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Original Article

A simple and feasible antimicrobial stewardship program in a neonatal intensive care unit of a Japanese community hospital☆

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ABSTRACT

Background: Although tertiary hospitals have successfully introduced ASPs by antimicrobial stewardship teams, lots of community hospitals without pediatric infectious disease specialists have difficulty implementing ASP. We present a successful implementation of simple and feasible NICU antimicrobial stewardship program in a Japanese community hospital.
Method: We developed a protocol of antimicrobial treatment in our NICU department and have implemented the protocol from September 2017. The protocol consists of start and stop of criteria antimicrobial treatment, weekend report of blood culture result from microbiology department and stopping ordering antimicrobials beforehand for the next day. We compared days of therapy (DOT) during the post-implementation period (September 2017 to August 2018) with that of pre-implementation period (March 2013 to August 2017).
Result: In pre- and post-ASP implementation periods, 913 and 194 patients were analyzed. DOT was 175.1 and 41.6/1000 patient-days, respectively ($p < 0.001$) with 76.2% reduction. The percentage of neonates who had any antimicrobials and the percentage of prolonged antimicrobial treatments among neonates who had any antimicrobials decreased significantly (55.3% vs 20.6%, $p < 0.001$ and 65.0% vs 32.5%, $p < 0.001$). The protocol compliance rates were also significantly different (55.4% vs 95.4%; $p < 0.001$). The methicillin-resistant rate of *S.aureus* rates were significantly reduced in post-ASP period (31.1% vs 12.9%; $p = 0.002$).
Conclusion: This ASP program was easily implemented in a NICU department of a community hospital and significantly reduced antimicrobial prescription. This kind of simple protocol may be successfully scaled-up in resource limited community hospitals without no pediatric infectious disease specialists or antimicrobial stewardship team.

1. Introduction

Antimicrobials are widely used to treat infectious diseases [1]. Although antimicrobials have saved the lives of millions of patients with severe infectious diseases, unnecessary overprescription of antimicrobials has led to antimicrobial resistance (AMR) [2–4]. AMR is a cause for global concern due to the current and potential impacts on global population health, costs to healthcare systems and the impacts on gross domestic product (GDP) [5]. The absolute numbers of infections due to resistant microbes are increasing worldwide [6]. A systematic review with 214 studies revealed that the estimated economic burden ranged from $21,832 per case to over $3 trillion in GDP loss [7]. Another study estimated the impact on mortality of reduced prophylactic antibiotic efficacy in the United States because of increasing AMR [8]. This study estimated that a 30% reduction in the efficacy of antibiotic prophylaxis for certain surgical and chemotherapeutic procedures would result in 6300 infection-related deaths.

☆ All authors meet the ICMJE authorship criteria.

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Neonates with serious infections often present with nonspecific clinical symptoms and laboratory findings, which makes it difficult for clinicians to distinguish infections from other noninfectious diseases. While timely antimicrobial treatment is crucial for serious neonatal infections, unnecessary treatment with broad-spectrum antimicrobials is also associated with invasive candidiasis, necrotizing enterocolitis (NEC), and neonatal death [9–15]. One study analyzed the effect of intrapartum antimicrobial prophylaxis on neonatal intestinal microbiota [16]. The study showed an altered pattern of intestinal microbiota in neonates born to women who received intrapartum antimicrobial prophylaxis, with lower relative proportions of *Actinobacteria* and *Bacteroidetes* and increased relative abundance of *Proteobacteria* and *Firmicutes* compared to those without intrapartum antimicrobial prophylaxis. The study also demonstrated a delay in the increase of acetate levels, which indicated a decrease in *Propionibacterium* species, in neonates with intrapartum antimicrobial prophylaxis. Genetic analyses of antibiotic resistance revealed a higher incidence of β-lactamase coding genes in neonates with intrapartum antimicrobial prophylaxis. Another study revealed that antimicrobial-induced disturbance in the early microbiota may have significant negative impacts on later health, including increased risk for autoimmune and metabolic diseases and behavioral changes [17,18]. In addition, repeated exposure to β-lactam antimicrobials during infancy may be related to being overweight later in life [19]. All these data suggest the rationalization of antimicrobial use to minimize the impact of early-life antimicrobial exposure on the developing intestinal microbiota.

