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ORIGINAL RESEARCH ARTICLE

FACTORS PREDICTING FAILURE OF EMPIRICAL ANTIBIOTIC THERAPY IN NEONATAL SEPSIS IN THE FIRST ONE WEEK OF LIFE

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ABSTRACT

Background: World Health Organization recommends ampicillin and gentamicin as empirical antibiotics for treatment of neonatal sepsis. However not all neonates respond to the empirical antibiotics. This study was conducted to find out the risk factors associated with treatment failure to these antibiotics so that alternative antibiotics can be started at the outset to ensure a successful discharge from hospital.

Methods: A prospective, observational study was conducted in the neonatal intensive care unit of a tertiary-level hospital of Western Nepal from January 15 2019 to January 14 2020. Neonates < 7 days old with neonatal sepsis were enrolled into the study. Babies who died or whose antibiotics were changed from the empirical antibiotics to second-line antibiotics within 48 hours were classified as treatment failure. Various parameters were compared between the treatment failure group to the group who did not fail on the empirical antibiotics. Binary logistic regression analysis was carried out keeping treatment failure as the dependent variable and various independent variables were identified which predicted the chances of treatment failure.

Results: Out of 173 neonates admitted for sepsis, 19 (11%) developed treatment failure. Binary logistic regression analysis found 5 min Apgar <7 (p-value=0.005), need for vasoactive support (p-value= <.001) and culture positivity (p-value= 0.009) correctly predicted treatment failure.

Conclusions: In presence of Apgar score <7 at 5 minutes, need for vasoactive support and culture positivity, it would be beneficial to start alternative antibiotics according to the local microbiological flora to minimize complications and ensure better outcome.

INTRODUCTION

Nearly 3 million neonates suffer from sepsis globally every year and three out of 10 neonatal sepsis-related deaths are due to resistant pathogens.[1,2] The major pathogens causing neonatal sepsis in low and middle income countries are gram negative bacteria (*Klebsiella spp*, *E.coli*, *Enterobacter spp*, *Acinetobacter spp*,) and some gram positive bacteria like *methicillin-resistant Staphylococcus aureus (MRSA)*.[3-5] World Health Organization (WHO) recommends benzylpenicillin/ampicillin and gentamicin in newborns with documented risk factors for infection. For staphylococcal infection, cloxacillin and gentamicin are recommended.[6] But neonatologists working in neonatal intensive care units (NICUs) are frequently faced with cases of empiric antibiotic failure. This could be due to development of antimicrobial resistance, growth of organisms not susceptible to the empirical antibiotics or fungal etiology of sepsis.[5,7-11] Besides these factors, certain maternal, perinatal or inherent neonatal factors might render them unsusceptible to the first-line antibiotics.

Several studies in adults have shown that delay in starting appropriate antibiotics in sepsis can be associated with higher mortality and prolongation of hospital stay.[12-14] A study conducted in neonates with gram negative bacteremia found inappropriate antibiotic therapy was associated with worse outcomes, a higher risk of organ damage and higher mortality.[15]

Therefore, there is a need to analyze the risk factors associated with empiric antibiotic failure to minimize the chances of complications, shorten hospital stay as well as reduce hospital costs. The aim of our study was to find the various clinical factors associated with failure of empirical antibiotics in neonates with sepsis in the first one week of life.

METHODS

This prospective, observational study was conducted in the neonatal intensive care unit (NICU) of a tertiary level hospital of Western Nepal from January 15 2019 to January 14 2020. This study was conducted after receiving ethical approval from the institutional review board (IRB) of Manipal Teaching Hospital. The study participant's parents were explained about the study and its objectives in local Nepali language and written informed consent was taken from the parents before enrolling them into the study. All neonates less than one week of age receiving ampicillin and gentamicin as first line antibiotics and admitted for suspected neonatal sepsis or with risk factors for sepsis were included in the study. Those babies who received antibiotics other than mentioned previously, presence of severe infection like meningitis clinically suspected at time of admission, extremely preterm babies or those babies who were

