Editorial Commentary

Antibiotic stewardship in neonates: challenges and opportunities

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Antibiotics are the most frequently used medications in neonates. The neonatal intensive care unit (NICU) houses immunocompromised newborn who are highly susceptible to overwhelming infections. Early and decisive treatment with powerful antibiotics for neonates with suspected infection is the preferred clinical doctrine owing to the fear of potentially disastrous consequences. The high associated mortality from the infections leads neonatal care providers to initiate empirical antibiotic therapy. However, antibiotics are often continued in clinical situations in which a clear indication or benefit has not been demonstrated. There is increasing evidence of adverse outcomes, such as increase in mortality, various morbidities, and even short-term neurodevelopmental outcomes from prolonged antibiotic use without evidence of sepsis in neonates (1,2).

Lu *et al.* recently shared their experience with reduction in the use of unnecessary antibiotics in their 150-bed outborn tertiary NICU in an article published in the journal *Critical Care Medicine* (3). The study team implemented a multi-disciplinary antibiotic stewardship program (ASP) named "Smart Use of Antibiotics Program" or "SMAP" from June 2016 onwards, targeting prolonged and unnecessary use of antibiotics, as part of their Joint Commission International accreditation process. A multi-disciplinary team was established to look at the strategies to achieve the goal, focusing on audit-and-feedback, prior authorization, and point-of-prescription interventions. They categorized antibiotic use into three, namely non-restricted (e.g., ampicillin), restricted (e.g., third-generation cephalosporin), and selected/special (e.g., meropenem and linezolid), as predefined by the Chinese Ministry of Health (3). To assess the safety matrices of their intervention programme, they also evaluated the hospital readmission rates related to infection, sepsis-related mortality rate, and overall mortality rates at the baseline phase (Jan 2015 to May 2016) and the intervention phase (Jun 2016 to May 2017).

The total usage of antibiotics significantly decreased from 543 days of therapy (DOT) per 1,000 patient-days (PD) during the baseline phase to 380 DOT per 1,000 PD in the intervention phase with a 30% decrease in the overall antibiotic consumption (3). While significant reduction in the use of antibiotics from the non-restricted and restricted categories was achieved, the group of selected/special use antibiotics (e.g., meropenem and linezolid) did not show significant change when compared with the baseline (162 *vs.* 155 DOT/1,000 PD). The proportion of infants colonized with multi-drug resistant organisms (MDRO) during the study decreased from 1.4% at the baseline to 1.0% post-intervention. The safety matrices like readmission for sepsis (1.2% *vs.* 1.1%) and sepsis-related mortalities (0.24% *vs.* 0.23%) did not show significant changes over time (3). The authors concluded that the SMAP was effective in reducing antibiotic exposure without affecting the quality of care.

The methodology and findings from Lu's study were comparable to those of the prospective interrupted time series study, "*Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT)*", by Cantey *et al.* (4), in which the researchers described how a stewardship

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strategy aimed at decreasing antibiotic exposure was safely and effectively implemented in their level 3C, 90-bed, predominantly inborn NICU. After the baseline period (Oct 3, 2011, to Nov 30, 2012), continuation of empirical antibiotic therapy for ruled-out sepsis courses beyond 48 h, pneumonia, and "culture-negative" sepsis was selected as targets for antibiotic stewardship interventions. During the intervention period (Oct 1, 2013, to June 30, 2014), empirical antibiotic therapy was set to discontinue after 48 h in the electronic medical record, and the duration of therapy for pneumonia and culture-negative sepsis was limited to 5 days (4). Antibiotic use decreased from 343 DOT/1,000 PD during the baseline period to 252 DOT/1,000 PD in the intervention period (P<0.01). A 27% reduction in the overall antibiotic consumption was achieved using prospective audit, targeted stewardship interventions, and collaborative implementation, with no difference in safety outcomes observed between the intervention and baseline periods (4).

Prolonged antimicrobial use without evidence of sepsis can be associated with increase in short-term morbidities, death, and/or neurodevelopmental outcomes (1,2). However, unlike the adult or pediatric ASP, which has proven to be effective, lack of evidence-based strategies and easy-to-use guidelines at the point of care preclude adoption of best practices for the use of antimicrobials by clinicians on neonates (5). We are not aware of any validated antimicrobial usage guideline that addresses the unique challenges of the NICU environment, such as culture-negative clinical sepsis and empirical treatment of early-onset sepsis (EOS) (6); nor do we find validated sepsis calculators for empirical antibiotic coverage for use among infants born <34 weeks (7).