Antimicrobial stewardship programs (ASPs) aim to support appropriate and timely antimicrobial treatment and to reduce unnecessary antimicrobial prescriptions [20]. ASPs have been implemented in many hospitals, including neonatal intensive care unit (NICU) departments [21,22]. Although tertiary hospitals with infectious disease specialists have successfully introduced ASPs by antimicrobial stewardship teams, many community hospitals without pediatric infectious disease specialists have difficulty implementing ASPs. Our study aimed to create, implement and evaluate the ASP in a NICU department of a Japanese community hospital.

2. Materials and methods

2.1. Design and setting

The retrospective study (pre-post study) was conducted in the NICU department of the Nara Prefecture General Medical Center (Level III), which has 15 beds and approximately 200 admissions/year. The ASP started on Sep 1, 2017. Participants were all neonates admitted to the NICU before (pre-ASP, March 2013 to August 2017) and after (post-ASP, September 2017 to Mar 2018) the implementation of the ASP. In the study period, the unit was staffed with 5–6 neonatologists and 1–3 pediatric residents. All infants younger than 36 weeks' gestation or weighing less than 2000 g at birth were admitted to the NICU in addition to infants with specific problems, such as circulatory, respiratory and infectious disorders. Neonates with surgical conditions were transferred to other hospitals with pediatric surgery teams. The study was approved by the Institutional Review Board of the Nara Prefecture General Medical Center.

As empirical treatment, ampicillin plus amikacin were used for suspected early-onset sepsis, and cefotaxime was used for suspected late-onset sepsis. Vancomycin was used only for cases with suspected/confirmed methicillin-resistant *Staphylococcus aureus* infections. Usually, one set of peripheral blood culture was obtained at the time of admission, and two sets of blood cultures were recommended when clinicians suspected infections, such as sepsis, meningitis and catheter-related blood stream infections. A maternal antimicrobial prophylaxis protocol was used to prevent early-onset neonatal group B streptococcal infections throughout the study periods. Although an infection control team was present at the hospital throughout the study periods, no pediatric infectious disease specialist was available. The department of microbiology was not open on weekends or holidays throughout the study period.

In the pre-ASP period, the result of the blood culture was not available on weekends and holidays. There was no agreement or consensus for the criteria of starting antimicrobials or for the duration of antimicrobial treatments.

2.2. ASP

The ASP protocol was developed by relevant literature reviews and discussions with all neonatologists at the unit [21–27]. First, we reviewed previous literature about ASPs in other NICU departments and selected interventions that could also be applied in our NICU department. Then, we modified and integrated these interventions to develop our protocol through team discussions.

The protocol consisted of the following (Fig. 1):

1. If a neonate had any signs of sepsis, sepsis score ≥2 (see Table 1 [23]) or maternal chorioamnionitis (CAM), then blood cultures should be obtained from the neonate and the neonate should receive antimicrobial therapy. Signs of sepsis included general (lethargy, irritability, abnormal vital signs), skin (pallor, mottling, jaundice, petechiae, purpura), neurological (seizure, coma, hypotonia), respiratory (retraction), circulatory (prolonged capillary refill), and gastrointestinal (abdominal distension) symptoms. Neonates who had a clear alternative diagnosis, such as transient tachypnea of newborns, were not considered to have signs of sepsis. The sepsis score we adopted in our program has been used in University of Pennsylvania Healthcare System hospitals and contributed to discontinuing antimicrobials when sepsis is unlikely [23]. We started antimicrobials for those who had 2 points or more in the sepsis score. We monitored the sepsis score in cases that antimicrobials were started. Antimicrobials were stopped when the score became less than 2 to avoid prolonged antimicrobial treatments unless other diagnoses to warrant prolonged treatments were established.
2. If a neonate had a positive blood culture, then the neonate was treated with appropriate antibiotics for the proper duration of antimicrobial treatment.
3. If a neonate had resolved symptoms within 24 h, had the sepsis score <2, and had a negative blood culture result for 48 h without clinical suspicion of sepsis, then their antimicrobials should be stopped within 48 h.
4. Each case with controversial antimicrobial management was discussed with all neonatologists at a daily unit round.

