Predictors of Poor Outcome in Neonates with Bacterial Sepsis Admitted to the University Hospital of the West Indies

H Trotman[1], Y Bell[1], M Thame[1], AM Nicholson[2], M Barton[1]

ABSTRACT

To determine factors that affect outcome in neonates with culture-proven sepsis, the charts of all neonates with culture-proven sepsis admitted to the University Hospital of the West Indies between January 1995 and December 2000 were reviewed retrospectively. Neonates who survived without developing any complications (favourable outcome group) were compared with those who died and/or developed severe complications during the course of treatment (poor outcome group). Chi-square tests were done to determine factors associated with poor outcome; univariate and multivariate logistic regression analyses were also performed. One hundred and thirty-five neonates had culture-proven sepsis, of which 89 (66%) were term infants and 46 (34%) were preterm. Male to female ratio was 1.6:1. One hundred and twenty-six (93%) survived and 9 (7%) died. Case fatality rates were higher for premature infants (15%) than for term infants (2%). Twenty-four (18%) of the neonates with culture proven sepsis had a poor outcome. Gram negative organisms accounted for 19 (70%) of the cases with poor outcome. Prematurity (p < 0.001), very low birthweight (p < 0.001) and female gender (p < 0.05) were factors associated with poor outcome. Strategies aimed at decreasing morbidity and mortality in neonates with sepsis must include measures that will decrease the incidence of prematurity and low birthweight.

Predictores de Resultados Clínicos Pobres en Recién Nacidos con Sepsis Bacteriana, Ingresados en el Hospital Universitario de West Indies

H Trotman[1], Y Bell[1], M Thame[1], AM Nicholson[2], M Barton[1]

RESUMEN

A fin de determinar los factores que afectan la evolución clínica de los recién nacidos con sepsis probada por cultivo, se realizo un estudio retrospectivo de las estadísticas de todos los neonatos con sepsis probada por cultivo, ingresados en el Hospital Universitario de West Indies entre enero de 1995 y diciembre de 2000. Los neonatos que sobrevivieron sin desarrollar complicación alguna (el grupo de resultados clínicos favorables) fueron comparados con los que murieron y/o desarrollaron complicaciones severas durante el curso del tratamiento (el grupo de resultados clínicos pobres). Se realizaron pruebas de chi-cuadrado para determinar los factores asociados con los resultados clínicos pobres. También se llevaron a cabo análisis de regresión logística univariable y multivariable. Ciento treinta y cinco recién nacidos presentaron sepsis probada por cultivo. De ellos, 89 (66%) eran infantes de término y 46 (34%) de pre-término. La proporción varón/hembra fue 1.6:1. Ciento veintiséis (93%) sobrevivieron y 9 (7%) murieron. Las tasas de fatalidades fueron más altas para los infantes prematuros (15%) que para los infantes de término (2%). Veinticuatro (18%) de los neonatos con sepsis probada por cultivo tuvieron resultados clínicos pobres. Organismos gram-negativos fueron la causa de 19 (70%) de los casos con resultado clínico pobre. La prematuridad (p <0.001), el peso extremadamente bajo al nacer (p <0.001) y el sexo femenino (p <0.05) fueron factores asociados con el resultado clínico pobre. Las estrategias dirigidas a disminuir la morbilidad y la mortalidad en los recién nacidos con sepsis tienen que incluir medidas que reduzcan la incidencia de la prematuridad y el bajo peso.

From: Departments of Obstetrics Gynaecology and Child Health[1] and Microbiology[2], The University of the West Indies, Kingston 7, Jamaica.

Correspondence: Dr H Trotman, Department of Obstetrics Gynaecology and Child Health, Section of Child Health, The University of the West Indies, Kingston 7, Jamaica. Fax: (876) 927-1446, e-mail: helen.trotmanedwards @uwimona.edu.jm

INTRODUCTION

In developing countries, sepsis is an important contributor to neonatal mortality and morbidity, accounting for just over a third of all neonatal deaths annually, as well as being the major reason for admission to the neonatal unit (1–6).

