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RISK FACTORS FOR MORTALITY IN SERVICE NEONATAL SEPSIS*

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ABSTRACT

Objectives: To determine the mortality rate of patients with severe sepsis and to determine the risk for mortality within three days after severe sepsis is diagnosed

Methods: 55 neonates admitted at the intensive care unit of a tertiary hospital who fulfilled previously established criteria for severe sepsis were cohorted prospectively and followed to determine the final outcome.

Results: The mortality rate was 90% (50/55), with 72% of the deaths (36/50) occurring within three days after the onset of severe sepsis. In the univariate analysis, factors associated with death were gestational age and bradycardia. The multivariate analysis identified 6 variables which suggested survival beyond 3 days: gestational age (OR 2.86, 95% CI 1.40-5.88), appropriateness of weight for gestational age (OR 4.69, 95% CI 1.302-163.94), exchange transfusion (OR 2.24, 95% CI 0.31-15.98), prenatal care (OR 1.65, 95% CI 0.14-18.89), antenatal steroids (OR 6.27, 95% CI 0.68-58.03, and temperature instability (OR 1.4, 95% CI 0.19-10.42). Only gestational age and appropriate weight for age were significant, but due to the wide confidence interval of the latter, it could not provide a precise estimate. The rest of the variables did not show any significance.

Conclusions: The results of our preliminary study were inconclusive because of the small sample size to date, and no interaction between the variables could be ascertained. It is recommended that the study be continued to acquire a larger sample size that would enable us to generate a model predictive of mortality risk, and the benefits of exchange transfusion should be further investigated in a randomized controlled trial.

INTRODUCTION

Major contributors to neonatal mortality include respiratory failure associated with prematurity, perinatal asphyxia, congenital malformations and severe infections[1]. In the past 15 years, with the advent of broad-spectrum antibiotics and enhanced knowledge of life support techniques, the case fatality rate for non-infectious illnesses has continued to decline, while that for infectious diseases has remained unchanged at approximately 15% for late-onset sepsis and 15-50% for early-onset sepsis, and this is still unacceptably high[2,3,4]. In the PGH NICU, our sepsis rate averaged 11.6% in 2000. Our mortality rate averaged 3.6%, with sepsis accounting for 54% of the deaths[5]. The manisfestations of sepsis include those related to the systemic response to infection and those related to organ-system dysfunction. Sepsis is said to be severe when it is associated with hypoperfusion and hypotension[6]. While these associations confer a poorer prognosis, they are not precise enough to predict the mortality or survival of patient. This study was undertaken to determine the mortality rate in patients with severe sepsis, and risk factors for mortality within 3 days after severe sepsis is diagnosed.

METHODS

Study population. This prospective cohort study was done on neonates admitted at the UP-PGH Neonatal Intensive Care Unit. Inclusion criteria were age <28 days with signs of severe sepsis.

Definition of terms:

(1) Sepsis-the diagnosis of sepsis will require at least one of the following:
- Positive blood culture
- Chest radiograph consistent with necrotizing enterocolitis

Plus presence of signs of systemic response to infection as manifested by 2 or more of the following:
- Tachycardia>160 bpm
- Tachypnea>60bpm
- Temperature instability
- Significant pathologic alteration of the WBC count[7]

(2) Severe sepsis – sepsis associated with any of the following:
- Hypotension - <55/35mmHg for term neonates, <45/25mmHg for preterm neonates, with inotropic support
- Hypoxemia – requiring oxygen support >50%FiO2

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- End-organ hypoperfusion and perfusion abnormalities which may include lactic acidosis, oliguria and acute alteration in mental status.

All patients were given antimicrobial therapy and general supportive care consisting of oxygenation and ventilation, correction of acid-base imbalances, repletion of intravascular volume, preservation of body temperature, maintenance of fluid and electrolyte balance and inotropic support. An exchange transfusion was given at the discretion of the service on duty, if clinically warranted.

The clinical condition of each neonate was recorded prior to their entrance into the study, and appropriate laboratory data were obtained as follows: CBC, blood culture, chest radiographs, ABGs. Neonates were followed up to determine the final outcome.

Statistical Methods. For the analysis presented in this report, the investigators chose parameters in the maternal and neonatal history which were already shown in previous studies and by experience to have an effect on neonatal mortality. Univariate analysis was done to determine the strength of the effect on mortality within 3 days of the onset of severe sepsis, and this was reported as relative risk with their 95% confidence intervals. Logistic regression was done to determine the collective effects these parameters had on the outcome.

RESULTS

Mortality rate. In this preliminary study, 55 infants admitted at the UP-PGH Neonatal Intensive Care Unit from January 1, 2001 to September 30, 2001 (9 months) fulfilled the criteria for severe sepsis. 50 of these infants died while 5 were eventually discharged, giving a mortality rate of 90%. Of the 50 deaths, 36 (72%) occurred within 3 days after the patients were diagnosed to have severe sepsis.