referred to other centers within first 24 hours of admission were excluded from the study. After enrolment, maternal demographics as well as baby's characteristics were noted on a pre-designed proforma. Resuscitation details at delivery, examination and laboratory investigation findings were noted. Certain criteria were pre-specified as indications for changing the antibiotics: 1) No improvement in clinical status even at 48 hours of starting empirical antibiotics, 2) appearance of clinical signs of deterioration, 3) isolation of bacteria resistant to empirical antibiotics, 4) suspicion of nosocomial infection and 5) any situation where the treating physician considered it necessary to change antibiotics.

For the purpose of this study, following case definitions were used:

1. Clinical signs of sepsis was defined if there were presence of at least two or more signs of the following: a) Body temperature: <36^{o} C or > 38.5^{o} C or temperature instability; b) Cardiovascular signs: bradycardia or tachycardia and/or rhythm instability or hypotension or mottled skin or impaired peripheral perfusion (capillary refill time > 2 seconds or low urine output (< 1 ml/kg/hour); c) Respiratory signs: apnea or tachypnea or increased oxygen requirements or requirement of ventilator support; d) Gastrointestinal signs: feeding intolerance or poor sucking or abdominal distension; e) Skin or subcutaneous tissue signs: petechiae or sclerema; f) Non-specific signs: irritability or lethargy or hypotonia.[16]

2. Laboratory signs of sepsis was defined if there were presence of at least two or more of the following: a) White blood cell count < 4000/ cu.mm or > 20,000/ cu.mm; b) Immature to total neutrophil ratio (I/T ratio) >0.2; c) Platelet count < 1,00,000/ cu.mm; d) C-reactive protein (CRP) > 15 mg/L; e) Hypoglycemia (<45 mg/dl) or hyperglycemia (>180 mg/dl) on two or more occasions; f) metabolic acidosis.[16]

3. Confirmed sepsis was defined if cases had at least two clinical signs with at least two laboratory evidence of sepsis and growth of any pathogen on blood, urine or any body fluid culture. This definition was adapted from guidelines provided by the European Medicine Agency (EMA).[16]

4. Cases where antibiotics were changed at ≤ 48 hours or cases of neonatal mortality within 48 hours were considered as treatment failures

Data were analyzed by SPSS ver 20. Normality was tested by Shapiro-Wilk test. Quantitative data were presented as absolute numbers (%) where required or mean (±SD) for normally distributed data. Where data were non-normally distributed, it was presented as median (IQR). The two groups (treatment failure and no treatment failure) were compared for various characteristics. Bivariate analysis was done using Chi-square tests to compare the two groups. For analysis of continuous variables we used independent sample t-test or Mann-Whitney test as necessary. A p-value of <0.05 was taken as statistically significant. All the predictor variables which showed a statistically significant finding were then entered into a binary logistic regression model keeping treatment failure as the dependent variable. Data were then presented as odds ratio with 95% confidence interval with level of significance if p-value was <0.05.

RESULTS

A total of 638 neonates were admitted to NICU during the study period during which time 240 neonates were admitted with the diagnosis of neonatal sepsis. Of them 173 neonates were admitted on ampicillin and gentamicin while 67 neonates were excluded as 42 of them had severe signs of sepsis at admission and were started on alternative antibiotics, 12 were transferred to higher center on parent's request within 24 hours of admission and 13 neonates were extremely premature. Culture positivity was seen in 38 (22%) cases; it was higher in inborn as compared to outborn babies (26.3% versus 12.7%). Resistance to ampicillin, gentamicin and combined ampicillin-gentamicin was seen in 26 (86.7%), 12 (40%) and 11 (36.7%) of inborn babies as compared to 7(100%), 2 (28.6%) and 2 (28.6%) of outborn babies respectively; however these findings were not statistically significant. Pathogen isolation was highest in case of blood 33 (76.7%) followed by urine 6 (14%). Table 1 elaborates the general demographic characteristics of patients admitted for neonatal sepsis in our study.