Due to the immaturity of their immune system, neonates exhibit a high propensity for infections as well as a limited ability to confine these infections. These factors increase the neonate's likelihood of developing severe infection with a higher probability of unfavourable outcome (7). Any factor that reduces the ability of the already compromised immune system to combat infection has the potential to increase morbidity and mortality. In addition, bacterial virulence factors as well as timing of intervention and choice of antimicrobial therapy impact on outcome. Defining the clinical profile of the neonate at risk for poor outcome will promote early identification of neonates most in need of close monitoring and critical care, thus allowing for earlier initiation of aggressive therapy. Determining the clinical risk profile sets the stage for the development of strategies directed at preventing poor outcome.

Few studies address factors predicting outcome in neonates with bacterial infections in developing countries, particularly in the English-speaking Caribbean. This study seeks to identify factors associated with poor outcome in neonates with bacterial sepsis in order to institute preventive strategies that will decrease morbidity and mortality.

MATERIALS AND METHODS

The University Hospital of the West Indies (UHWI) is located in urban Jamaica and is affliated with the University of the West Indies (UWI). The neonatal unit at the UHWI is a 30-bed unit; 95% of the neonates admitted to the unit are inborn.

This was a retrospective, hospital-based, single- centre study looking at all neonates aged 0–30 days admitted to the neonatal unit at the UHWI during the six-year period January 1, 1995 to December 31, 2000 with a diagnosis of culture proven bacterial sepsis. These neonates were categorized into one of two groups (Poor Outcome or Favourable Outcome) based on outcome at end of therapy. Data on characteristics such as age, gestational age, gender and birthweight as well as clinical and laboratory features were collected and compared between the two groups.

DEFINITIONS

Neonatal sepsis was defined as the presence of positive bacterial cultures in the blood, cerebrospinal fluid (CSF), or urine, associated with systemic clinical signs of infection such as fever, temperature instability, irritability, poor feeding and respiratory distress.

Coagulase-negative Staphylococcus was considered a pathogen if the organism was isolated within 24–48 hours from the set of blood cultures taken from a peripheral vein in association with two or more clinical and/or laboratory features of sepsis. (This definition was developed by consensus among the investigators).

Poor outcome was defined as death or the development of severe complications (anaemia, prolonged thrombocytopaenia, disseminated intravascular coagulopathy, bleeding, shock, organ failure, seizures and hydrocephalus) as sequelae of sepsis. (This definition was also developed by consensus among the investigators).

Preterm – liveborn infant delivered before 37 completed weeks from the first day of the last menstrual period (WHO definition).

Early onset infection (EOD) – infections occurring during the first 6 days of life.

Late onset infection (LOD) – infections occurring at 7–30 days of life.

Prolonged rupture of membranes (PROM) – rupture of membranes for more than 18 hours.

Death as a sequel of sepsis – death occurring within ten days of a positive culture.

Complications of sepsis – complications occurring within seven days of a positive culture.

Ethical approval was granted by the UHWI/UWI Ethics Committee.

Continuous variables were expressed as means ± SD; differences between the two groups were determined using an independent Student's t-test. Categorical variables were analyzed using the chi-square test with $\propto$ significance at 5%. The Mann-Whitney test was used for non-parametric values. Predictors of poor outcome were analysed using logistic regression. Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 11.

RESULTS

One hundred and thirty-five neonates had culture-positive bacterial infection of which 89 (66%) were term and 46 (34%) were preterm. A total of 126 (93%) survived and nine (7%) died. The case fatality rate was higher for premature infants (15%) than for term infants (2%). There were 83 (61.5%) males and 52 (38.5%) females. Five (55%) of the infants who died were male; the male to female ratio of the survivors and non-survivors was 1.6:1 and 1.25:1 respectively. The male non-survivors were heavier and more mature than the female non-survivors, with a mean birthweight of 2.0 ± 1.3 kg and gestational age of 33.6 ± 6 weeks compared to 0.97 ± 0.32 kg and 28 ± 4 weeks for females.