In the post-ASP implementation period, blood culture results were returned to neonatologists at 9:00 a.m. on the weekend or holiday if they requested results to be returned. This required overtime work of lab technicians for 30 min per order.

Unless the patient clearly needed antimicrobials (e.g., bacteremia, meningitis, pneumonia and culture-negative sepsis), ordering antimicrobials in advance for the next day was discouraged in a prolonged treatment case, and neonatologists ordered antimicrobials for the same day in the morning as needed. The duration of antimicrobial treatment was 5–7 days for culture-negative sepsis.

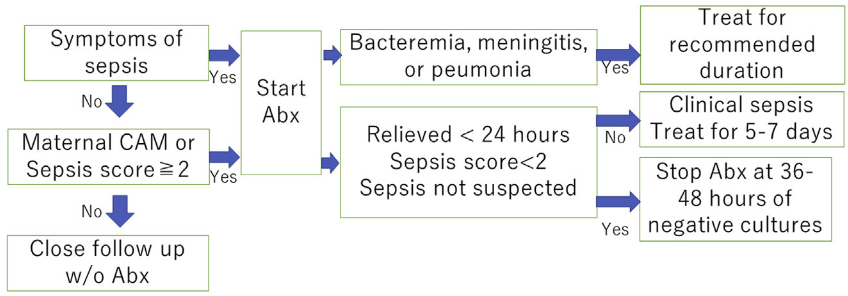

Fig. 1. Flowchart of ASP in Nara Prefecture General Medical Center. Abx: antibiotics, CAM: chorioamnionitis, w/o: without.

2.3. Outcome measures

Antimicrobial exposure was calculated as days of therapy DOT/1000 patient-days. DOT was calculated by multiplying the number of antibiotic doses by the dosing interval and dividing by 24 h. Antimicrobials administered for more than 48 h were defined as prolonged courses.

The primary outcome was DOT/1000 patient-days. Secondary outcomes were protocol compliance rate, methicillin-resistant rate of *S.aureus*, mortality rate, mortality rate due to infection, treatment failure, length of stay, culture-positive sepsis and culture-negative sepsis. The methicillin-resistant rate of *S.aureus* was calculated from our data of active surveillance cultures. Throughout the study period, nasal cultures were biweekly obtained for all admitted neonates. Treatment failure was defined as the retreatment of antimicrobials within 14 days after the last antimicrobials. In cases of treatment failure, we performed an additional workup to confirm the source of infection and to choose appropriate antimicrobials considering the patient's previous infection and clinical course.

2.4. Statistical analysis

Wilcoxon rank sum and χ^2 tests were used where appropriate to compare demographic and outcome characteristics between the pre- and post-intervention periods. All statistical analyses were performed using StataCorp (2015, *Stata Statistical Software: Release 14*, College Station, TX: StataCorp LP) and Microsoft Excel 2016 (Redmond, WA, USA).

3. Results

Overall, 1107 patients were analyzed. In pre- and post-ASP implementation periods, 913 and 194 patients were admitted to the NICU, respectively. Background and outcomes in the pre- and post-ASP are shown in Table 2. DOT, the primary outcome, was 175.1 and 41.6/1000 patient-days, respectively ($p < 0.001$). Compared to the pre-ASP period, there was a 76.2% reduction in antimicrobial DOT in the post-ASP period. The percentage of neonates who had any antimicrobials decreased significantly (55.3% vs 20.6%, $p < 0.001$). In addition, the percentage of prolonged antimicrobial treatments among neonates who had any antimicrobials was also significantly reduced (65.0% vs 32.5%, $p < 0.001$).