In the recent few years, several groups have published their initial experiences on applying antimicrobial stewardship strategies to their NICU populations, in terms of both successes and challenges. Nzegwu *et al.* (8) conducted a quasi-experimental, interrupted time-series study to evaluate the effects of their ASP attempts on antibiotic utilization rates, where the overall antibiotic utilization decreased by 4.3% from 270 DOT/1,000 PD in the pre-intervention period to 259 DOT/1,000 PD in the stewardship period); however, it was not statistically significant. The ASP initiative in Vancouver targeted use of broad-spectrum antimicrobials in NICU, with a resultant drop in inappropriate antibiotic-days/1,000 DOT with cefotaxime [RR: 0.49 (0.33, 0.71)] and vancomycin [RR: 0.37 (0.22, 0.60)] in the post-ASP era. However, there was no improvement in the very-low-birth-weight sub-group (9). Thampi conducted a retrospective cohort study to evaluate the effectiveness of the audit-and-feedback scheme on the antimicrobial consumptions in a tertiary NICU in Ontario (10). The overall antibiotic use decreased by 14% (P<0.01), from 395 to 339 DOT/1,000 PD, with no difference in the duration of therapy in culture-negative or culture-positive sepsis, rates of necrotizing enterocolitis, or breadth of antibiotic exposure. Recently, McCarthy *et al.* reported that with monitoring of antibiotic prescription data and audit-and-feedback mechanisms, their neonatal unit achieved a significant overall reduction in the primary outcome of DOT/1,000 PD from 572 to 417 DOT. This represents a 27% decrease in total antibiotic use (11).

Lu's study concluded that the antimicrobial stewardship programme was feasible and effective in reducing the DOT among the neonates in a predominantly outborn tertiary center. This is particularly important as their center used to operate at higher DOT per 1,000 PD, similar to that experienced by McCarthy's group (11).

Data from different neonatal units may not be comparable directly owing to the differences in admission populations, baseline rates of sepsis, and variations in practices. Of note, use of aminoglycosides is forbidden in the neonatal populations in China. As a result, third- or fourth-generation cephalosporins and carbapenems have become the mainstay of empirical coverage for gram-negative organisms. Studies have shown that early and/or prolonged exposure to third-generation cephalosporins is associated with increased risk of mortality and emergence of MDRO, such as cephalosporin-resistant *Enterobacteriaceae* and invasive *Candidiasis* (12,13). This may partly explain the difference in the microbiology of late-onset sepsis (LOS) among preterm infants in China from that in other developed countries, dominated by gram negative pathogens instead of coagulase negative *Staphylococcus* (14).

Despite the variations in practices, as illustrated by studies by Lu *et al.* and others (3,4), certain fundamental principles of ASP still hold true across all the NICUs: formation of antimicrobial stewardship groups to oversee the strategies, clear documentation of baseline data, application of appropriate audit-and-feedback mechanisms, avoidance of unnecessary prolonged empirical antimicrobial use especially in the EOS evaluations among preemies by automatic discontinuation of antibiotic use after 36–48 hours.

Empiric antibiotic use for "rule-outs" is a major contributor of overall antibiotic use in neonatal units,

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which make finding strategies for safe antibiotic restriction challenging, especially among preterm infants (6). Certain practices in antibiotic prescriptions must be improved in the neonatal units, as highlighted by multiple review and editorials lately. Restricting initiation or duration of antibiotics in infants based on delivery characteristics, such as risk of chorioamnionitis can have a substantial impact on the overall use of antibiotics for EOS evaluations in preterm infants (15). Culture-negative LOS was frequently diagnosed in preterm infants and was associated with increased risks of adverse outcomes (14). There is an emerging need for more precise diagnostic strategies for culture-negative LOS. Utilization of biomarker-decision tools have been successful in achieving decrease in antibiotic duration; however, more studies are necessary on the effectiveness and safety profiles among most preterm infants (16). Biomarkers with excellent sensitivity and specificity to identify true bacterial infection are desperately needed to differentiate sepsis from other non-infective causes with similar clinical pictures (e.g., respiratory distress, feeding intolerance) (17). Optimizing blood culture volume in sepsis evaluation and development of reliable rapid molecular diagnostic tests to reduce the turnaround time for cultures are also important ways to allow safe and early discontinuation of antimicrobial consumptions among infants with labile status (18).

It is encouraging to hear the successful story of 34% decrease in antibiotic utilization from the Vermont Oxford Network, which involved 146 NICUs participating in an internet-based quality improvement collaborative (19). How to continue the momentum after the initial success from the antibiotic stewardship is not well studied. The inter- and intra-center wide variations in antibiotic prescribing practices have been well described in multiple studies, and the best stewardship strategies are yet to be found. Diagnoses of relatively common conditions, such as urinary tract infection and ventilator-associated pneumonia in preterm infants are not standardized, and the optimal choice and duration of antimicrobial treatment is not available (1). The cost-effectiveness and cost-benefit of ASP in adults have been clearly articulated; however, they have not been evaluated in the pediatric and neonatal setting (20). The economic analyses can be complicated because of the potential impact of prolonged antimicrobial exposure on the long-term neurodevelopmental outcomes (2).

Further research is required to understand the most impactful stewardship interventions for very preterm infants. Readjustment of our risk-benefit mindset to acknowledge the untoward side-effects of unnecessary antibiotic exposure is probably the most important point for all neonatal clinicians.

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Footnote

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