Seven (78%) of the nine infants who died were preterm infants. The mean birthweight and gestational age of the non-survivors were 1.6 ± 1.2 kg and 30.7 ± 6 weeks respectively. The median age at the time of diagnosis was seven (range 0–24) days. Four (44%) babies were born to primigravid mothers and two (22%) babies were born to mothers who had prolonged rupture of membranes. Six (67%) babies had Gram-negative sepsis, *Klebsiella sp* accounted for four (44.4%) of the deaths. Four (44%) non-survivors had anae-

mia and thrombocytopenia, three (33%) had glucose abnormalities at presentation, one was hypoglycaemic and two were hyperglycaemic. Seven (78%) inborn babies died.

Major complications seen as sequelae of sepsis included abnormal counts (thrombocytopenia and anaemia) in 11 (8%) babies, bleeding in five (45%) and disseminated intravascular coagulation with shock in two (18%). One preterm infant who had intraventricular bleeding went on to develop hydrocephalus. Three (2%) neonates developed multiorgan failure and six (4%) neonates developed seizures. Mechanical ventilation was required by seven (5%) of the neonates.

Twenty-four (18%) of the neonates fulfilled criteria for poor outcome whilst 111 (82%) were considered to have a favourable outcome. Table 1 shows the maternal charac-

Table 1: Maternal characteristics of infants with culture positive sepsis by outcome

Characteristic	Favourable outcome n = 111	Poor outcome n = 24	p value
Mean ± SD age (years)	27.7 ± 5	24.9 ± 5	0.04
Primigravid (%)	68 (61)	18 (75)	0.10
Mode of delivery vaginal (%)	78 (70)	14 (58)	0.10
Ceaserian section (%)	33 (30)	10 (42)	
PROM > 18 hours (%)	9 (8)	5 (21)	0.08
Pre-term delivery (%)	29 (26)	17 (71)	0.00

Age and parity were unknown for one mother and length of rupture of membranes was unknown for two mothers in the favourable outcome group.

teristics of neonates with culture positive sepsis by outcome. Mothers of babies in the poor outcome group were significantly younger and had a higher proportion of preterm deliveries than the mothers of the babies in the group who had a favourable outcome. Of the 16 preterm infants in the poor outcome group, 11 (69%) had mothers who were primigravid. There was also a higher proportion of mothers who had prolonged rupture of membranes in the poor outcome group compared to the favourable outcome group but this did not achieve statistical significance.

Table 2 shows the characteristics of neonates with culture positive sepsis, by outcome. Babies in the poor outcome group were less mature and had a lower birthweight than those in the favourable outcome group and at presentation had a significantly lower median haemoglobin level ($p < 0.001$). Their median platelet count at presentation was also lower than that of the infants in the favourable outcome group ($p < 0.05$).

Table 3 shows the isolates cultured from the neonates with sepsis, by outcome. Gram negative organisms accounted for 19 (70%) of the cases with poor outcome. *Klebsiella sp* accounted for 14 (52%) of the isolates in infants with poor outcome. Thirty-five percent of infants with *Klebsiella*

Table 2: Characteristics of neonates with culture positive sepsis by outcome

Characteristic	Favourable Outcome Result	n	Poor Outcome Result	n
Median age at presentation/ range (days)	5.0 (0–30)	103	7.5 (0–30)	22
Median gestational age/range (weeks)	38.0 (29–42)	111	34.0 (26–40)**	24
Median birthweight/range (Kg)	3.1 (0.85–4.9)	111	1.4 (0.6–4.2)**	24
Median duration of therapy/ range (days)	10.0 (7–21)	96	10.0 (1–21)	20
M: F	1:0.5	111	1:1.6	24
Median Hb/range (g/dl)	14.2 (4.6–19.6)	92	11.1 (4.9–20.6)**	20
Median WBC/range (10^6/L)	13.1 (3.8–47.2)	89	13.7 (2.8–33.7)	20
Median platelet count/ range (10^9/L)	222 (11–676)	91	159 (14–426)*	20