Pathogen distribution. There were 69 episodes of sepsis as evidenced by positive blood culture results. Majority of the infections were caused by Gram-negative infections (88.4%), followed by fungal infections (11.6%). 23 out of 55 (41%) also had pneumonia, while one neonate was diagnosed to have NEC (0.1%)

Table 1. Pathogen distribution and survival rate of the study population

	No. of Cases	%
Bacterial isolates		
Enterobacter cloacae	19	27.5
Enterobacter aerogenes	16	23.2
Pseudomonas spp.	11	15.9
Klebsiella spp	8	11.6
Hafnia alvei	5	0.7
Others	2	0.2
Fungal (Candida sp)	8	11.6
Pneumonia	23	41.2
NEC I	0.1	
Mortality rate	50	90
Survival rate	5	10

Table 2. Pathogen distribution and survival rate of the study population

Variable	R_c	R_f	RR	95% Confidence interval
Gravidity (primigravid)	0.61	0.74	1.20	0.8293-1.7532
Prenatal care	0.68	0.5	0.73	.3574-1.5088
Maternal hypertension	0.63	0.71	1.11	0.7557-1.6529
Antenatal steroids	0.71	0.53	0.74	0.4556-1.2187
Apgar score<6 at 5 minutes	0.57	0.66	1.15	0.5885-2.2639
Birth weight	0.51	0.9	1.75	1.2288-2.4922
Gestational age	0.65	0.67	1.02	0.6151-1.6987
Appropriate wt. for gest. age	0.72	0.62	0.86	0.5879-1.2601
Sclerema	0.63	0.7	1.11	0.7605-1.6291
Temperature instability	0.7	0.61	0.79	0.5478-1.1436
Bradycardia	0.62	0.88	1.41	1.00-2.00
Poor perfusion	0.12	0.13	1.02	0.5594-1.8628
Hypotension	0.63	0.73	1.17	0.7958-1.7300
Neutropenia	0.63	0.64	1.00	0.6060-1.6753
Metabolic acidosis	0.56	0.73	1.3	0.8699-1.9713
Pulmonary hemorrhage	0.62	0.75	1.11	0.8366-1.7756
Exchange transfusion	0.67	0.58	0.86	0.5135-1.4568

In the univariate analysis of the risk factors for mortality within 3 days, only early gestational age (RR 1.02, 95% CI 0.6151-6987) and presence of bradycardia (RR 1.41, 95% CI 1.00-2.00) seemed to increase the risk of mortality. Among maternal factors, having prenatal check-ups (RR 0.73) and antenatal steroids (RR 0.74) would indicate a decreased risk, while a primigravid mother (RR 1.20) and maternal hypertension (RR 1.11) would have an increased risk for mortality.

Table 3. Multivariate analysis

Logit estimates — Number of obs = 54
Log likelihood = 23.87657 — LR chi2 (17) = 22.29
Prob > chi2 = 0.1737
Pseudo = 0.3183

Variable	Odds Ratio	Std. Err	z	P>[z]	(95% conf. Interval)	
B. weight	.9949109	.001855	-2.737	0.006	.9912819	.998532
Gest. age	2.869917	1.050168	2.881	0.004	1.400862	5.879541
App. wt.	14.69491	18.08445	2.184	0.029	1.317124	163.9484
AS 5min	.7174806	.181117	-1.315	0.188	.437459	1.176747
Exch. trn	2.244194	2.24789	0.807	0.420	.315106	15.98321
Primigrav	.8455392	.2111991	-0.672	0.502	.5182273	1.379581
Prenatal	1.653548	2.055333	0.405	0.686	.1446729	18.89933
Ant. sterd	6.279036	7.124361	1.619	0.105	.6793553	58.03485
Pulm hge	.6241072	.5789928	-0.508	0.611	.101295	3.845302
Mat. HPN	.3522577	.3895612	-0.943	0.345	.0403198	3.077533
Bradycar	.0425678	.0606268	-2.216	0.027	.0026107	.694061
Hypotens	.8338169	.7738021	-0.196	0.845	.1352494	5.140509
Sclerema	.2780856	.2951457	-1.205	0.228	.0346681	2.230624
Temp. ins	1.422085	1.445037	0.347	0.729	.1940825	10.41993
Poor perf	.8545105	1.251452	-0.107	0.915	0.484296	15.07731
Neutropen	.327653	.3406811	-1.073	0.283	.042694	2.514555
Met acid	.7060638	.7201356	-0.341	0.733	.0956485	5.212066

Multivariate analysis suggested several risk factors which could be associated with survival beyond 3 days in patients with severe sepsis: maternal prenatal check-ups, antenatal steroids, advanced gestational age, appropriateness weight for age, exchange transfusion and temperature instability. Of these factors, only gestational age and appropriateness of weight for age were significant, but due to the wide confidence interval of the latter, this was not a precise estimate. The model accounted for 32% of the variability.

As a whole, the results of the multivariate analysis were inconclusive because of the small size (55) to date and thus, no interaction the variables could be ascertained.

