EDITORIAL

Antibiotic Consumption and Consequence: Lessons from the Neonatal Units

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Sepsis with multidrug resistant bugs is a major public health concern that poses a global threat [1]. The epidemic of superbugs is more relevant to India as it is being reported from all intensive care units and also in all health care settings. The number of deaths caused by sepsis due to drug-resistant organisms in India are more than the all-cause neonatal deaths in the United States of America. Antibiotics are the most common medications prescribed to hospitalized children, more so in the neonatal intensive care units (NICUs) [2,3]. One main reason for the overuse of antibiotics in the NICUs is that neonates have limited repertoire of signs and symptoms for infectious and non-infectious illnesses. This overlap in the presentation creates difficulty when developing clinical management guidelines, including selection and duration of antibiotic regimen.

Antibiotics used in circumstances where patient benefits are not clearly demonstrable would constitute overuse [4]. If overuse is occurring in the neonatal units, the consequences extend beyond unwarranted resource use and increased cost of care. Neonatal antibiotic exposure is associated with increased risk of necrotizing enterocolitis (NEC), nosocomial infection and mortality [5]. Additionally, antimicrobial use is associated with selection of multidrug-resistant pathogens, which further increase morbidity, mortality, cost, and length of stay. Prolonged exposure to antibiotics is also associated with increased risk of colonization with Candida, and invasive candidiasis. Cotton, *et al*. [5], in their multicentric study involving 5693 extremely low birth weight (ELBW) neonates, documented increased risk of NEC and death in neonates who received empiric antibiotic therapy for more than 5 days despite sterile cultures. The alterations in the neonatal microbiome that occur secondary to prolonged use of antimicrobials has potential long-term consequences. In a multicenter study that examined fecal samples from infants at time of discharge from NICU, antibiotic use (≥5 days) was associated with increased risk of colonization with resistant gram-negative bacilli, resistant to 3rd/4th generation cephalosporins and carbapenems [6].

Although restricting antibiotic use is a major goal for all intensive care units, there is no uniformity in the assessment tool for determining the degree of antibiotic use. These tools are mainly confined to research projects rather than bedside assessment. The most widely used tool across all age groups for expression of drug utilization is WHO's Anatomical Therapeutic Chemical (ATC)/ Defined Daily Dose (DDD) per 100 patient-days. Drugs are divided into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Each drug is assigned at least one ATC code. DDD is the average maintenance dose per day for a drug used for its main indication in adults [7]. These data are obtained from pharmacy, based on the dispensed quantity of the drug. This pharmacy-driven tool has advantage of its ability to allow comparison of antimicrobial use across time and units within hospital or across different hospitals. The applicability of this tool for pediatric and neonatal population is questionable because the dose in children or newborn is dependent on widely variable body weight. The actual prescribed dose is typically lower in pediatric patients and neonates than the average dose defining the DDD. Due to these concerns, many authors use antibiotic use rate (AUR) as another tool to assess the degree of antibiotic use [8]. AUR is the number of patient-days that infants are exposed to one or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days, expressed as percentage. AUR is mostly influenced by the patient-level and hospital-level characteristics, and hence one should balance these factors when comparing different units or hospitals. Another simple consumption parameter is to calculate the proportion of neonates in NICU who received antibiotics.

Though there are guidelines to curtail the use of antibiotics, antimicrobial stewardship strategies should be tailored to the NICU needs. Patel and Saiman [9] from Columbia University suggested NICU-tailored approach by using the principles of the CDC. Some of the cornerstone strategies of antimicrobial stewardship in NICU include optimal use of diagnostic biomarkers, using unit-specific antibiotic policy based on local antibiogram, constant re-evaluation of the antimicrobial regimen, monitoring of toxicity, consideration of shorter antimicrobial courses, and daily review of the continued need for antibiotics [10]. Some authors suggested obtaining two blood cultures of at least 0.5 mL of blood for evaluating late-onset sepsis (LOS) for improving the yield of cultures, and to use narrowest spectrum of antibiotics so that one can avoid excess use of drugs like meropenem and colistin. We documented that restricting the use of cephalosporins resulted in significant reduction in the incidence of septicemia caused by extended spectrum β-lactamase (ESBL)-producing gram-negative organisms (47% before and 25% after restricting the cephalosporin use, P=0.03) [11].

Limiting antibiotic duration is another important strategy to reduce antibiotic usage. The fixed antibiotic duration based on sepsis category (probable sepsis *vs.* culture positive sepsis) is questionable, and there has been constant attempt to reduce the duration of antimicrobial therapy based on quantitative biomarkers. Stocker, *et al.* [12] documented that procacitonin-guided decision-making can reduce antibiotic duration in suspected early onset sepsis. Caouto, *et al.* [13] showed CRP-guided approach shortens length of antimicrobial treatment in culture proven late onset sepsis. Saini, *et al.* [14] compared short course (48-96 hrs) of antibiotics with standard seven day course for probable sepsis (septic screen positive), and documented no difference in treatment failures.

In this issue of *Indian Pediatrics*, Jinka, *et al.* [15], in their single center retrospective study, report impact of antibiotic policy on antibiotic consumption in their NICU. The overall antibiotic consumption was compared one year prior and one year after introduction of antibiotic policy. There was no significant change (12.47 *vs*. 11.47 DDD/100 patient-days; P=0.57) in overall antibiotic consumption after introduction of antibiotic policy. They documented that higher proportion of neonates received first-line antimicrobials (66% *vs.* 84%; P<0.001), and consumption of third generation cephalosporins was decreased (1.45 *vs*. 0.45 DDD/100 patient-days; P=0.002) after antibiotic policy. After introduction of antibiotic policy, increase in the first line agents is expected, but this did not translate into overall reduction in the antibiotic usage in the current study. One reason could be because they had chosen pharmacy-driven assessment tool *i.e* ATC/DDD, and lacked the individual-level patient data. Another reason could be that the sample size was not calculated to evaluate the differences from the baseline data of their unit. However, the results are encouraging as the proportion of neonates started on antibiotics decreased after initiation of antibiotic policy.

Antibiotic stewardship is the need of the hour for all NICUs, and to obtain best results the strategies should be modified to the needs of NICU. Unit-specific antibiotic policy based on local antibiogram and optimal duration of therapy in suspected or proven sepsis is crucial to limit the unnecessary usage of broad-spectrum antibiotics. Implementing the customized Quality Improvement (QI) tools is the way forward to restrict unnecessary antibiotic use in Indian health care settings. The last published National Neonatal Perinatal Database for India was in 2002-03. There is compelling need to obtain, analyze and disseminate the reliable data for India by using such a quality collaborative, which can guide us to restrict overuse and to avoid wide variability of use prevailing across different units.

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