RESEARCH PAPER

Impact of Antibiotic Policy on Antibiotic Consumption in a Neonatal Intensive Care Unit in India

Dasaratha Ramaiah Jinka, [#]Sumanth Gandra, [*]Gerardo Alvarez-Uria, [‡]Nuria Torre, [**]Durgesh Tadepalli and [##]RaghuPrakash Reddy Nayakanti

From Departments of Pediatrics, [*]Infectious Diseases, and [##]Clinical Microbiology, Rural Development Trust Children's Hospital, Bathalapalli, Andhra Pradesh,India; [#]Center for Disease Dynamics, Economics & Policy, New Delhi, India; [**]Department of Pediatrics, Rural Development Trust Hospital, Kanekal,AP, India; and [‡]Department of Neonatology, SJD Hospital, Barcelona, Spain.

Correspondence to:
Dr Dasaratha Ramaiah Jinka,
Head, Department of Paediatrics,
Rural Development Trust Children's Hospital, Bathalapalli, Andhra Pradesh, India.
jdashrath86@gmail.com.
Received: October 06, 2016;
Initial review: February 08, 2017;
Accepted: June 07, 2017.

Objective: To study the impact of initiating antibiotic policy on antibiotic consumption in a neonatal intensive care unit (NICU). **Methods:** This retrospective study was conducted between January, 2013 and December, 2014 in a 30 bed NICU. The antibiotic policy for neonatal sepsis was initiated on January 1st, 2014. The overall antibiotic consumption (Daily Defined Dose [DDD] per 100 patient-days), one year before and one year after the initiation of antibiotic policy was evaluated using interrupted time-series analysis. **Results:** There was no significant change (12.47 *vs*. 11.47 DDD/100 patient-days; *P* = 0.57) in overall antibiotic consumption. A significant increase in the proportion of patients on first-line agents (ampicillin and gentamicin) (66% (*n*=449) *vs.* 84% (*n*=491); *P* <0.001) and significant decrease in consumption of third generation cephalosporins (1.45 *vs*. 0.45 DDD/100 patient-days; *P* =0.002) was observed. **Conclusion:** Antibiotic policy increased the use of first-line agents and decreased the consumption of third generation cephalosporins.

Keywords: *Antibiotic resistance, Infection control*, *Rational prescription.*

Misuse of antibiotics is one of the primary reasons for the escalating problem of antibiotic resistance [1]. Several studies have reported high and inappropriate use of antibiotics in neonatal intensive care units (NICU) in India, and recommended implementation of antibiotic policy in these units [2,3]. However, there are no published studies evaluating the impact of antibiotic policy on antibiotic consumption in NICU setting in India in the era of high antimicrobial resistance. In this study, we examined the impact of an antibiotic policy for neonatal sepsis on overall antibiotic consumption in a single NICU.

Methods

This study was conducted between January 1st, 2013 and December 31st, 2014 in a rural hospital with 30 NICU beds which caters to both inborn and out-born babies. The antibiotic policy for neonatal sepsis was initiated on January 1st, 2014. A protocol was developed for empirical therapy of neonatal sepsis based on the review of blood culture susceptibility data obtained from NICU between January and December 2013. Ampicillin and gentamicin were considered as first line antibiotics for community acquired infections (CAIs). Combination of amikacin and ciprofloxacin was considered if there was deterioration on first line antibiotics for CAIs and as first line for healthcare associated infections (HAIs). Meropenem was recommended for empiric therapy only in very severe cases of HAIs. Third generation cephalosporins were recommended only when an intracranial infection was suspected. Empirical treatment choices were adjusted subsequently to narrow spectrum antibiotics whenever possible based on culture and antibiotic susceptibility results.

Accompanying Editorial: Pages 723-25.

Standard definitions for "possible sepsis", "probable sepsis" and "confirmed sepsis" were used. The duration of therapy for "possible sepsis" was 48-72 hours; 5-7 days for "probable sepsis"; 10-14 days for "confirmed sepsis" and 21 days for "meningitis" [4].