DISCUSSION

Sepsis is said to be severe when it is associated with organ dysfunction, hypoperfusion (lactic acidosis, oliguria, or altered mental status), or hypotension (septic shock)[6]. It is often difficult to determine a single cause of death in patients with multiple orgran system failure, or to say that the cause of death was attributable only to sepsis. Needles to say, it would be prudent to investigate other risk factors inherent in the patient which could have contributed to the patient's early demise.

Maternal risk factors which suggested increased survival beyond 3 days were prenatal care and antenatal steroids, although their values were not significant. A study by Stoll et al, showed that mothers who had prenatal check-ups were significantly less likely to have infants in whom early-onset sepsis developed. The risk of delivering a very low birth weight neonate with subsequent early-onset sepsis was almost half as likely for mothers who had at least one prenatal visit[8]. Antenatal steroids have also been proven in numerous studies to give multiple postnatal benefits for prematures such as maturational effects on the lungs and possible maturational effects on the brain, gastrointestinal system and other organs. It decreases the incidence and severity of respiratory distress syndrome, and the incidence of intraventricular hemorrhage, significant patent ductus arteriosus and decreases the mortality rate[9]. In the same study by Stoll, neonates whose mothers had hypertension were significantly less likely

to have early-onset sepsis; this was contrary to our data which suggested on increased risk for mortality. This may be explained by the need for the obstetrician to terminate the pregnancy immediately because of the uncontrolled hypertension, thus prematurity could be another aggravating circumstance for development of sepsis in our patients.

The most important risk factor for neonatal sepsis is low birth weight, with the rate of neonatal infection (and mortality) inversely related to birth weight and gestational age[10, 11]. In our study, neonatal risk factors which seemed to be significantly associated with survival beyond 3 days were gestational age and appropriateness of weight for age. Raghavan and associates have identified prematurity and low birth weight as risk factors for septicemia[12], while Mathur and colleagues have determined weight and gestational age to be significantly associated with death[13]. Stoll et al showed that in as many as 25% of very low birth weight infants surviving beyond 3 days of life, one or more episodes of blood-culture proven sepsis developed and that these infants were significantly more likely to die (17% mortality rate) than infected infants of the same weight (7% mortality rate). Gram negative infections and fungal infections elevated the mortality rates even further[11]. Neonates inherently have qualitative and quantitative defects of both humoral and cellular immunity, and the deficiency in premature infants is heightened by the lack of transplacental transfer of maternal immunoglobulins (IgG) during the third trimester[10]. The rest of the neonatal factors which we investigated were found to be significantly associated with sepsis and mortality in other studies, although these were not shown to be significant in our analysis. Our study found temperature instability to be a factor associated with increased survival, in contrast with findings of Mathur et al in their univariate ananlysis which showed that hypothermia was significantly associated with death in neonatal sepsis (along with other factors such as age at onset of sepsis, requirement for IPPV, presence of refractory septic shock, neutropenia, metabolic acidosis and raised prothrombin time). However, in their multivariate analysis, only neutropenia, metabolic acidosis, increased prothrombin time and refractory septic shock retained their significance[13]. A study by Ashkenazi and coworkers also identified neutropenia as a variable that independently and significantly affected mortality due to bacteremia and fungemia in children[14]. These were not found to be significant in our analysis.

Our data also suggest a role for exchange transfusion has traditionally been used for hyperbilirubinemia, but its use as an adjunctie therapy for overwhelming sepsis was commonplace in the 1970s and 1980s. The exchange transfusion has been postulated to improved the outcome of septic neonates by removal of endotoxins, improvement of perfusion and tissue oxygenation, decrease of hemorrhagic complications and enhancement of the humoral and cellular inflammatory response[4]. However, its effectiveness has not been thoroughly established because majority of the studies done at the time were non-randomized, predominantly retrospective or were uncontrolled.

CONCLUSION AND RECOMMENDATIONS

It is very difficult to determine the exact cause of death in the very sick neonate, and it is recognized that sepsis occurs more frequently in patients with a myriad of maternal, perinatal and neonatal risk factors which may have a collective effect on the patient's outcome. Due to our limited sample size, our study failed to generate a model which could predict mortality risk in patients with severe neonatal sepsis. The multivariate analysis was inconclusive as it could only identify 2 risk factors which were significantly associated with survival beyond 3 days – gestational age and appropriateness of weight for gestational age. However, the wide confidence interval of the latter variable could not give us a precise estimate. Other risk factors which suggested increased survival such as prenatal care, antenatal steroids, temperature instability and exchange transfusion were not found to be significant.

In an attempt to summarize and quantify individual variables, studies have been undertaken precisely to identify risk factors, correlate them with mortality rates with the aim of generating scoring systems as a means of predicting mortality risk/severity of illness[17]. It is this predicted risk of mortality which may have a role in identifying patients who will benefit from therapeutic interventions such as immunotherapy or exchange transfusion.

It is our recommendation that this study be continued to produce a larger sample size in order to significantly correlate the identified risk factors with the risk for mortality. We also recommend exploring further the therapeutic benefits of exchange transfusion in septic neonates within a randomized controlled trial.

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