Decreasing the Rate of Antibiotics Administration to Newborns of Mothers With Prolonged Rupture of Membranes and Unknown Group B *Streptococcus* Status Using the Plan-Do-Study-Act Quality Improvement Model

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Background: Prolonged rupture of membranes (PROM) and maternal group B *Streptococcus* (GBS) colonization are major risk factors for early-onset sepsis. Managing asymptomatic newborns remains burdensome, as exposing them to unnecessary antibiotics or withholding them when needed is potentially harmful. Decreasing the rate of antibiotics administration to newborns of mothers with PROM and unknown GBS status is important.

Methods: A quality improvement project applying the Plan-Do-Study-Act model was conducted to test the efficacy of a proposed protocol to lower the rate of antibiotics administration. This protocol uses information on clinical status and biochemical markers, as well as the recommendation of the neonatal early-onset sepsis calculator, to decide whether to start antibiotics administration to newborns of mothers with PROM and unknown GBS status who are asymptomatic at birth. Neonates born at ≥34 weeks' gestation to mothers with PROM and unknown GBS status were included in this work.

Results: Sixty-six babies were included, 2 (3%) of whom had positive blood cultures, and a total of 24 (41.8%) newborns did not receive antibiotics. The rate of antibiotics administration for 2 days only was 55 times lower than the current practice. The rate of no antibiotics administration was 35 times higher than the current practice ($P < 0.0001$). None of the included newborns were readmitted because of sepsis.

Conclusions: The rate of antibiotics administration was significantly decreased. None of the infants were readmitted because of sepsis, proving protocol safety. The implemented protocol will be adopted, as the aim of this quality improvement project was achieved.

Key Words: PDSA, quality improvement project, PROM, neonate

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Neonatal infection is one of the leading causes of neonatal mortality in developing countries.[1] Early-onset sepsis (EOS) occurring in the first 3 days of life[2] is associated with multiple risk factors, such as prematurity, maternal chorioamnionitis, fever, maternal group B *Streptococcus* (GBS) colonization, and prolonged rupture of membranes (PROM).[2,3]

Screening of pregnant ladies for GBS colonization is not yet part of our antenatal care, and as a result, most of the mothers admitted to our institution have unknown GBS status. Prolonged rupture of membranes is defined as rupture of amniotic membranes for more than 18 hours before delivery.[4] Its relationship with neonatal early onset sepsis as a risk factor increases substantially with the duration of membrane rupture.[3]

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The current practice at our unit is to admit all neonates with PROM whose mothers' GBS status is unknown to the neonatal unit and start them on empirical broad-spectrum antibiotics for a minimum of 48 hours. However, this practice carries the risk of exposing healthy neonates to unnecessary antibiotics, which increases the risks of disturbing the neonatal microbiome,[5] raising antibiotic resistance,[6] acquiring nosocomial infections,[7] interrupting breastfeeding,[8] developing later childhood wheezing,[9] and overwhelming healthcare units with limited capacities, such as ours.

A previous study[10] at our institution evaluated our practice. It assessed the variables that could help differentiate newborns who have sepsis from those who do not. It was evident that most of the admitted newborns were not septic, and yet they had received antibiotics. Our findings initiated the current quality improvement study, which was considered as the "Plan" phase of the Plan-Do-Study-Act (PDSA) cycle. This project aimed to safely decrease the use of antibiotics in neonates born to mothers with unknown GBS status and PROM.

One of the investigated tools was the neonatal EOS calculator developed by Kaiser Permanente.[11] Its implementation has safely decreased empirical antibiotics use in developed countries with universal GBS screening.[12]

The results of the EOS calculator application and laboratory studies, as well as the relationships of these variables to each infant's clinical outcomes, were evaluated. Accordingly, a management protocol was proposed to determine the following: "who," or the infant in question, by defining the inclusion criteria; "what," or the intervention that will lead to the desired change; and "when," or the time of application in relation to the infant's age.[13]

The PDSA cycle is the most commonly used model in healthcare quality improvement.[14] This article will present the implementation of this protocol, the "Do" phase; the analysis of the collected data, the "Study" phase; and the outcomes of the project, the "Act" phase.

METHODS

This quality improvement study was conducted at Jordan University Hospital's neonatal intensive care unit (NICU). It used the PDSA cycle quality improvement model. The aim of this project was to safely decrease the administration of antibiotics to neonates born to mothers with unknown GBS status and PROM. This aim was achieved through the implementation of a proposed management protocol[10] that uses the newborn's clinical status, neonatal EOS calculator recommendation, and biochemical markers to identify EOS and decide whether to start antibiotics therapy in neonates born to mothers with unknown GBS status and PROM.