The primary outcome was to compare overall antibiotic consumption in the year before and after the initiation of antibiotic policy using WHO's Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) per 100 patient-days [5]. DDD is the average

Copyright of Indian Pediatrics 2017
For personal use only. Not for bulk copying or unauthorized posting to listserv/websites

maintenance dose per day for a drug used for its main indication in adults [6]. Secondary outcomes included proportion of admitted newborns on any antibiotic, the choice of antibiotics, overall mortality, and sepsis-related mortality. The clinical and laboratory data were collected from a computerized clinical database, case sheets and laboratory records.

Chi-square test and Fisher's exact test were used for comparing categorical variables and Student t-test was used to compare continuous variables. Interrupted time-series (ITS) analysis was utilized to examine the impact of antibiotic policy change on overall antibiotic consumption. A *P*-value of <0.05 was considered to be statistically significant. Statistical analysis was performed using STATA 13. The institutional ethics committee at the RDT hospital, Bathalapalli approved the study.

RESULTS

Overall, 1176 newborns were admitted to NICU in the year prior and 1279 newborns in the year after antibiotic policy initiation. There were 7,409 patient-days in the year prior to and 7,748 patient-days in the year after antibiotic policy initiation. There was a significant decrease in the number of VLBW babies in the year after the antibiotic policy initiation (9% *vs*. 6% *P*<0.001) (***Table* I**).

Total antibiotic consumption decreased from 12.47 to 11.47 DDD/100 patient-days before and after the implementation of antibiotic policy (***Table* II**). However, in ITS analysis adjusted by average weight per month there was no statistically significant change neither in the level (*P*=0.57) nor the slope (*P*=0.17) of antibiotic consumption (Supplementary material). There was a significant decrease in the consumption of third generation cephalosporins (1.45 *vs*. 0.45 DDD/100 patient-days) that was confirmed in the ITS analysis (level change -7.6 DDD/100 patient-days, *P*=0.002).

Overall, the proportion of babies on antibiotics decreased significantly (58% (*n*=681) *vs*. 46% (*n*=584); *P*<0.001) and the proportion of babies on first line antibiotics (ampicillin/gentamicin) increased signi-ficantly (66% (*n*=449) *vs*. 84% (*n*=491); *P*<0.001) (***Table* II**). There was a significant decrease in the proportion of babies on 3GCs whereas, the proportion of babies on colistin and ciprofloxacin increased signi-ficantly. There were no significant differences in overall mortality (4% (*n*=50) *vs*. 3% (*n*=38); *P*=0.10) and sepsis-related mortality (3% (*n*=35) *vs*. 2% (*n*=28); *P*=0.28) for the two years.

DISCUSSION

With antibiotic policy, the proportion of babies on antibiotics decreased, the proportion of babies on first

TABLE I PATIENT CHARACTERISTICS AND INVASIVE PROCEDURES IN THE YEAR PRIOR TO AND AFTER INITIATION OF ANTIBIOTIC POLICY

Variable	*Year Prior to Antibiotic policy No. (%) (n=1176)*	*Year Post Antibiotic policy No. (%) (n=1276)*
Male babies	696 (59)	775 (61)
VLBW babies*	106 (9)	74 (6)
LBW babies	406 (35)	480 (37)
Normal weight	664 (56)	725 (57)
Length of stay# (days)	6.4 (7.7)	6.0 (8.3)
Procedures		
Intubation	92 (8)	104 (8)
Umbilical venous line	61 (5)	83 (7)
Umbilical arterial line	3 (0.3)	3 (0.2)
PICC line	7 (0.6)	12 (0.9)

**P=.002; #mean (SD); VLBW- Very Low Birth Weight, LBW- Low Birth Weight, PICC- Peripherally inserted central catheter, SD- Standard Deviation*

TABLE II ANTIBIOTIC CONSUMPTION AND PROPORTION OF BABIES ON ANTIBIOTICS PRIOR TO AND AFTER INITIATION OF ANTIBIOTIC POLICY

