database.

### 2.2. Analysis

Comparison of mean antibiotic DOT per 1000 PD among time periods (pre-implementation, implementation, and post-implementation) was performed using a one-way analysis of variance (ANOVA). A two-sided p value less than 0.05 was considered statistically significant. The change in antibiotic utilization, rate of LOS, NEC and mortality from pre to post-implementation period are reported as a percentage.

## 3. Results

Overall, the mean DOT per 1000 PD for the NICU decreased 32% from the pre-implementation to the post-implementation phase (635.36 vs 480.81 vs 431.90 DOT/1000 PD,  $P < 0.01$ ; Figure 1). Hospital-wide the mean DOT per 1000 PD decreased by 22% from the pre-implementation to post-implementation phase (857.09 vs 667.76,  $P < 0.01$ ; Figure 1). There was a 24% and 13% reduction from the pre-implementation to implementation phase for the NICU and hospital-wide, respectively. Individual antibiotic assessment found a decrease in vancomycin use by 42% (69.87 vs 43.28 vs 40.18 DOT/1000 PD,  $P < 0.01$ ), ampicillin by 36% (182.68 vs 134.08 vs 116.14,  $P < 0.01$ ), gentamicin by 49% (176.96 vs 119.19 vs 90.8,  $P < 0.01$ ), metronidazole by 61% (18.24 vs 5.43 vs 7.12,  $P < 0.01$ ), and meropenem by 30% (7.12 vs 9.38 vs 5.01,  $P < 0.19$ ) (Figure 2). Piperacillin/tazobactam (2.49 vs 2.36 vs 2.83,  $P < 0.89$ ) and 3<sup>rd</sup>/4<sup>th</sup> generation cephalosporin (83.79 vs 68.44 vs 72.86) use remained stable (Figure 2).

The NICU LOS rates trended down from 2.1% to 1.5%. The NEC and mortality rate remained stable from 4.2% to 4.9% and 3.4 to 4.4%, respectively.

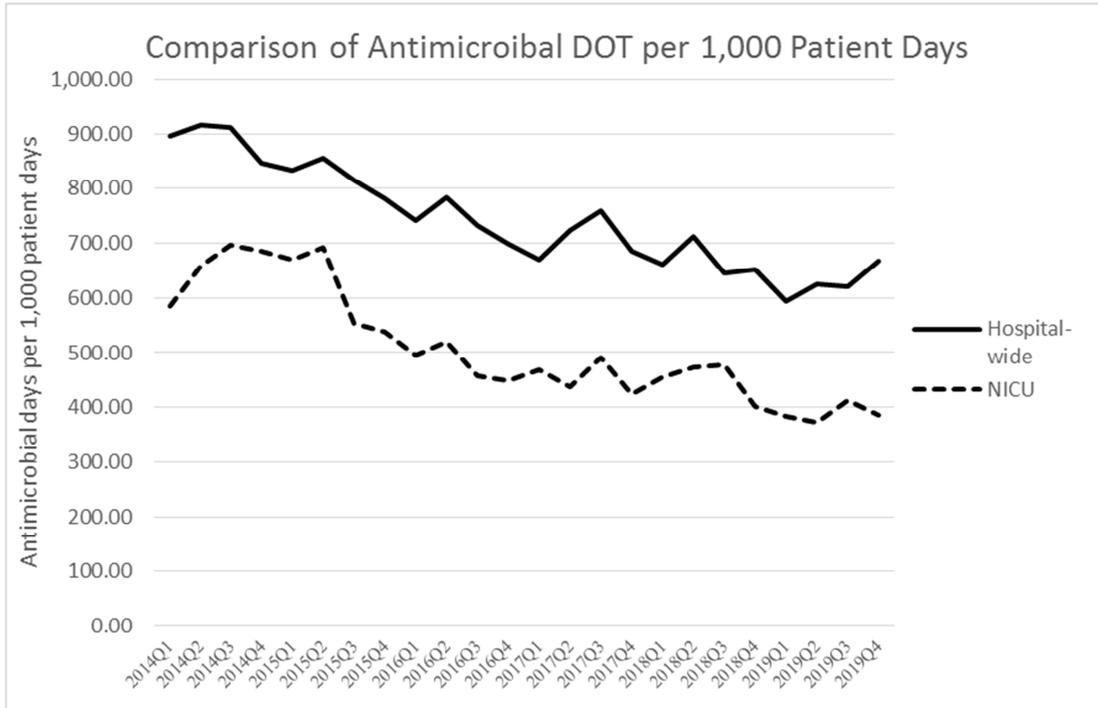


Figure 1. Antibiotics utilization by NICU by quarter in comparison to the Hospital.

