Antibiotic Use in Neonates of Birth-weight < 2000 G Surviving to Discharge

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Abstract

Background: Symptoms and signs of infection are non-specific in neonates. Hence, neonates, especially low birth-weight and premature ones, often receive empirical antibiotics. This study was conducted to assess the use of antibiotics in newborns with a birth-weight of < 2000 g at a tertiary care service hospital.

Methods: All infants < 2000 g at birth admitted to NICU were included. Data on symptoms, investigations for infection and use of antibiotics were collected in addition to baseline data. The data of those surviving to discharge was analyzed.

Results: Out of 52 eligible infants, 3 died; thus data from 49 neonates was analyzed. Preterm infants formed 89.8% of this group while 36.73% were Small for Gestational Age (SGA). Symptoms were present in 22 (44.9%) of whom 13 (59.1%) received antibiotics. Lower birth weight, lower gestational age and male sex predisposed to increased antibiotic use. A total of 21 courses of antibiotics were administered which averaged to 1.6 course or 15 days of therapy per patient. The most common combination used was cefotaxime-amikacin in 42.9% followed by ampicillin-gentamicin in 33.3%. The overall mortality for this group was 5.8% while mortality due to infection was 1.9%.

Conclusion: Attention to asepsis in the NICU, close monitoring and judicious use of antibiotics only when indicated can result in decreased empirical use of antibiotics and better outcome. Low birth-weight, prematurity and male sex are significantly associated with antibiotic use in this study.

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Key Words: Low birth-weight; Neonate; Sepsis; antibiotic use

Introduction

Bacterial infections are a major cause of morbidity and mortality in neonates. Symptoms are non-specific and diagnosis is rendered difficult as no single laboratory investigation can predict infection accurately [1]. Apart from predisposing maternal risk factors for infection, intrinsic immunological immaturity and underdevelopment of various general systems like skin and mucosa predispose neonates to infection [2]. The risk of infection increased with decreasing birth weight and prematurity [3-6]. Difficulty in diagnosis of neonatal bacterial infection leads to widespread use of antibiotics [7-9]. This study presents prospectively collected data on antibiotic use in newborns weighing < 2000 g, born at a tertiary care service hospital.

Material and Methods

Study setting: A Level III NICU of a tertiary care service hospital.

Study period : 01 January 2001 to 31 August 2003 (32 months)

Study subjects: All inborn neonates with birth weight < 2000 g surviving to discharge.

Data on Birth weight, Gestational age, Sex, Symptoms,

Sepsis screen, Blood culture, Chest radiograph, and Antibiotic use was prospectively collected.

Sepsis screen was done for all symptomatic infants and asymptomatic infants with maternal factors predisposing to infection. The screen was considered positive if at least two of : Total leukocyte count, Absolute neutrophil count, Immature to total ratio, Micro ESR, C-Reactive protein were abnormal.

Chest radiograph was done in all infants with respiratory symptoms. Blood culture was done for all symptomatic infants. In all infants being started on antibiotics, blood was drawn prior to the administration of the first dose of antibiotics.

The treating Neonatologist decided antibiotic use based on unit policy which consisted of starting antibiotics in the following situations:

- For all infants whose mothers had frank chorioamnionitis;
- For asymptomatic infants with specific maternal factors predisposing to infection (PROM, intrapartum fever, maternal urinary tract infection) only if sepsis screen was positive;
- For all symptomatic infants who had a positive sepsis screen, and;
- For those symptomatic infants who had negative sepsis

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screens but whose symptoms could not be attributed to any specific etiology (other than infection).

The drugs used, number of courses (one course was defined as ≥ 5 days of uninterrupted antibiotic use) and duration of therapy were recorded.

Statistical analysis was done using EPI Info 2000 and SPSS ver 7.5 statistical software packages.

