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Treatment patterns and clinical outcomes in neonates diagnosed with Respiratory Distress Syndrome in a Low-Income Country: A report from Bangladesh

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Abstract

Respiratory Distress Syndrome (RDS) remains a leading cause of neonatal mortality worldwide. This retrospective study describes practice patterns for RDS in a resource-limited setting, and seeks to identify both risk factors for mortality and beneficial treatment modalities. Health, demographic and treatment data was collected. Potential associations were analyzed utilizing univariable and multivariable logistic regression. Of 104 children included for analysis, 38 died. Although most children were initially treated with non-invasive respiratory support, 59 progressed to invasive ventilation. Requirement for invasive ventilation was associated with death. A clear trend towards improved survival in mechanically ventilated patients was seen with surfactant administration.

Introduction

Respiratory Distress Syndrome (RDS) is a disease of inadequate endogenous surfactant production and immature lung anatomy, typically affecting premature neonates[1]. Advances in neonatal critical care, especially the introduction of surfactant replacement therapy (SRT), have led to a mortality reduction of 85% in the United States[2]. For the 10 million children born prematurely in low-income countries (LICs), however, RDS remains a leading cause of death, with published mortality rates roughly 10-fold higher than wealthy nations at 40–60%[1–6]. This stark contrast is largely due to resource availability. A large percentage of births occur at home and babies often die without receiving any care[2]. Even if care is sought, regional clinics in many locations can provide little more than oxygen to neonates in distress[2,7]. A lack of skilled personnel, especially in rural areas, remains a constant problem[2,8,9].

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Dr. Hubbard: This author designed the study, analyzed results, and wrote the body of the text. Dr. Choudhury: This author was responsible for study design, data gathering, and draft review. Dr. Lim: This author served as senior advisor in study design, data analysis, and draft review.

As LICs attempt to develop their critical care capacity, tertiary centers have begun to open neonatal intensive care units (NICUs). Such facilities may be able to provide advanced respiratory support modalities, including continuous positive airway pressure (CPAP), mechanical ventilation, and surfactant replacement therapy (SRT)[6,9]. However, availability rarely meets demand, and equipment may be out of date and prone to breakdown[2,10]. Importantly, the cost of advanced treatments often falls on poor families, and care may be withheld if payment is not forthcoming[6].

Previous research in this field has focused on the impact of introducing new treatment modalities for RDS into LICs, or on the incidence or natural progression of this disease in such settings[3–7,10]. This study seeks instead to describe practice patterns in the care of RDS-afflicted neonates in a resource-limited setting, to isolate predictors of mortality in this environment, and to identify care modalities which may improve outcomes.

Methods

Approval for this retrospective, observational study was obtained from the Institutional Review Boards of BIRDEM General Hospital (Bangladesh) and The University of Pittsburgh (United States). Written informed consent was waived by both institutions. This manuscript adheres to the applicable STROBE guidelines. The study site was an academic, semi-private referral center in Dhaka, the capital and largest city of Bangladesh. This institution's NICU consists of 27 beds, and is staffed in daylight hours by neonatologists, with trainee and non-specialized physicians in-house overnight. Nursing to patient ratios vary from 1:3 in daylight hours, to 1:7 overnight. A total of 4 CPAP machines and 5 mechanical ventilators are stocked on-site. Management of these devices is left solely to the physicians, as no respiratory therapists are on staff. Surfactant is available in multiple centers in Bangladesh (including the study site), but its use is limited to those patients whose families are able to pay its cost ($250 per dose compared to an average annual income of $1,331).[11]

All neonates diagnosed with RDS at the host institution between July 1st, 2015 and June 31st, 2016 were included. Diagnosis was made via clinical features (respiratory distress within 4 hours of birth, grunting on expiration, intercostal retractions, cyanosis, and apnea) and radiographic findings on chest x-ray (diffuse granular opacification, air bronchograms). Of note, this institution has no protocols to guide the management of patients with RDS, with clinical decisions left to the neonatologist and limited to those treatments the families can afford.

For each neonate diagnosed with RDS in the study period, specific health and general information (including sex, gestational age & weight, and mode of delivery) were recorded via retrospective chart review. Evidence of sepsis was recorded, based on positive blood cultures, or elevated blood concentrations of either calcitonin or C-reactive protein. Finally, the highest level of respiratory support provided during admission was recorded, with those in the "invasive" group requiring endotracheal intubation and mechanical ventilation, and those in the "non-invasive" group receiving either CPAP or supplemental oxygen.

Statistical Analysis

Multivariable logistic regression analysis was used to investigate the associations between several potential risk factors and the primary outcome of death prior to discharge. Those factors included birth site (born at the study site or elsewhere), level of respiratory support (invasive versus non-invasive), sex, diagnosis of sepsis (defined as above), mode of delivery (vaginal or via cesarean), and gestational age & weight at birth. The analysis was not designed to determine a specific exposure vs. outcome relationship of any individual factor, but rather to analyze the association of all the factors with the primary outcome, adjusting for each other. Univariable logistic regression identified factors associated with the primary outcome of death. Adjusted odd ratios for mortality were obtained by multivariable logistic regression analysis. Confounding was assessed by comparing unadjusted and variable-adjusted log-odds of the outcome for a 10% change. The independent variables considered were respiratory support, birth location, mode of delivery, sex, septicemia, gestational age, and birth weight. Variable screening was also performed using a backward elimination procedure and the likelihood ratio test, using a *P*-value cutoff of 0.1 to retain variables in the model. Final model selection was made based on considerations of clinical judgement, weighed together with the results of these analyses. All reported *P*-values were two-sided and an alpha of 0.05 was required to reject the null hypothesis. Sample size was determined by the available data within the time parameters of the study, as agreed upon by the researchers and the host institution. The number of variables included in the analysis was limited by the sample size available for analysis. Univariable and multivariable logistic regression analyses were performed using The SAS System (SAS Institute Inc, 1976, Cary NC) and Stata SE 14.1 (Stata Corp, 1985, College Station, TX).