The plan phase of the project was covered in the exploratory study[10] that documented the clinical practice and helped define the opportunity for improvement. The roles of the interventions in identifying nonseptic newborns were analyzed, and the protocol

TABLE 1. Comparison of Demographic Characteristics Between the Standard Practice Cohort and the Cohort of the New Protocol

Character	Standard Practice	Implemented Protocol	*P*
Gestational age, wk	36 ± 1.8	37 ± 2	0.000
Birth weight, g	2767 ± 777	2900 ± 501	0.20
Small for age	9.0 (5%)	5.0 (7.6%)	0.53
Male sex	126 (71.66%)	38 (57.6%)	0.045
Cesarean delivery	81 (46%)	33 (50%)	0.664

to be implemented was designed. This article describes the implementation of this protocol and the steps taken in this study, discusses the results, and concludes with an explanation of the appropriate action.

This project was approved by The University of Jordan's Deanship of Scientific Research and the university hospital's institutional review board. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All admitted neonates of gestational age 34 weeks or older and born between July 2019 and August 2020 to mothers with unknown GBS status and PROM were included. All included newborns were admitted to the NICU, and the neonatal EOS risk calculator was applied at admission in each case.

Because safety is our goal and we are in the process of shifting from universal antibiotics administration (standard practice) to a more expectant management approach, the local incidence of EOS was set at the highest incidence (4/1000). Moreover, the definition categorizing infants with mild to moderate respiratory distress was modified from ill to equivocal, as the provision of continuous positive airway pressure is considered the standard of care at our unit for all neonates with any degree of respiratory distress (as we argued in our previous article[10]).

All the admitted newborns were placed on cardiorespiratory monitoring, and vital signs were measured every 2 hours. Complete blood count (CBC) and C-reactive protein (CRP) were recorded at both 6 to 12 hours and 48 hours. C-reactive protein is considered negative if <5 mg/dL.

Antibiotics could be started for an infant at birth if any 1 of the 3 case scenarios applied: if they were ill, if the sepsis calculator recommended empirical antibiotics administration, or if the sepsis calculator advised a blood culture. The total treatment duration was determined according to the resolution of the infant's symptoms, blood culture results, and normalization of their biochemical markers.

The conservatively managed neonates were placed on cardiorespiratory monitoring, and their vital signs were measured every 2 hours. Their CBC and CRP were tested at both 6 to 12 hours and 48 hours. The decision to start antibiotics was based on the development of symptoms and the infant's biochemical markers.

An abnormal white blood count was defined as a count greater than 25×10^9/L (leukocytosis) or less than 5.0×10^9/L (leukopenia). Thrombocytopenia was defined as a count less than 150×10^9/L, and CRP was considered negative for values <5 mg/dL.

Sepsis was defined as a positive blood culture, or the presence of symptoms or abnormal biochemical markers without a positive blood culture.

The protocol's safety was defined as its ability to identify the septic newborns. This parameter was calculated as the rate of hospital readmission due to sepsis within 1 week of age.

The protocol's efficacy was defined as the rate of decrease in antibiotic administration.

RESULTS

Sixty-six neonates born at ≥34 weeks' gestational age to mothers with PROM and unknown GBS status were included in this study. Of these, 57.6% were male (Table 1). The mean gestational age was 37 ± 2 weeks. The mean birth weight was 2900 ± 500 g. Duration of membrane rupture was typically <2 days (45.5%), and almost all mothers had unknown GBS status (Table 2).

Moreover, 51 (77.3%) were completely asymptomatic at birth. Two (3%) infants had positive blood cultures, and 22 (33.3%) infants had culture-negative sepsis (Table 3).

A total of 32 babies were started on antibiotics at birth. Two of them were ill, whereas the sepsis calculator recommended starting antibiotics or drawing blood cultures for the remaining. According to the results, 18 (55%) were not septic, and antibiotics in these cases were discontinued at 48 hours. Furthermore, 14 babies were considered septic, and antibiotics were continued for at least 7 days. Another 10 babies were started on antibiotics after 48 hours because of rising CRP levels at the age of 48 hours. One of the babies for whom the sepsis calculator advised against starting antibiotics had a positive blood culture.

Regarding infection risk factors, this study cohort had a significantly higher incidence of maternal urinary tract infection (UTI; Table 2).

Applying this protocol decreased the overall rate of antibiotic use from 100% to 64%. The administration of antibiotics for 2 days decreased from 82% to 27%. Implementation of the protocol also improved the rate of no antibiotics administration from 0% to 24% (Table 3).

DISCUSSION

Prolonged rupture of membranes and unknown maternal GBS status are well-recognized risk factors for neonatal EOS.[15] The management protocol for symptomatic newborns is universal and includes taking cultures and starting antibiotics. However, the management approach for asymptomatic newborns has changed significantly in the past few years.[16] The minimization of the adverse effects of antimicrobial therapy by efficient identification of newborns with sepsis remains the biggest challenge.

This quality improvement study was based on previous phase 1 exploratory research that documented the actual practice at our units and its clinical outcomes.[10] This study aimed to implement the protocol proposed by Al-lawama et al[10] and investigate its safety and efficacy. Our goal of protocol implementation was to decrease the antibiotics administration rate for infants who did not require them.