Variable	*Year Prior to Antibiotic policy*	*Year Post Antibiotic policy*
Antibiotic Consumption (in DDD/100 patient-days)		
Amikacin	1.05	0.42
Ampicillin	5.68	5.8
Chloramphenicol	0.02	0.08
Ciprofloxacin	0.08	0.39
Gentamicin	3.01	3.02
Meropenem	0.52	0.61
Piperacillin-tazobactam	0.24	0.21
Vancomycin	0.41	0.29
Colistin	0	0.18
3 GC	1.45	0.45
$Babies on antibiotics, No.(%)		
*Ampicillin/gentamicin	449 (66%)	491 (84%)
*Amikacin	301 (44%)	116 (20%)
*Ciprofloxacin	5 (1%)	45 (8%)
*Colistin	0 (0%)	11(2%)
#Meropenem	58 (9%)	58 (10%)
#Piperacillin-tazobactam	109 (16%)	81 (14%)
*3GC	281 (41%)	39 (7%)

**P<0.001; #P>0.05; $N= 681 for year prior to antibiotic policy and N=584 for year post antibiotic policy; 3GC–Third generation cephalosporins; DDD- Daily Defined Dose.*

Copyright of Indian Pediatrics 2017
For personal use only. Not for bulk copying or unauthorized posting to listserv/websites

WHAT THIS STUDY ADDS?

- Antibiotic policy implementation in NICU can increase the use of first-line agents and decrease the unnecessary use of broad spectrum antibiotics without increasing mortality.

line antibiotics (ampicillin and gentamicin) increased and the consumption of third generation cephalosporins decreased significantly without affecting NICU mortality. However, there was no significant change in the overall consumption of antibiotics. We observed an increase in the consumption of ciprofloxacin and colistin in the year after the initiation of antibiotic policy. Although, gentamicin was used empirically more often, subsequent change to ciprofloxacin was done based on antibiotic susceptibility results, and thus its consumption increased. The increase in colistin consumption was due to a temporary outbreak of carbapenem-resistant *Klebsiella* species sepsis in our NICU.

Our study has limitations. Firstly, we do not know if the empiric choice and duration of antibiotics for various sepsis categories have been followed as we lacked individual patient level data. Secondly, we only looked at one year data; it will be important to monitor further to know if the results remain sustained.

In this study, there was no significant change in overall consumption of antibiotics with antibiotic policy, the increased use of first line agents and reduction in use of third generation cephalosporins is encouraging because the quality of antibiotic use determines the prevalence of multi-drug resistance infections. Decreased consumption of broad spectrum antibiotics is associated with reduction in infections due to multi-drug resistant pathogens in NICUs [6]. Thus, our findings indicate the utility of antibiotic policy in the era of high antimicrobial resistance. However, the success of antibiotic policy could be compromised by poor infection control practices. Thus, implementation of strict infection control practices is essential in order to maximize benefits of an antibiotic policy.

Contributors: DRJ: conception or design of the work; DRJ, SG, GA-U: Analysis and Interpretation of Data: All authors are accountable for drafting the work or revising it critically for important intellectual content and final approval of the version to be published.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, *et al*. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13:1057-98.
2. Suryawanshi S, Pandit V, Suryawanshi P, Panditrao A. Antibiotic prescribing pattern in a tertiary level neonatal intensive care unit. J Clin Diagn Res. 2015;9:FC21-4.
3. Chatterjee S, Mandal A, Lyle N, Mukherjee S, Singh AK. Drug utilization study in a neonatology unit of a tertiary care hospital in eastern India. Pharmacoepidemiol Drug Saf. 2007;16:1141-5.
4. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr. 2008;75:261-6.
5. World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Norway: WHO, 2004. Available from: *http://www.who.int/classifications/atcddd/en/*. Accessed February 22, 2008.
6. 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.

Copyright of Indian Pediatrics 2017
For personal use only. Not for bulk copying or unauthorized posting to listserv/websites