SHORT COMMUNICATION

Restriction of Cephalosporins and Control of Extended Spectrum β-Lactamase Producing Gram Negative Bacteria in a Neonatal Intensive Care Unit

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This interventional study with historical controls was conducted to study the effect of cephalosporin restriction on the incidence of extended spectrum beta-lactamase (ESBL) gram negative infections in neonates admitted to intensive care unit. All gram negative isolates from the blood were evaluated for beta lactamase production. The incidence of ESBL production was compared before (year 2007) and after cephalosporin restriction (year 2008). Thirty two neonates (3% of NICU admissions) in the year 2007 and fifty six (5.2%) in the year 2008, had gram negative septicemia. The incidence of ESBL gram negatives decreased by 22% (47% to 25%, *P*=0.03). Restriction of all class of cephalosporins significantly decreased the incidence of ESBL gram negative infections.

Key words: *Cephalosporin, ESBL, Gram negative sepsis, India, NICU.*

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Indiscriminate use of broad spectrum antibiotics, prolonged courses of antibiotic therapy, dependence on C-reactive protein, and absence of culture facilities have resulted in increased incidence of extended spectrum betalactamases (ESBL), methicillin resistant *staphylococci aureus* (MRSA) and multi-drug resistant bacteria(1). Implementation of infection control measures, restricting the use of broad-spectrum antibiotics, rotation of antibiotics, and rationalizing the use of antibiotics can decrease antibiotic resistance(2,3). A few studies done in adult and pediatric intensive care units reported decreased incidence of ESBL gram negative infections after cephalosporin restriction(4-6).

METHODS

This study was conducted in the neonatal intensive care unit (NICU) of Fernandez Hospital, a tertiary care hospital with a delivery rate of approximately 4000 births per year. From January 2007 to December 2008, all neonates admitted to the NICU were eligible for the study. All neonates suspected to have infections either due to perinatal risk factors or due to clinical signs were subjected to sepsis screen and a blood culture was obtained before starting antibiotics. In the year 2007, the empirical antibiotic therapy included cefotaxime or ampicillin with amikacin. For treating a documented gram-negative organism, preference was given to cephalosporins over pipericillin-tazobactum, quinolones and imipenem/meropenem; in that order. From 1 January 2008, the policy was to restrict cephalosporins; ampicillin with amikacin was used for empiric antibiotic therapy. For blood culture positive infections, preference was given to quinolones, pipericillin-tazobactum, imipenem/meropenem over cephalosporins; in that order. If a baby had meningitis, cefotaxime/cefaperazone was the preferred drug.

The primary outcome was the incidence of ESBL gram-negative infections. The secondary outcome was gram-negative resistance to cefotaxime, amikacin, ciprofloxacin and pipericillin-tazobactum. Blood cultures were done with Bact Alert. Antibiotic susceptibilities were determined by disc diffusion method(7). Organisms showing resistance to ceftazidime, cefotaxime and ceftriaxone were taken as indicators of ESBL production. To confirm the presence of ESBL, double disc synergy test was performed.

The clinical and laboratory data of all eligible babies was collected prospectively in a structured proforma for the year 2008. The data for the year 2007 was collected retrospectively from the computerized clinical database, case files and the laboratory records. If more than one gram-negative organism was isolated in a baby, only the resistant organism was included in the study.

The primary and secondary outcomes were compared between years before and after antibiotic policy change. $P<0.05$ was considered significant. The institute ethics committee approved the study.

RESULTS

One thousand and forty six neonates were admitted to the NICU in the year 2007 and 1074 neonates in the year 2008. Among the admissions; the sex ratio, proportion of premature infants, VLBW infants, and infants requiring ventilation (synchronized ventilation or CPAP) were similar during the two epochs (***Table* I**). However, more babies received CPAP and central venous lines in 2008.

TABLE I BASELINE VARIABLES OF NICU ADMISSIONS

Variable	Pre restriction (year 2007) (*n*=1046) (%)	After restriction (year 2008) (*n*=1074) (%)	*P* value
Male	2194 (49)	2415 (50)	0.23
Preterm	845 (19)	960 (20)	0.18
VLBW	197 (4.4)	197 (4.1)	0.49
Ventilation	124 (2.8)	149 (3.1)	0.34
CPAP	83 (1.9)	120 (2.5)	0.03
Central lines	12 (0.2)	48 (1)	0.00001

VLBW=very low birth weight; CPAP = continuous positive airway pressure.