The protocol compliance rates were significantly different in the pre- and post-ASP periods (55.4% vs 95.4%; $p < 0.001$). The major protocol non-compliant reasons in the pre- and post-ASP periods were inappropriate start of antimicrobials without meeting the protocol criteria (premature rupture of membrane; 145 cases vs 0 case, increased inflammatory markers; 71 cases vs 3 cases, maternal GBS suspected or confirmed; 18 cases and 0 case, and unknown reasons; 54 cases and 0 case) and prolonged treatment for ruled out sepsis (301 cases and 3 cases), respectively. Compared to that of pre-ASP period, the methicillin-resistant rate of *S.aureus* rates were significantly reduced in post-ASP period (31.1% vs 12.9%; $p = 0.002$).

The percentages of culture-positive and culture-negative sepsis, mortality rates and treatment failure were 0.9% and 0.0% ($p = 0.185$), 11.3% and 7.7% ($p = 0.109$), 0.8% and 0.0% ($p = 0.211$), and 2.4% and 0.0% ($p = 0.346$) in the pre- and post-ASP periods, respectively. In the post-ASP period, 11 orders from 10 patients for blood culture results on weekends or holidays were made, which were negative and contributed to holding their antimicrobial treatments.

In terms of types of antimicrobials, significant reductions of all types of antimicrobials, including penicillins, cephalosporins, carbapenems, aminoglycosides and vancomycin, were confirmed in the post-ASP period compared with those in the pre-ASP period (Fig. 2). DOT/1000 patient-days by year is shown in Fig. 3, which revealed a stable baseline in the pre-ASP period.

Table 1
Sepsis score (positive if ≥ 2 points).

Test	Score
Absolute neutrophil count <1750/mm3	1
Total white blood count <7500/mm3 or >40,000/mm3	1
Immature/total neutrophil ratio ≥0.20	1
Immature/total neutrophil ratio ≥0.40	2
CRP ≥1 mg/dL	1
CRP ≥5 mg/dL	2

4. Discussion

This ASP successfully reduced antimicrobial prescriptions from 175.1 to 41.6 DOT/1000 patient-days without any significant changes in safety outcomes, such as sepsis, mortality and treatment failure. However, the lack of difference among safety outcomes may be due to the lack of sufficient power. Because neonatal mortality due to infection is very small in Japan, it may be difficult to conclude if the ASP influenced mortality.

The reasons the ASP decreased the use of antimicrobials by as much as 76.2% were the reductions in both starting and prolonging antimicrobial treatments. The protocol that only those who had any symptoms of sepsis, maternal CAM, or 2 or more sepsis score are eligible for antimicrobials contributed to the reduction of starting antimicrobials. In addition, the daily evaluations to stop antimicrobials (symptoms, laboratory results and cultures), the returns of blood culture results from the microbiology department on weekends and holidays, the policy of not ordering antimicrobials in advance for the next day and the policy of treating culture-negative sepsis for an indicated length of helped reduce prolonged treatments.

Table 2
Outcomes and background.

	Pre-ASP N = 913	Post-ASP N = 194	p-value
DOT (/1000 patient-days)	175.1	41.6	<0.001
Any antimicrobial used	55.3%	20.6%	<0.001
Prolonged antimicrobials	65.0%	32.5%	<0.001
Protocol compliance rate	55.4%	95.4%	<0.001
Methicillin-resistance rate of *S.aureus*	98/315 (31.1%)	8/62 (12.9%)	0.002
Gestational weeks	36.0 (31.9–40.1)	36.0 (32.3–39.7)	0.728
Birth weight	2330 (1474–3337)	2325 (1510–3247)	0.941
Apgar score at 1 min	8 (4–9)	8 (5–9)	0.869
Apgar score at 5 min	9 (7–10)	9 (8–10)	0.846
ELBW	2.0%	1.5%	0.644
VLBW	10.4%	10.3%	0.967
LOS	18.0 (6.0–45.0)	17.0 (5.0–48.1)	0.297
Culture-positive sepsis	0.9%	0.0%	0.185
Culture-negative sepsis	11.3%	7.7%	0.109
Pneumonia	1.1%	0.5%	0.460
Meningitis	0.5%	1.0%	0.441
Urinary tract infection	0.0%	0.5%	0.030
Necrotizing enterocolitis	0.0%	0.0%	N/A
Death due to any cause	0.8%	0.0%	0.211
Death due to infection	0.2%	0.0%	0.533
Treatment failure	2.4%	0.0%	0.346