All the newborns included in this study were admitted to the NICU and categorized according to clinical status at birth as well, ill, or equivocal. Their risk of sepsis was calculated using the EOS calculator. They were started on antibiotics if they were ill. Alternatively,

TABLE 2. Comparison of Infection Risk Factors Between the Standard Practice Cohort and the Cohort of the New Protocol

Risk Factor	Standard Practice	Implemented Protocol	*P*
PROM <2 d	101 (57.3%)	30 (45.5%)	0.11
PROM 2–6 d	36 (20.5%)	15 (22.7%)	0.72
PROM >7 d	39 (22.2%)	21 (31.8%)	0.13
Maternal UTI	26 (14.8%)	25 (37.9%)	0.009
Unknown GBS	176 (100%)	65 (98.5%)	0.27
Chorioamnionitis	2 (1.1%)	2 (3%)	0.29
Maternal fever	9 (5%)	3 (4.5%)	1.0

TABLE 3. Comparison of Clinical Outcomes Between the Standard Practice Cohort and the Cohort of the New Protocol

Character	Standard Practice	Implemented Protocol	*P*
Well	131 (74.4%)	51 (77.3%)	0.74
Ill	4 (2.3%)	2 (3%)	0.67
Equivocal	45 (25.6%)	13 (19.6%)	0.4
White cell count >25 × 10^9	7 (4%)	4 (6%)	0.5
White cell count <5 × 10^9	2 (1.1%)	1 (1.5%)	1.0
Platelets <150 × 10^9	11 (6.3%)	7 (10%)	0.27
Positive baseline CRP	11 (19.6%)	3 (4.5%)	0.01
Positive 48-hour CRP	40 (27.2%)	18 (27.3%)	1.0
Blood culture positive	9.0 (5.1%)	2.0 (3%)	0.7
Septic newborns	32 (18%)	24 (36%)	0.0057
Antibiotics at any time	176 (100%)	42 (64%)	0.0001 (down 36%)
2-d antibiotics	144 (82%)	18 (27%)	0.0001 (down 67%)
No antibiotics	0.0 (0)	24 (36%)	0.0001 (up 3900%)
Length of hospital stay, d	5.0 ± 3.0	5.0 ± 3.0	1.0
Mortality	1.0 (0.57)	0.0	1.0

the EOS calculator recommended starting antibiotics or taking blood cultures. The protocol was followed as illustrated in the Methods section. The study was carried out exactly as planned.

Of the 66 newborns included in the study, 24 (36.6%) were considered to have sepsis due to a positive blood culture (8%) or development of symptoms/abnormal biochemical markers at 48 hours of age (28.4%).

This definition of negative-culture sepsis might have led to an overestimation of the rate of sepsis in our cohort; intrapartum antibiotics therapy given to mothers with PROM might inhibit bacterial growth in vitro and result in negative blood cultures in neonates.[17] In our study, 71.2% of mothers had received intrapartum antibiotics.

Regarding infection risk factors, both groups were similar in terms of the duration of membrane rupture, maternal fever, or chorioamnionitis; however, the current study cohort had a significantly higher rate of maternal UTI ($P = 0.009$), which might have contributed to the higher rate of sepsis.

There were no significant differences between the groups regarding their clinical status at birth and CBC results. However, the 2 groups were significantly different in terms of their baseline CRP, which was higher in the universal antibiotics group ($P = 0.01$). Note that the CRP level was not checked for the entire antibiotics cohort, which might explain the higher percentage of positive CRP. Because the previous study was a retrospective one, some tests were not conducted. Moreover, performing some tests (e.g., CRP) might have subjected the research to selection bias and could bear some relation to undocumented clinical opinions of the treating physician regarding an infant's clinical status.

No significant difference was noted in the rate of positive blood cultures; however, the number of all newborns who received the diagnosis of sepsis was significantly higher in the expectant management group ($P = 0.006$). This can be partially explained by the higher rate of maternal UTI in the current study. Nonetheless, this aspect might be a potential drawback to the strict definition of sepsis, namely, a positive CRP test result at 48 hours in the absence of a positive blood culture. Notably, none of the infants who did not receive antibiotics were readmitted within 1 week of discharge because of potential sepsis.

Implementing this protocol resulted in increasing the rate of infants who did not receive antibiotics at all by 35 times ($P < 0.0001$) and increasing the rate of the infants who received antibiotics for 2 days only by 55 times ($P < 0.0001$). The study protocol is safe, as none of the infants were readmitted with sepsis. Because all the included infants were admitted to the neonatal unit, the length of hospital stay was not affected.

The "study" phase of this work showed that the aim of decreasing the rate of antibiotics administration was achieved with no extra risks to the infants. Thus, confirmation that the protocol can be adopted in practice is the ultimate outcome of this analysis.

The next cycle/study will explore 2 aims, namely, decreasing the admission rate to the neonatal unit if the newborn does not need antibiotics and implementing the protocol while the infant is rooming in with the mother.

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