** $p < 0.001$ * $p < 0.05$ Mann-Whitney

Table 3: Isolates cultured from neonates with sepsis by outcome

Gram negative bacteria	Favourable outcome n (%)	Poor outcome n (%)
Klebsiella sp	26 (22)	14 (52)
Escherichia coli	23 (19)	1 (4)
Enterobacter sp	11 (9)	3 (11)
Pseudomonas sp	3 (2)	1 (4)
Proteus sp	3 (2)	–
Serratia sp	2 (2)	–
Acinetobacter sp	2 (2)	–
Citrobacter sp	2 (2)	–
Alkaligines sp	1 (1)	–
Gram positive bacteria		
Coagulase negative staphylococci	11 (9)	2 (7)
Staphylococci aureus	9 (8)	3 (11)
Group B Streptococci	14 (12)	1 (4)
Streptococcus viridans	2 (2)	–
Anaerobic Streptococcus	1 (1)	–
Streptococcus Group D	8 (7)	2 (7)
Total	**118**	**27**

An individual neonate could have organisms isolated from more than one site

sepsis had a poor outcome. There was however no significant difference in outcome based on type of organism.

Thirteen (54%) infants in the poor outcome group presented with EOD while 46 (41%) babies in the favourable outcome group presented with EOD. There was no difference in outcome based on the age at presentation. The most common presenting clinical symptoms were fever (43, 37%), respiratory distress (35, 30%), poor feeding (26, 22%) and lethargy (25, 21%). No significant differences in presenting symptoms between the two outcome groups were noted.

Predictors of poor outcome
Male infants were less likely to have a poor outcome than female infants (OR 0.3; CI 0.12, 0.75) however the female

infants were significantly smaller and less mature than the male infants, with a mean birthweight of 2.5 ± 1 kg and 2.9 ± 1 kg respectively ($p = 0.01$) and mean gestational age of 35.8 ± 4 weeks and 37.2 ± 4 weeks respectively ($p = 0.04$). Neonates with birthweight less than 1500g and preterm infants were more likely to have a poor outcome than heavier infants and term infants (OR 8.64; CI 2.79, 26.74) and (OR 7.17; CI 2.54, 20.32) respectively. When entered into a multivariate logistic regression model, female gender, very low birthweight and decreased gestational age were predictors of poor outcome.

DISCUSSION

The case fatality rate found in this study is low when compared to that of other developing countries (5, 8). As shown in this study, the case fatality rate for preterm infants is much higher than that for term infants. The majority of the babies in this study however were term infants; lack of ventilatory support for extremely premature infants may result in these infants dying from other complications of their prematurity, leading to them being under-represented in this study.

Males accounted for more of the deaths in this study; this gender difference with greater survival likelihood in females has been previously documented (9). Conversely, female neonates accounted for a greater proportion of those developing morbidity, measured as the occurrence of severe complications other than death in this series. Poor outcome, as defined in this study, combined mortality and morbidity and was more prevalent in females. The finding of female infants being at greater risk for poor outcome seems contradictory. If death alone is considered, the male disadvantage is seen. Amongst those neonates who developed sequelae of sepsis, the proportion of females was greater, suggesting that females although more likely to survive than males tended to have more complications from their sepsis. This is not unexpected as the females in this study were smaller and less mature than their male counterparts and therefore were at greater risk for complications from their sepsis. The combined effect of very low birthweight and prematurity with increasing susceptibility to complications gave rise to the apparent gender reversal of risk for poor outcome seen in this study. The male disadvantage however is still demonstrated as the female neonates of equivalent maturity and weight as the male babies in this study did not develop infections.