Values are expressed as the median value (10th percentile-90th percentile).
DOT: days of therapy, ELBW: extremely low birth weight, VLBW: very low birth weight, LOS: length of stay.

The significant decline of the methicillin-resistant rate of *S.aureus* was not due to improvement of infection prevention and control measures but due to the reduction of antimicrobial use by the ASP because the detection rate of methicillin-sensitive *S.aureus* were similar between the pre- and post-ASP periods (23.8% vs 27.8%; p = 0.23).

Some previous studies on ASPs in NICU departments showed the effectiveness of using comprehensive ASP teams, including pediatric infectious disease physicians, pharmacists and nurses on the ASP, and a microbiology department available for 24/7 [20–22]. Cantey et al. reported a 27% reduction in DOT following the implementation of an ASP in a NICU department without any changes in safety outcomes other than necrotizing enterocolitis [21]. This study was performed in a Level IIIC NICU department in Texas with 90 beds and approximately 1400 admissions in a year. Antibiotic use declined from 343 DOT per 1000 patient-days during the baseline period to 252 DOT per 1000 patient-days in the intervention period ($p < 0.0001$). In the study by Cantey et al., the incidence of NEC increased after the implementation of ASP. This result was because clinicians could prescribe antimicrobials for more than 5 days with a diagnosis of NEC instead of culture-negative sepsis. In our study, we could not assess the difference in the incidence of NEC by reducing unnecessary antimicrobials due to the low incidence in our hospital. Further studies are warranted to investigate the incidence of NEC by appropriate ASP implementation.

Nzegwu et al. reported that a multidisciplinary team developed guidelines for common infections, with a focus on prescriber audits and feedback, that successfully reduced antimicrobials by 14.7 DOT per 1000 patient days during the stewardship period [22]. The intervention was implemented in a 54-bed, level IV NICU in a regional academic and tertiary referral center in Connecticut. A unit-wide educational effort was launched to outline the principles and strategies of antibiotic stewardship, to introduce clinical guidelines, to review baseline data, and to describe outcome measures. Daily reports were reviewed by the ASP team for timely prescription audits and feedback. A monthly summary was distributed to all staff for further feedback. The mean antibiotic utilization rates were 270.4 DOT per 1000 patient-days in the preintervention period and 258.8 in the stewardship period, with a 4.3% decrease from baseline. Compliance with clinical guidelines was noted in 1738 of 1760 (98.75%) treatments during the stewardship period in this study. In our study, the reduction rate of antimicrobials was much greater than those in these previous studies.

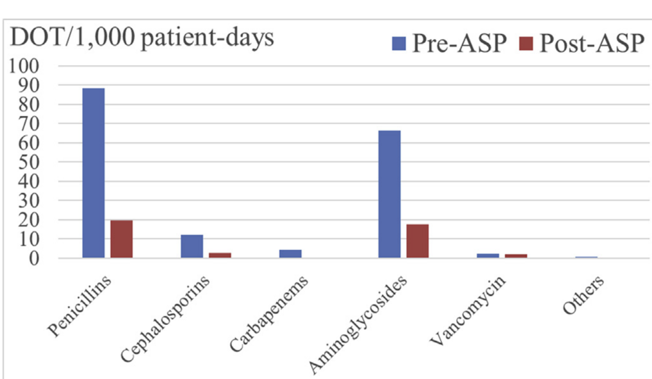

Fig. 2. DOT/1000 patient-days by year. DOT: days of therapy.