Results

Of 107 neonates diagnosed with RDS in the study period, 3 neonates were excluded due to incomplete medical records. Overall, 38 neonatal deaths were reported, a mortality rate of 36.5%. 79 patients were treated with non-invasive ventilation as a primary treatment modality. 34 (43.0%) of these eventually required invasive ventilation. Of 59 total patients requiring invasive ventilation, the mortality rate was 62.7% (N=37), compared to just 2.2% (N=1) of the 46 patients managed non-invasively.

Univariable analysis suggested a significant link between the primary outcome of death and several hypothesized associated factors, specifically birth outside the study facility, vaginal delivery, birth weight less than 1500 grams, gestational age less than 32 weeks, and need for invasive ventilation (Table 1). Both gestational age and birth weight were confounders in the relationship between respiratory support and the outcome of death (change in log odds >10%). Although statistically significant in univariable analysis, respiratory support was not included in the final model due to the rarity of the event in the non-invasive group (n=1). After backward elimination with likelihood ratio testing, birth location and birth weight emerged as variables to be retained in the model, whereas mode of delivery, gestational age, sepsis and sex were not retained. Based on clinical judgement coupled with these results, the final model included birth location, mode of delivery, gestational age, and birth weight. Adjusted odds ratios demonstrated significance only for birth weight less than 1500 grams.

Trends towards increased mortality were seen with birth outside the study facility and evidence of sepsis, but statistical significance was not reached.

While all intubated children were candidates for SRT, the decision to give the therapy was based solely on the families' ability to pay. Of 59 neonates requiring invasive ventilation, 12 (20.3%) were treated with SRT. Of those, 7 (58.3%) survived. Simultaneously, only 14 of 46 (30.4%) untreated neonates survived.

Discussion

The results of this study elucidate a number of key issues in the management of RDS in low-resource settings. First, in contrast to practice in the United States, where many centers intubate and mechanically ventilate neonates early in the disease process, providers adopted a practice of care escalation, reserving invasive treatments for the most critically ill patients. This conclusion is supported by the fact that the use of such therapy was associated with mortality. Conversely, the alarmingly high mortality rate in invasively ventilated patients suggests that the introduction of such modalities in isolation may be futile. Indeed, despite the availability of a number of advanced respiratory support modalities at the study institution, overall mortality was only modestly reduced when compared to previously published reports. The known effectiveness of SRT in high-resource settings, and the clear trend in mortality improvement in those few neonates receiving SRT in this study, suggests that appropriate introduction of this therapy in conjunction with invasive ventilation may reduce the overall mortality in this population. However, the costs of this strategy must be weighed against other areas of need, such as improving the nursing ratios, hiring skilled respiratory therapists, or increasing the complement of CPAP machines. Ongoing and future research will be powered to demonstrate the impact of universal SRT in neonates requiring invasive ventilation, and to determine the cost-effectiveness of such modalities in low-resource settings.

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Table 1

Univariable and multivariable analysis of suggested risk factors for mortality

Risk Factor	Survived	Died	Total	Mortality	Unadjusted OR (95% CI)*	Unadjusted p-value	Adjusted OR (95% CI)	Adjusted p-value
Respiratory Support								
Invasive	21	37	58	63.8%	85.1 (10.9–664.0)	<0.001	Not in final model	NA
Non-Invasive	45	1	46	2.2%				
Born at study site								
Yes	13	17	30	56.7%	3.3 (1.4–7.9)	0.008	3.19 (0.7–15.6)	0.153
No	53	21	74	28.3%				
Mode of Delivery								
Vaginal	12	19	31	61.3%	4.5 (1.8–11.0)	0.001	1.1 (0.2–4.9)	0.871
Cesarean	54	19	73	26.0%				
Sex								
Female	25	19	44	43.2%	1.6 (0.7–3.7)	0.23	Not in final model	NA
Male	41	19	60	31.7%				
Sepsis								
Yes	22	20	42	47.6%	2.2 (0.9–5.0)	0.055	Not in final model	NA
No	44	18	62	29.0%				
Gestational Age								
≥ 32 weeks	49	9	58	15.5%	6.8 (3.1–15.0)	<0.001	1.0 (0.1–7.9)	0.991
< 32 weeks	17	29	46	63.0%				
Birth Weight								
≥ 1500g	51	5	56	8.9%	9.7 (4.1–22.6)	<0.001	9.0 (1.2–69.3)	0.034
<1500g	15	33	48	68.8%				

*OR = Odds Ratio, CI = Confidence Interval, NA = not applicable.

A single model including the covariables birth location, mode of delivery, gestational age, and birth weight was used. Although statistically significant in univariable analysis, respiratory support was not included in the model due to the rarity of the event in the non-invasive group (n=1).