EDITORIAL

Antibiotic Consumption and Consequence: Lessons from the Neonatal Units

***Srinivas Murki and #Sai Sunil Kishore**

*From the Departments of Neonatology; *Fernandez Hospital, Hyderguda, Hyderabad, Telangana; and #MyCure Hospital, Vishakapatanm, Andhra Pradesh; India.*

**srinivasmurki2001@gmail.com*

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.

Funding: None*; Competing interests*: None stated.

REFERENCES

1. Gregory EC, MacDorman MF, Martin JA. Trends in fetal and perinatal mortality in the United States, 2006-2012. NCHS Data Brief. 2014;169:1-7.
2. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J. 2005;24: 766-73.
3. Depani SJ, Ladhani S, Heath PT, Lamagni TL, Johnson AP, Pebody RG, *et al*. The contribution of infections to neonatal deaths in England and Wales. Pediatr Infect Dis J. 2011;30:345-7.
4. Chassin MR. Improving the quality of health care: what's taking so long? Health Aff (Millwood). 2013;32:1761-5.
5. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, *et al*. NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009;123:58-66.
6. Clock SA, Ferng YH, Tabibi S, Alba L, Patel SJ, Jia H, *et al*. Colonization with antimicrobial-resistant gram-negative bacilli at neonatal intensive care unit discharge. J Pediatr Infect Dis Soc. 2016 Mar 28. pii: piw014. [Epub ahead of print]
7. Hutchinson JM, Patrick DM, Marra F, Ng H, Bowie WR, Heule L, *et al*. Measurement of antibiotic consumption: A practical guide to the use of the anatomical therapeutic

chemical classification and defined daily dose system methodology in Canada. Can J Infect Dis. 2004;15:29-35.
8. Schulman J, Dimand RJ, Lee HC, Duenas GV, Bennett MV, Gould JB. Neonatal intensive care unit antibiotic use. Pediatrics. 2015;135:826-33.
9. Patel SJ, Saiman L. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. Semin Perinatol. 2012;36:431-6.
10. Nash C, Simmons E, Bhagat P, Bartlett A. Antimicrobial stewardship in the NICU: Lessons we've learned. Neo reviews. 2014;15:e116-e112.
11. Murki S, Jonnala S, Mohammed F, Reddy A. Restriction of cephalosporins and control of extended spectrum beta-lactamase producing gram negative bacteria in a neonatal intensive care unit. Indian Pediatr. 2010;47:785-8.
12. Stocker M, van Herk W, El Helou S, Dutta S, Fontana MS, Schuerman FABA, *et al*. NeoPInS Study Group. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet. 2017 Jul 12. pii: S0140-6736(17)31444-7. [Epub ahead of print]
13. Couto RC, Barbosa JA, edrosa TM, Biscione FM. C-reactive protein-guided approach may shorten length of antimicrobial treatment of culture-proven late-onset sepsis: an intervention study. Braz J Infect Dis. 2007;1:240-5.
14. Saini SS, Dutta S, Ray P, Narang A. Short course versus 7-day course of intravenous antibiotics for probable neonatal septicemia: A pilot, open-label, randomized controlled trial. Indian Pediatr. 2011;48:19-24.
15. Jinka DR, Gandra S, Alvarez-Uria G, Torre N, Tadepalli D, Nayakanti RR. Impact of antibiotic policy on antibiotic consumption in a neonatal intensive care unit in India. Indian Pediatr. 2017;54:739-41.

EDITORIAL

Inflammatory Bowel Disease—Unclassified: How Much do we Know?

*Ujjal Poddar and Aathira Ravindranath

From the Department of Pediatric Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

ujjalpoddar@hotmail.com

Inflammatory bowel disease (IBD) is no longer a disease of the West as there are reports of increasing incidence of IBD in general, and Crohn's disease in particular, from India [1,2]. Though IBD is less common in children than in adults, almost one-fifth to a quarter of all cases are diagnosed in first two decades of life. There are three entities under the umbrella of IBD: ulcerative colitis (UC), Crohn's disease (CD) and IBD-unclassified (IBD-U). Proportion of these entities varies from country to country, and from region to region. In the West, around 60% of all cases of IBD in children are CD, 32% UC, and the remaining 8% IBD-U [3]. While in Northern India, UC is more common than CD, the reverse is true in Southern India [2]. Though there are set diagnostic criteria for CD and UC, IBD-U is basically a diagnosis of exclusion (cases of colonic phenotype of IBD that lacks features which will enable classification as CD or UC).

Understanding IBD-U assumes more importance in the pediatric population as the prevalence of IBD-U is higher among children than in adults (13% *vs.* 6%, respectively) [4]. The proportion of IBD-U declines with increasing age as evidenced by a large study of 1370 cases of IBD, where IBD-U (*n*=179) accounted for one-third of all IBD in children less than 2 years and the proportion dwindled to 9% in those above 13 years [5]. Clinically, this entity is indistinguishable from UC or CD with isolated colonic involvement. Nevertheless, the age of presentation is shown to be younger and disease severity is milder in IBD-U compared to UC or CD as evidenced by lower Physician Global Assessment scores (PGA), lower use of steroids, immunomodulators and colectomy rates in IBD-U [6]. The natural history suggests that IBD-U may be the early manifestation of either UC or CD in a proportion of cases. In EUROKIDS study, 38 of 117 (33%) cases of IBD-U were reclassified as UC (23, 60%) or CD (14, 37%) within median (IQR) 2.7 (1.0, 4.0) years of diagnosis [3]. Long-term follow-up studies in adults as well as in children have shown that almost half of the cases of IBD-U turned out to be non-IBD (non-specific colitis) [7,8]. Hence it is important to keep these patients on regular follow-up for reclassification (early) and to rule out IBD (in long run).