Table 1: General characteristics of neonates with sepsis

Total cases	173
Treatment failure	19 (11%)
Male gender; n(%)	108(62.4%)
Inborn; n(%)	118 (68.2%)
Prematurity; n(%)	78 (45%)
Small for gestational age; n(%)	20 (11.6%)
Low birth weight; n(%)	90 (52%)
Rupture of membranes >18 hours; n(%)	38 (22%)
Apgar score	
1 minute; median (IQR)	7(2, 9)
5 minute; median (IQR)	8(5,10)
Age at admission in hours; median (IQR)	2(1, 144)
At least two clinical signs of sepsis; n%	104(60%)
At least two laboratory signs of sepsis; n%	46(26.6%)
Confirmed sepsis; n%	10(5.8%)
No. of pathogens grown	
Single growth	32 (86.5%)
>1 growths	5 (13.5%)

SD, standard deviation; IQR, interquartile range

Out of the 173 neonates, 19 (11%) cases developed treatment failure. The treatment failure group consisted of one baby (5.26%) who died within 48 hours of admission while in 18 (94.7%) cases antibiotic was changed from ampicillin and gentamicin to second-line antibiotics. Reason for antibiotic change was clinical deterioration in 14 (73.6%), no improvement even after 48 hours of starting empirical antibiotic in 3 (15.7%) and growth of organism (Klebsiella spp) resistant to empirical antibiotics in one (5.26%) case. Twelve (63%) babies in treatment failure group had positive cultures and resistance to ampicillin, gentamicin and combined ampicillin-gentamicin was seen in 10 (83.3%), 5 (41.7%) and 4 (33.3%) respectively.

Table 2 shows the comparison between the two groups of treatment failure and no treatment failure. Treatment failure was seen in 16 (13.6%) cases of inborn babies while it was 3 (5.4%) of outborn babies.

Table 2: Comparison between the groups of treatment failure and no treatment failure

Variables	Treatment failure (n=19)	No treatment failure (n=154)	p-value*
Maternal risk factors :			
Intrapartum fever	3 (15.8%)	3 (1.9%)	**0.002**
Maternal UTI	2(10.5%)	8(5.2%)	0.347
Rupture of membrane in hrs; median(IQR)	0.0(0-120)	0.0(0-72)	0.381
No. of vaginal examinations; median (IQR)	2(0-2)	2(0-3)	0.987
Perinatal risk factors:			
Need of respiratory support in delivery room	7(36.8%)	51(33.1%)	0.746
1 minute Apgar score < 7	14 (73.7%)	54 (35.1%)	**0.001**
5 minute Apgar score <7	5(26.3%)	13(8.4%)	**0.016**
Neonatal risk factors:			
Gestational age in weeks; mean(SD)	34.5(3.9)	36.2(2.7)	0.081
Birth weight in grams; mean(SD)	2065(872)	2390(812)	0.137
SGA n(%)	1(5.3%)	19(12.3%)	0.363
Very low birth weight (VLBW); n(%)	7(36.8%)	22(14.3%)	**0.013**
Early onset sepsis; n(%)	19(100%)	149(96.8%)	0.425
Admission findings:			
Age at admission in hours; median (IQR)	1(1,20)	2(1,144)	**0.023**
Temperature abnormality	7(36.8%)	32(20.8%)	0.114
Respiratory distress	17(89.5%)	102(66.2%)	**0.039**
Hypoglycemia	3(15.8%)	6(3.9%)	**0.028**
At least 2 clinical signs of sepsis	16(84.2%)	88(57.1%)	**0.023**
At least 2 laboratory evidence of sepsis	10(52.6%)	36(23.4%)	**0.006**
Laboratory findings:			
Abnormal WBC count; n(%)	9(47.4%)	76(49.4%)	0.87
Low platelet count; n(%)	3(15.8%)	13(8.5%)	0.297
I/T ratio>0.2; n(%)	7(36.8%)	23(14.9%)	**0.017**
CRP>15 mg/L; n(%)	6(31.6%)	23(14.9%)	0.067
Culture positivity; n(%)	12(63.2%)	26(17%)	**<.001**
Events in 1st 48 hours of admission:			
Seizures	4 (21%)	8 (5.2%)	**0.01**
Need for mechanical ventilation	4 (21%)	4 (2.6%)	**<.001**
Need for vasoactive support	11 (58%)	10 (6.5%)	**<.001**
Clinical deterioration	13 (68.4%)	23 (15%)	**<.001**