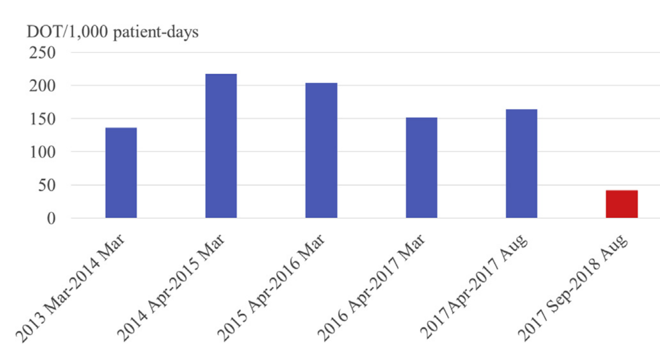

Fig. 3. DOT/1000 patient-days by type of antimicrobial.

Traditionally, ASPs have been implemented in large tertiary hospitals over the past few decades; however, ASPs should be expanded to smaller hospitals or clinics, as these hospitals are responsible for most of the prescribed antimicrobials in the world. Therefore, there is no "one size fits all" approach to meet the demand of all healthcare settings, and each facility needs to create their own ASP to make a maximal use of limited resources with their best available resources [28].

Unlike these previous studies in large tertiary centers, this study took place in a resource-limited setting without the availability of consultation to pediatric infectious disease specialists or a microbiology laboratory on weekends and holiday. However, we successfully reduced antimicrobial prescription without any increase in adverse outcomes. Therefore, the study showed that this simple and feasible ASP could be safely implemented in a NICU department of a community hospital.

There are some limitations of our study. First, because our NICU is level III and admits few neonates with extremely low body weight, our findings cannot be generalized to this subset of infants because of the lack of enough cases. Second, the results of this ASP intervention may not be generalizable to other facilities. For example, without the cooperation of lab technicians, checking the result of blood culture on weekends and holidays would not be possible. Therefore, an ASP in each facility should be supported by multidisciplinary teams, although their situations would differ depending on many factors, including antimicrobial resistance rate of the community, characteristics of neonates, human resources, and availability of infectious disease consultations. Third, we did not monitor the amount of blood taken in a culture bottle and the compliance rate of taking 2 sets of blood cultures when infections were suspected. The low compliance of these recommendations could lower the culture-positive sepsis rate.

Regarding the length of treatment for culture-negative sepsis and pneumonia, there is a controversy. There are several reasons for the difficulty in determining the length of treatment for these conditions [29]. First, it is difficult to diagnose these diseases in neonates because of the lack of apparent clinical signs [30]. Second, viral infections can cause these conditions [31]. Third, some other noninfectious conditions, such as transient tachypnea of newborn and respiratory distress syndrome, can mimic these conditions [32,33].

Although this study did not show that appropriate antimicrobial use reduced the length of hospital stay, a previous study about an ASP in a NICU department revealed a longer length of stay after ASP implementation [21]. This result could be because neonatologists wanted to observe neonates for longer periods in cases without antimicrobials. However, another study shortened the length of stay after the ASP period, although this study was not a NICU setting [34]. Although this study did not measure the long-term effects on development, behavioral issues, and obesity, an evaluation of the effect of the ASP on these outcomes should be explored in future studies. To further explore the effect of an ASP on these conditions in NICU settings, more studies are warranted.

Sustainability of the ASP will require further observation. Cooperation of the microbiology department is crucial. Although the burden of lab technicians on weekends has been slightly increased, we all agree that this burden is worth bearing for timely and appropriate discontinuation of antimicrobials.

In conclusion, our simple ASP successfully reduced the use of antimicrobial prescriptions in the NICU department of a community hospital without pediatric infectious disease specialists or a 24/7 open microbiology department. ASPs could be developed, applied and scaled up to other NICU departments in community hospitals with resource-limited settings. Because most neonates who need treatments in the NICU are hospitalized in small community hospitals without pediatric infectious disease specialists or 24/7 open microbiology departments, this simple ASP can be used for these situations.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content in and writing of the paper.

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