IBD is now diagnosed and classified according to the revised Porto criteria [9], which mandates ileocolonoscopy, esophagogastroduodenoscopy, histology and small bowel imaging in all cases (except for typical cases of UC). Though there is an exhaustive list of features to aid in classification of IBD, the picture gets complicated when ambiguity creeps in a case with colitis phenotype (thus labeled as IBD-U), like transmural inflammation without acute severe UC, macroscopic and microscopic rectal sparing, nonspecific inflammation and ulcers in upper gastrointestinal tract, ambivalent serological markers (pANCA, ASCA), reverse gradient of mucosal inflammation (more severe in proximal colon) and significant growth delay [9]. The importance of complete diagnostic work-up and strict adherence to the Porto criteria before labeling as IBD-U has been highlighted in a recent study that showed a reduction of prevalence from 7.7% to 5.6% on follow-up with complete re-investigation [3].

The study by Paul, *et al.* [10], published in this issue of *Indian Pediatrics*, is commendable in its effort to unveil the course of IBD-U in children. It emphasizes the importance of thorough work-up at diagnosis as per the revised Porto criteria, and also the readiness for repeat assessment and reclassification at follow-up. The inherent drawback of a retrospective study is obvious here as some information is missing. The detailed information about three cases that were later reclassified in another center was not available, and reasons for reclassification of these cases are unclear. In the present study [10], 40% were reclassified; of these, 70% were categorized as CD and 30% as UC, which is in contrast to previous studies. In the EUROKIDS registry (*n*=3, 461 IBD cases), 33% of IBD-U were reclassified out of which 60% were categorized as UC [3]. In another large pediatric IBD cohort (*n*=210), 50% of IBD-U were reclassified, within a median follow-up of 18.5 months, to UC (75%) or CD (25%) [11]. The long-term outcomes of

IBD-U in terms of treatment response, remission and requirement of surgery are not clear from the present study. More often remission is achieved and maintained in IBD-U with aminosalicylates alone, and the remission rate is higher than in CD or UC [6,7]. It has been suggested that aminosalicylates should be the first line of treatment in active IBD-U [6]. In light of the paucity of recommendations on treatment of IBD-U and exclusion of IBD-U from clinical trials on treatment strategies for IBD, there is a dire need to appraise treatment responsiveness and formulate evidence-based recommendations for IBD-U.

In view of the variations in prevalence, natural history, treatment response and a potential for reclassification of IBD-U, there is a need for further exclusive studies on IBD-U to better delineate this abstruse disease entity.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Avinash B, Dutta AK, Chacko A. Pediatric inflammatory bowel disease in South India. Indian Pediatr. 2009;46:639-40.
2. Sathiyasekaran M, Bavanandam S, Sankarnarayanan S, Mohan M, Geetha M, Wadhwa N, *et al.* A questionnaire survey of pediatric inflammatory bowel disease in India. Indian J Gastroenterol. 2014;33:543-9.
3. Winter DA, Karolewska-Bochenek K, Lazowska-Przeorek I, Lionetti P, Mearin ML, Chong SK, *et al.* Pediatric IBD-unclassified is less common than previously reported; Results of an 8-year audit of the EUROKIDS Registry. Inflamm Bowel Dis. 2015;21:2145-53.
4. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD - a metaanalysis. J Crohns Colitis. 2009;3:277-81.
5. Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, *et al.* Children with early-onset inflammatory bowel disease (IBD): Analysis of a pediatric IBD consortium registry. J Pediatr. 2005;146:35-40.
6. Aloi M, Birimberg-Schwartz L, Buderus S, Hojsak I, Fell JM, Bronsky J, *et al.* Treatment options and outcomes of pediatric IBDU compared with other IBD subtypes: A retrospective multicenter study from the IBD Porto Group of ESPGHAN. Inflamm Bowel Dis. 2016;22:1378-83.
7. Malaty HM, Mehta S, Abraham B, Garnett EA, Ferry GD. The natural course of inflammatory bowel disease-indeterminate from childhood to adulthood: within a 25 year period. Clin Exp Gastroenterol. 2013;23:115-21.
8. Notteghem B, Salomez JL, Gower-Rousseau C, Marti R, Lemahieu M, Nuttens MC, *et al.* What is the prognosis in unclassified colitis? Results of a cohort study of 104 patients in Norther-Pas-de-Calais region. Gastroenterol Clin Biol. 1993;17:811-5.
9. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, *et al.* ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58: 795-806.
10. Paul SP, Sandhu BK. Long-term outcome of inflammatory bowel disease–unclassified in children. Indian Pediatr. 2017;54:742-5.
11. Newby EA, Croft NM, Green M, Hassan K, Heuschkel RB, Jenkins H, *et al.* Natural history of pediatric inflammatory bowel diseases over a 5-year follow-up: A retrospective review of data from the register of pediatric inflammatory bowel diseases. J Pediatr Gastroenterol Nutr. 2008;46: 539-45.