IQR, interquartile range; UTI, urinary tract infection; SD, standard deviation; SGA, small for gestational age; VLBW, very low birth weight; WBC, white blood cell count; I/T ratio, immature to total neutrophil ratio; CRP, C-reactive protein
* p-values were calculated by Chi-square test or independent sample t-test where required

Binary logistic regression analysis showed that the overall model explained 21.3% to 43% variance in treatment failure and it correctly classified treatment failure 91% of the time. After controlling for all others factors, only five minute Apgar <7 (p-value= 0.005; 95% CI: 1.9-33), culture positivity (p-value= 0.009; 95% CI: .1.5-17.3) and need for vasoactive support (p-value= <.001; 95% CI: 4.25-55) were found to correctly predict treatment failure (Table 3).

Table 3: Results of binary logistic regression with treatment failure as dependent variable

Variables	OR	95% CI
5 minute Apgar <7	7.9	1.9-33
Positive growth on culture	5.12	1.5-17.3
Vasoactive support	15.2	4.25-55

DISCUSSION

Our study was conducted to find out the factors associated with treatment failure in neonates admitted for sepsis in the first one week of life. We found that 19 (11%) of the neonates started on WHO recommended empiric antibiotics developed treatment failure. Most common reason for failure was change of antibiotics due to clinical deterioration in the first 48 hours of admission. In one case antibiotic was changed due to growth of organism *(Klebsiella spp)* resistant to the first-line empiric antibiotic. One baby died within 48 hours of admission and hence was regarded as treatment failure. This baby had poor respiratory efforts at birth requiring assisted respiratory support and had clinical and laboratory signs of sepsis but blood culture was negative for growth. This baby was categorized into the treatment failure group as per the criteria we had set; but we have no way of identifying whether this baby died due to birth asphyxia or empirical antibiotic failure.

Initial bivariate analysis identified several clinical parameters predicting treatment failure, however final results of logistic regression show only 5-minute Apgar score <7, culture positivity and need for vasoactive support as being predictive of treatment

failure. A low Apgar score is seen in asphyxiated babies; asphyxia causes an immunological insult and the resuscitative efforts during delivery like suctioning and endotracheal intubation have been cited as a source of bacteremia leading to sepsis.[17,18] In sick neonates there are no clinical signs which differentiate sepsis from asphyxia and those neonates who have sepsis with asphyxia are likely to undergo rapid clinical deterioration hence needing an early change in antibiotics. In a study conducted in Bangladesh by Hasan et al, 70% out of 50 neonates with an Apgar score < 7 developed sepsis (p=<0.046) and the chances of developing sepsis was 2.8 times greater in this group.[18] Similar findings have been observed in other studies as well.[19-21]