Results

During the study period, 860 infants were admitted to the NICU, 52(6%) infants were eligible for inclusion in the study. Of these, 49 (94.2%) inborns < 2000 g survived to discharge. Infants who died included a male born at 23 weeks/540 g and a female born at 25 weeks/720g. Both these infants had severe respiratory distress syndrome and succumbed to ensuing complications. The third infant who died was a 34-weeks/1670g male who succumbed to sepsis following surgical repair of a tracheo-esophageal fistula. The overall mortality in the cohort was 5.8%(3/52) while mortality due to infection was 1.9%(1/52).

The 49 survivors had a mean birth weight of 1610.5g (s.d.310.9g; range 960-1990g); the mean gestational age was 34 weeks (s.d.2⁺⁴ weeks; range 27-39 weeks). Preterm (<37 weeks) infants constituted 89.8% (44/49) of the study population. There were 27 (55.1%) females and 22 (44.9%) males. There was no significant difference in the birth weight between the two sexes. Small for gestational age (SGA) infants formed 36.7% (18/49) of the study group, there being no significant difference in the sex distribution of SGA infants.

Overall, 22 (44.9%) infants were symptomatic, of whom 13 (59.1%) received antibiotics. Infants with a positive sepsis screen formed 40.9% (9/22) of all symptomatic infants and all 9 of them received antibiotics. In addition, 4 (18.2%) infants who were symptomatic but had a negative sepsis screen also received antibiotics. There were 9(40.9%) infants who were symptomatic but had negative sepsis screens and whose symptoms could be attributed to etiologies other than infection (e.g. polycythemia, hypoglycemia). These infants did not receive antibiotics.

Increased antibiotic use was significantly associated with lower birth weight, lower gestational age and male sex. Details of these significant factors influencing antibiotic use are depicted in Table 1. There was no significant difference in antibiotic use between appropriate for gestational age and SGA infants.

Amongst the 22 symptomatic infants, blood culture was positive in 9.1% (2/22). Another infant's blood grew contaminants and this infant was symptomatic but had repeated negative sepsis screens and did not receive any antibiotics.

A total of 21 courses of 5 days or more of antibiotics was administered to 13 infants (1.6 courses per treated infant). Infants who received a single course constituted 46.2% (6/21); 6 (46.2%) infants got two courses each while 1 (7.6%) infant was given 3 courses. A total of 195 days of antibiotic therapy was administered to 13 treated infants (mean 15 days; s.d.6.9 days).

The frequency of drugs used for the 21 courses were as follows: cefotaxime and amikacin combination was used in 9 (42.9%); ampicillin and gentamicin in 7 (33.3%); ceftazidime and netilmicin in 2 (9.5%); cloxacillin and amikacin in 1 (4.8%) and vancomycin in 2 (9.5%).

Discussion

Prematurity and low birth-weight (<2000 g) are known risk factors for neonatal infection [2-7] and studies from across the world have reported varying rates of infection and antibiotic use. We decided to include infants <2000 g at birth as all such infants in our institution are admitted to the Neonatal Intensive Care Unit (NICU) for observation.

A number of studies from abroad have looked at infection in specific groups like very low birth-weight (<1500 g) and preterm (<37 weeks) infants. Our population is different in that there are a large number of SGA infants. In one study from Armed Forces, out of 5211 infants born, 522 (10.6%) were < 2000 g at birth and of these 249 (45.1%) were SGA [10]. Thus we chose a cut-off birth-weight < 2000 gm rather than gestational age which would have excluded some of the 36.7% SGA infants of our study group.

Of the 22 symptomatic infants in our study, only 13 (59.1%) received antibiotics. In a retrospective study of 18299 neonates weighing 2000 g or more at birth of whom 2785 (15.2%) were symptomatic, Escobar and co-workers report antibiotic use in 1217 (43.7%) infants [11]. In a Canadian study of 20488 neonates admitted to NICU, 75% received antibiotics[9]. In contrast, only 26.5% of our infants received antibiotics. This can be explained by the fact that the unit policy on antibiotic use was strictly adhered to. Our Unit policy

Table 1
Factors significantly affecting antibiotic use (N=49)