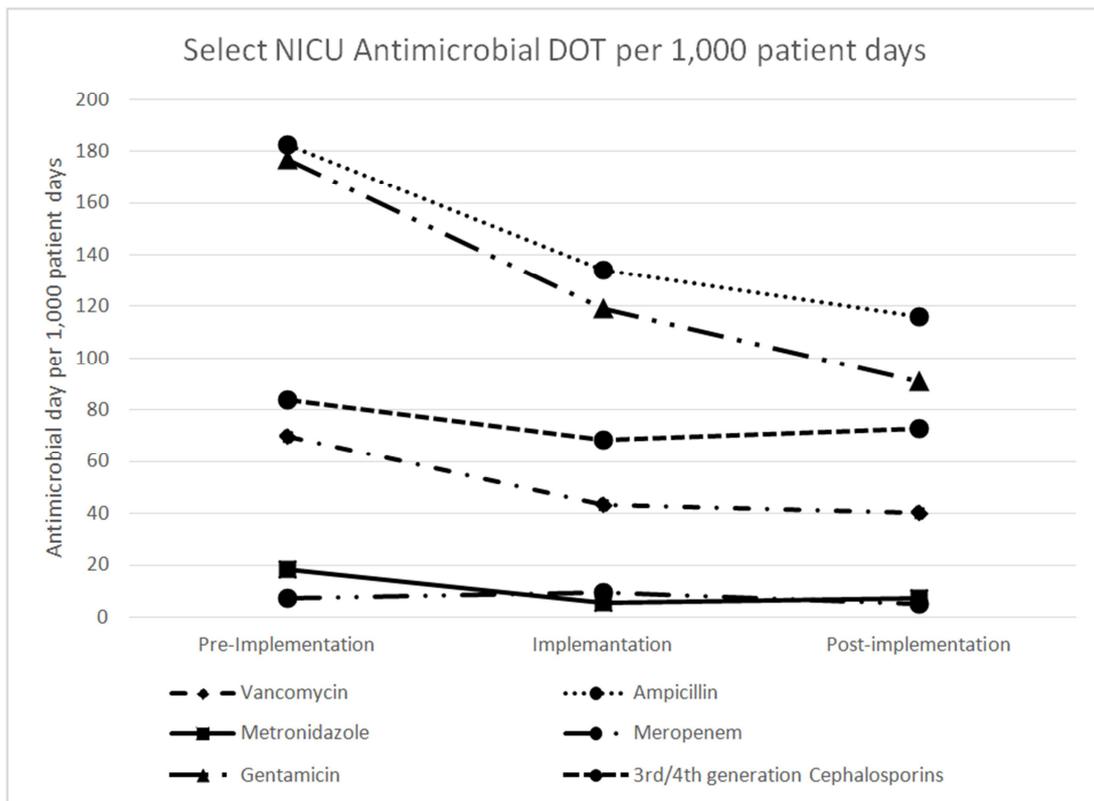


Figure 2. Antibiotic use in NICU during the three phases of Implementation.

### 4. Discussion

Prospective audits and with feedback are considered a core strategy for an effective antimicrobial stewardship program

and has illustrated a decrease in overall antibiotic use once implemented. [7, 14] Handshake stewardship, a novel approach introduced to existing strategies, not only proved to decrease antibiotic use but also improved relationships among the ASP team and other providers. [15, 16] Our study

also demonstrates the effectiveness of a handshake stewardship model with high antibiotic utilization especially in resource limited settings. To our knowledge, this study shows the largest reduction in antibiotic use within the NICU at 32% without an increase in broad spectrum antibiotic utilization. [14, 17, 18]

Implementation of an ASP program was not the only step taken to reduce inappropriate antibiotic use in our institution. Collaboration with the neonatologists along with "handshake" rounding appears to be an influential factor in reducing antibiotic utilization which has also been reported in previous studies. [15, 18, 24] Our providers reported a culture change where daily antimicrobial evaluation became a part of their routine. We believe these consistent discussions to optimize antimicrobial therapy in the NICU played a crucial role in the sustained reduction of antibiotic use. In one study, the neonatologists surveyed emphasized the need of developing NICU specific ASPs. [19] Additionally, we introduced an EOS risk calculator during the implementation phase. This tool predicts the risk of EOS for patient's  $\geq 34$  weeks gestational age using maternal risk factors and clinical presentation. [13] Kuzniewicz et al reported a decrease in the empiric antibiotic administration from 5% to 2.6% in the first 24 hours with no changes in the next 24-72 hours. [20] This novel tool was implemented to help reduce the inappropriate initiation of empiric therapy before the ASP team has the opportunity to intervene.

In our NICU, implementation of EOS guidelines limited empiric therapy to 48-72 hours in well appearing, asymptomatic neonates with negative blood cultures. In particular, a study by Ho et al also demonstrated that three quarters of infants who received antibiotics for  $> 48$  hours did not have culture proven infections. [21] Many units still routinely continue antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection this further underscores the importance of antibiotic stewardship in the newborn period. [22] Some studies demonstrated an effective reduction in antibiotic usage after implementing 48 hour automatic stop times. [23, 24] The SCOUT study demonstrated a 27% reduction in total antibiotic use by implementing an automatic discontinuation of empiric antibiotics at 48 hours. [23] In our institute, the neonatologists elected not to have automatic stop times as they preferred to evaluate the patient prior to antibiotic discontinuation between 48 to 72 hours. However, we were still able to demonstrate a significant reduction in antibiotic usage.

Hospital-wide antibiotic use declined by 22% due to a significant reduction in the NICU. The sustained reduction was seen over the three year post-implementation phases confirming the effectiveness of this approach.

Previous studies have demonstrated a correlation between prolonged use of broad-spectrum antibiotics in the NICU and an increased risk of fungal infections, NEC, LOS, and death. [1, 5, 6, 9, 25] We also evaluated the effects of decreasing antibiotic utilization to the rates of NEC, LOS and mortality. From the pre-implementation to the post-implementation phase, LOS rates decreased while the NEC and mortality rate

remained relatively unchanged.

Our study had some limitations. The use of single center studies limited the generalization of data to other institutes. Cost-effectiveness not assessed although assumptions indicate a decline based on decreased utilization. Data relative to length of stay and readmission rate were not evaluated, dismissing its impact on the study.

## 5. Conclusion

The implementation of a NICU focused stewardship program in our institute was associated with a significant decrease in antibiotic consumption with no significant change in morbidity and mortality. Hospitals with limited resources may consider targeted unit-based stewardship to help reduce unit-specific and overall antimicrobial utilization.

## Conflict of Interest

The authors have no financial relationships relevant to this article to disclose.

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