Blood culture is considered the "gold standard" for diagnosis of neonatal sepsis.[22] A report by WHO Sepsis Technical Expert Meeting states that the main pathogens causing sepsis in newborn period are gram-negative bacteria *(Klebsiella spp., Enterobacter spp., Acinetobacter spp.)* and *MRSA* among the gram-positive bacteria in low and middle-income countries.[3-5,23] In our study, although culture positivity was present in 38 (22%) cases; only 10 cases (5.8%) fulfilled the criteria for confirmed sepsis. *E. coli* was the most commonly isolated gram-negative pathogen isolated followed by *Acinetobacter spp.* and *Enterobacter spp*. In our study *Klebsiella spp.* was seen in 3 (6.9%) cases only and one of these three cases died within 48 hours of admission. *MRSA* was the most common gram positive bacteria isolated. Studies conducted in NICUs across Nepal have found culture positivity rates of 10.8-20%.[24-28] The bacteriological profile found at these centers were somewhat similar to ours with the exception being *MRSA* isolated in our studies as opposed to *Staphylococcus aureus* in those studies.[24-28] Some of these studies found that most of the isolates (gram positive as well as gram negative) were resistant to ampicillin.[25,27] Whereas the susceptibility to gentamicin was intermediate in some while some studies found most bacteria to be sensitive to gentamicin.[25,27,28] In a study conducted in Taiwan, 79% of the *E.coli* isolates were resistant to ampicillin while 16% were resistant to gentamicin.[29] A systematic review of studies across sub-Saharan Africa and the Indian sub-continent including Nepal conducted after year 2000 on community-acquired invasive bacterial infections and antibiotic resistance patterns show a high degree of resistance to the combination of ampicillin and gentamicin. However they were unable to draw any conclusion regarding *MRSA*.[9] Similarly a study conducted in Egypt found 100% of the gram negative isolates were resistant to ampicillin while 36-52% were resistant to gentamicin. They also found a high degree of resistance of *MRSA* to both ampicillin and gentamicin.[11] Our study shows a similar finding with higher resistance to ampicillin and intermediate resistance to gentamicin.

Our study found need for vasoactive support to be a significant predictor for treatment failure. In severe sepsis there is a systemic response to the pathogen which causes vasodilatation and capillary leak. Cardiovascular support with inotropic agents are key aspects of successful management in such scenarios.[30,31] Neonates with shock are usually more sicker and need more aggressive treatment than those babies without shock. These are the groups of babies who undergo rapid clinical deterioration and succumb to the illness if not identified in time. A study in neonates with early onset sepsis found that babies who developed shock had an adverse outcome as compared to those who were discharged home.[32] Metsvaht et al in their study also found need of vasoactive treatment as a significant predictor of empiric antibiotic failure in a cohort of 283 neonates with 11.6% treatment failure.[33]

Some interesting findings we observed in our study were that our inborn babies had a more complicated course, they required more resuscitative measures during delivery, there were more cases of culture positivity and treatment failure as compared to the outborn babies. The reason could be that our hospital is a tertiary care referral hospital and receives complicated unbooked delivery cases which could increase the chances of complications at delivery and might influence the outcome of the babies. Also neonates born outside this hospital are treated in private hospitals and are referred after complications develop which might have influenced the treatment failure rate.

The strengths of our study is that this is the first study of its kind conducted in our part of the world. Understanding the risk factors which might be associated with failure of ampicillin and gentamicin as empirical antibiotics in neonatal sepsis will guide us with management of neonates having increased likelihood for failure to these antibiotics.

The limitations of our study are the small sample size and this study being limited to a single center. As this was an observational study we analyzed only the factors associated with treatment failure; it would have been better if we could conduct a randomized control trial comparing ampicillin/gentamicin to other empirical regimens. We also could not identify the other confounding factors like death or clinical deterioration due to birth asphyxia or non-sepsis-related problems which might have influenced us to change antibiotics; this could have led us to believe the baby failed on empiric antibiotics.

CONCLUSION

Our study aimed to identify the risk factors associated with failure of ampicillin and gentamicin in neonatal sepsis. Our results show that an Apgar score <7 at 5 minutes, need for vasoactive support within 48 hours of admission and culture positivity are associated with treatment failure. In presence of these risk factors, it might be beneficial to start alternative antibiotics so as to manage the cases before complications occur. We would also like to suggest a larger study to identify the current microbial susceptibility pattern so that empiric antibiotic protocol can be revised in our institute based on susceptibility pattern.

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