Variable	Antibiotic group	No antibiotic group	p value
Number of infants	13 (26.53%)	36 (73.47%)	Not applicable
Birth weight (g)			
(a) Mean	1368.85	1697.78	p < 0.0001
(b) s.d.	391.66	224.72	
(c) Range	960-1990	1115-1990	
Birth weight Groups			
(a) < 1500 g	8 (61.53%)	5 (38.47%)	p < 0.001
≥ 1500 g	5 (13.89%)	31 (86.11%)	
(b) < 1250 g	7 (70.00%)	3 (30.00%)	p < 0.006
≥ 1250 g	6 (15.38%)	33 (84.62%)	
Gestational age (weeks^{+days})			
(a) Mean	31 ⁺³	34 ⁺⁶	p < 0.0001
(b) s.d.	2 ⁺⁵	3 ⁺²	
(c) Range	27-36 ⁺²	30 ⁺³ -39	
Sex			
(a) Females	4 (14.81%)	23 (85.19%)	p < 0.04
(b) Males	9 (40.91%)	13 (59.09%)	

on preventive measures including strict aseptic protocol, handwashing and close monitoring may have contributed to low antibiotic use. Data from other centers in the Armed Forces would shed more light on the prevalence of antibiotic use in newborns. We wish to emphasize the point that almost three quarters of infants < 2000 g at birth were not administered antibiotics in our unit.

Lower birth weight and lower gestational age were significantly associated with antibiotic use as in other studies [2-7]. In our study, 70% of infants < 1250 g received antibiotics while this proportion marginally decreased to 61.5% when all infants < 1500 g were considered. In fact, neonates < 1500 g are known to be at high risk for infection due to a number of predisposing factors like immaturity, high morbidity and increased intervention [12]. In a study on 7861 infants < 1500g, almost half were considered to have clinical sepsis and 98% received antibiotics for 5 days or more despite a negative blood culture [13]. Given the much smaller sample size of this subgroup, the 61.5% treated with antibiotics compares well with other studies.

The mean gestational age of the study population was 34 weeks while the mean gestation of infants who received antibiotics were significantly lower at 31⁺³ weeks.

Most studies do not mention the proportion of SGA infants. In our study, only 3 out of 18 SGA infants received antibiotics though this was not significantly different from non-SGA infants. Thus, SGA infants by themselves do not appear to be at higher risk of infection and antibiotic therapy.

Despite there being slightly more females compared to males (27/22); significantly lesser females received antibiotics. One Indian study on *Acinetobacter* sepsis in neonates reported a female preponderance [14]. Male sex appears to be a risk factor according to our study but this needs further confirmation by larger studies.

Amongst symptomatic infants, blood culture positivity rates vary widely in different studies, ranging from 0.79% [11] to 36.7% [5]. In our study, 9.1% of symptomatic infants had a positive blood culture.

In this study, the most common combination of antibiotics used was cefotaxime and amikacin (42.9%) which we use for late onset sepsis (onset > 72 hrs of life). The next common regime was ampicillin and gentamicin (33.3%) used by us for early onset sepsis. Though one African study concludes that gentamicin alone is sufficient[3], it is generally established that combination therapy of a penicillin/cephalosporin and aminoglycoside is effective. Due to emerging resistance to ampicillin, one Indian study recommends use of a cephalosporin and aminoglycoside combination as first

line therapy [5]. Our choice of antibiotics appears to be appropriate in view of the low sepsis related mortality in our patients.

In conclusion, this study reveals the possibility of restricted use of antibiotics in neonates <2000g at birth. Birth-weight < 1500g, male sex and a gestational age < 34 weeks were significantly associated with increased antibiotic use. Based on our experience, we recommend use of antibiotics for low birth weight infants (<2000g) only in situations enumerated in the Material and Methods.

This study has the drawback of a relatively small number of infants. Analysis of pooled data from neonatal units of the Armed Forces will enable us to draw realistic conclusions on the prevalence and pattern of antibiotic use in low birth-weight neonates.

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