The relationship of younger maternal age to poor outcome probably represents a proxy for gravidity as the younger the mother the greater the likelihood that she has not had previous pregnancies. The poor outcome group had a greater proportion of mothers who were primigravid; in addition, a greater proportion of these women had preterm infants than their counterparts in the group with favourable outcome. This finding is not unusual as the preterm infant is at increased risk for complications from sepsis.

The association of low birthweight and prematurity with poor outcome has been demonstrated in other studies (10–14). The less mature preterm infant is at increased risk for developing complications of sepsis because of deficiencies in humoral and cellular immunity. Transplacental maternal antibodies primarily mediate humoral immunity, hence preterm infants are less likely to receive as many immunoglobulins as term infants. T-cell function and phagocytic function are also deficient (15–17).

This study was limited by the fact that it was a retrospective review of neonatal dockets and laboratory reports. As such, data collection was restricted to information previously recorded and this was incomplete for some of the variables under review.

This study has identified prematurity, very low birthweight and female gender as predictors of poor outcome in neonates with bacterial sepsis. Strategies aimed at decreasing morbidity and mortality in neonates with sepsis must include measures that will decrease the incidence of prematurity.

REFERENCES

1. Bang AT, Bang RA, Baitule SB, Reddy HM, Deshmukh MD. Effect of home based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. Lancet 1999; **354:** 1955–61.
2. Stoll BJ. The global impact of neonatal infection. Clin Perinatol 1997; **24:** 1–21.
3. Jalil F, Linblad BS, Hanson LA, Khan SR, Yaqoob M, Karlberg J. Early child health in Lahore, Pakistan: IX. Perinatal events. Acta Paediatr Suppl, 1993; **82 (suppl 390):** 95–107.
4. Boo NY, Chor CY. Six year trend of neonatal septicemia in a large Malaysian maternity hospital. J Paediatr Child Health, 1994; **30:** 23–7.
5. Airede AI. Neonatal septicaemia in an African city of high altitude. J Trop Pediatr, 1992; **38:** 189–91.
6. Singh M, Paul VK, Deorari AK, Ray D, Murali MV, Sundaram KR. Strategies which reduced sepsis-related neonatal mortality. Indian J Paediatr, 1988; **55:** 955–60.
7. Wilson CB. Immunologic basis for increased susceptibility of the neonate to infection. J Pediatr, 1986; **108:** 1–12.
8. Ali Z. Neonatal bacterial septicaemia at the Mount Hope Women's Hospital, Trinidad. Ann Trop Paediatr 2004; **24:** 41–4.
9. Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. Pediatrics 1971; **48:** 902–6.
10. Fanaroff AA, Korones SB, Wright LL, Verter J, Poland RL, Bauer CR et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network. Pediatr Infect Dis J 1998; **17:** 593–8.
11. Bhutta ZA, Yusuf K. Neonatal sepsis in Karachi: factors determining outcome and mortality. J Trop Paediatr 1997; **43:** 65–70.
12. Gladstone IM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J 1990; **9:** 819–25.
13. Grauel EL, Halle E, Bollmann R, Buchholz P, Buttenberg S. Neonatal septicemia: incidence, etiology, and outcome: a 6-year analysis. Acta Paediatr Scand Suppl 1989; **360:** 113–9.
14. Tessin I, Trollfors B, Thiringer K. Incidence and aetiology of neonatal septicemia and meningitis in western Sweden, 1975–1986. Acta Paediatr Scand 1990; **79:** 1023–30.
15. Schelonka RL, Infante AJ. Neonatal immunology. Semin Perinatol (abstract) 1998; **22:** 2–14.
16. Berger M. Complement deficiency and neutrophil dysfunction as risk factors for bacterial infections in newborns and the role of granulocyte

transfusion in therapy. Rev Infect Dis (abstract) 1990; **12(suppl 4):** S1401–9.

17. Shigeoka AO, Santos JL, Hill HR. Functional analysis of neutrophil granulocytes from healthy, infected, and stressed neonates. J Pediatr 1979; **95:** 454–60.