TABLE II ANTIBIOTIC USAGE PROFILE OF NICU ADMISSIONS

Variable	Pre restriction (year 2007) (*n*=1046)(%)	After restriction (year 2008) (*n*=1074)(%)	*P* value
Any antibiotics	324 (31)	376 (35)	0.05
Any cephalosporin	165 (15.8)	32 (3)	<0.001
Amikacin/ gentamicin	228 (21.8)	296 (27.6)	0.002
Ampicillin	133 (12.8)	276 (25.7)	<0.001
Ciprofloxacin	36 (3.4)	79 (7.3)	<0.001
Pipericillin-tazobactum	42 (4)	51 (4.8)	0.40
Meropenam	26 (2.5)	32 (3)	0.48

Similar proportion of NICU admissions were on antibiotics during the two epochs. In the year 2008, there was nearly five-fold decrease in the use of cephalosporins and nearly two folds increase in the use of ampicillin and ciprofloxacin compared to the year 2007 (***Table* II**).

Thirty-two neonates (3% of NICU admissions) in the year 2007 and fifty-six (5.2%) in the year 2008 had gram-negative septicemia; the mean weight (1592 ±719g *vs* 1618 ± 856g, *P* value 0.88), mean gestation (32 ± 3 wks *vs* 32 ± 3.6 wks, $P = 0.84$) and the age of onset of infections (5.2 ± 4 d *vs* 7.6 ± 9 d, $P=0.17$) were similar in the two groups. During the study period (both the epochs) the organisms isolated were *Klebsiella pneumoniae* (*n* = 44), *Pseudomonas aeruginosa* (*n*=16), *E.coli* (*n*=13), *Enterobacter sp* (*n*=12) and others (*n*=3). After cephalosporin restriction, the prevalence of ESBL gram negative organisms significantly decreased by 22%, cefotaxime resistant gram negatives decreased by 30% and that of ciprofloxacin resistant gram negatives by 27%. There was no change in the prevalence of gram negatives that are amikacin resistant or pipericillin-tazobactum resistant, and resistant to either ampicillin or amikacin (***Table* III**). The need to upgrade the empiric antibiotics significantly increased in the year 2008 as compared to year 2007 (48% vs. 26% respectively, $P <0.0001$). However, change in the antibiotic policy did not

WHAT THIS STUDY ADDS?

- Cephalosporin restriction leads to a decrease in the incidence of extended spectrum β-lactamase producing gram negative bacterial sepsis in a neontal unit.

TABLE III ANTIBIOTIC SUSCEPTIBILITY OF GRAM NEGATIVE INFECTIONS AND ESBL

Variable	Pre restriction(2007) (*n*=32)	After Restriction(2008) (*n*=56)	*P* value
ESBLs	15 (47)	14 (25)	0.035
Amikacin RGN	10 (31)	11 (20)	0.21
Cefotaxime RGN	26 (81)	29 (51)	0.006
Ciprofloxacin RGN	18 (56)	16 (29)	0.01
Pipericillin-tazobactum RGN	11 (34)	10 (18)	0.08
Ampicillin or Amikacin RGN	10 (31)	11 (20)	0.21

ESBL: Extended Spectrum β-Lactamase Producing Gram Negative Bacteria; RGN: resistant gram negative bacteria.

affect the mortality [(*n*=9 (28%) *vs*. *n*=13 (23%), *P* value 0.79] or duration of hospitalization (18 ± 14 d *vs*. 23 ± 19 d, *P* = 0.20) among infants with gram negative sepsis.

DISCUSSION

This study demonstrated that restricted use of cephalosporins significantly reduced the incidence of ESBL producing, cefotaxime resistant and ciprofloxacin resistant gram negatives. This reduction in ESBL was seen, eventhough the incidence of gram-negative sepsis was higher. The profile of organisms in our study is similar to that reported in other Indian studies(8,9). Antibiotic sensitivity before cephalosporin restriction is also similar to other reports from our region. In a study from North India, 61.5% of gram negative isolates were ESBL producers(9).

This experience of cephalosporin restriction is similar to that reported from pediatric and adult intensive care units(4-6). In a study on adult intensive care patients, 44% reduction in ceftazidime resistant *Klebsiella* infection was possible with 80% reduction in the use of cephalosporin antibiotics(4). In a study on pediatric patients by Lee, *et al*.(5), the incidence of ESBL gram negatives decreased from 39.8% to 22.3% with cephalosporin restriction. Third generation cephalosporins select for gram-negative bacilli that produce ESBLs, which render the bacteria resistant to many antibiotics and not just beta-lactams. Hence, reduced incidence of ESBLs also contributes to reduced resistance to other antibiotics. In our study, cephalosporin restriction resulted in 27% reduction in ciprofloxacin resistance, in-spite of a two fold increase in the use of ciprofloxacin.

A major limitation of the study is that it is not a randomized controlled trial. Many practices in the unit would have changed with time. In 2008, we used bubble CPAP for early management of RDS in place of mechanical ventilation, babies were started on aggressive parenteral nutrition and hence more babies were on central lines. Antibiotic usage was measured as percent of patients on specific antibiotics and not as duration of antibiotic days; and we included all babies with neonatal sepsis and not those only with nosocomial infections. No change was made in the antibiotic policy given to the mothers.

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