Medical Education Systems, Inc.

Neonatal Respiratory Failure

Medical Education Systems, Inc

TOLL FREE: 877-295-4719
LOCAL: 619-295-0284
FAX: 619-295-0252
EMAIL: Info@mededsys.com
WEBSITE: www.mededsys.com
P.O Box 81831 San Diego, CA. 92138-3939.

Neonatal Respiratory Failure:

A 12-Month Clinical Epidemiologic Study from 2004 to 2005 in China

Learning Objectives

Upon successful completion of this course, you will be able to:

- Identify the factors relating to neonatal respiratory failure
- Identify conditions that prompt neonatal respiratory support
- Identify the role of surfactant therapy in neonatal respiratory therapy
- Identify the role of mechanical ventilation in neonatal respiratory therapy

ABSTRACT

OBJECTIVES. In the past decade, neonatal special care services in China have been established, during which time various therapies for neonatal respiratory failure have been introduced. The objective of this study was to investigate the incidence, management, outcome, and cost of neonatal respiratory failure treated by mechanical ventilation in 23 tertiary NICUs of major hospitals in southeastern and Midwestern China.

METHODS. Data were collected over 12 consecutive months from 2004 to 2005 for neonates with neonatal respiratory failure. Eligible infants were those who required endotracheal intubation and mechanical ventilation and/or nasal continuous positive airway pressure for at least 24 hours and infants who died within 24 hours of ventilation during their first 7 days of life. Data characterized demographics, antenatal and perinatal history, illness severity score, primary disease, respiratory care, complications, survival, and clinical burden.

RESULTS. From a total of 13070 NICU admissions, there were 1722 (13.2%) cases of neonatal respiratory failure with respiratory distress syndrome, pneumonia/sepsis, and meconium aspiration syndrome as major causes. For infants who survived until discharge, the median length of ventilation was 70 hours.

Overall, in-hospital mortality for neonatal respiratory failure was 32.1%. Logistic regressions showed that lower gestational age, vaginal delivery, fetal distress before delivery, presence of a major anomaly, and high severity score in preterm infants were associated with an increased risk for death. In term and post term infants, only the presence of a major anomaly and a high severity score were significant risk factors for death. Mean length and cost of stay in hospital were 19.2 ± 14.6 days and 14966 ± 13465 Yuan in the survivors.

CONCLUSIONS. Neonatal respiratory failure in the NICU of the provincial cities of China has high mortality and cost that are linked to geographic variability, a male predominance, and low proportion of very preterm infants, characteristic of sociocultural confounding background.

Abbreviations: NRF—neonatal respiratory failure • CMV—conventional mechanical ventilation • HFV—high-frequency ventilation • nCPAP—nasal continuous positive airway pressure • SNAPPE-II—score for neonatal acute physiology perinatal extension II • GA—gestational age • CLD—chronic lung disease • ROP—retinopathy of prematurity • OR—odds ratio • CI—confidence interval • RDS—respiratory distress syndrome • MAS—meconium aspiration syndrome • TT—transient tachypnea • LOV—length of ventilation • LOS—length of stay • ELBW—extremely low birth weight • VLBW—very low birth weight.

Neonatal respiratory failure (NRF) is one of the most common, serious clinical problems and a major cause of death in newborn infants.

In the past 2 decades, several factors have significantly reduced overall neonatal death, especially in extremely immature infants with NRF, in industrialized countries. These include aggressive intervention at delivery, establishment of an NICU, and development of advanced respiratory therapies.[1,2] In contrast, in developing countries, there remains a high in-hospital death and high morbidity in survivors. In China over 15 years, the mortality in children who are younger than 5 years has been reduced to an average of 30 per 1000 live births, albeit with wide geographic variation. Neonatal care services in an NICU are currently an important focus in further reducing this mortality rate. Data from industrialized countries suggest that efforts to build a highly cost-intensive environment may assist in reducing mortality,[3–5] but the Western route for improvement of perinatal-neonatal care may not be the most appropriate for China. Because comparisons of regional differences in outcomes of clinical practice of NICU have been useful in other settings,[6,7] we sought to assess performance across southeastern and midwestern regions in China.

In high-growth regions of China, there is a trend to centralize neonatal service in local maternity hospitals or medical center for women's and children's health. This has led to the availability of modern equipment and facilities in many NICUs at provincial and subprovincial pediatric and medical centers, each serving populations of 1 to 5 million; however, there are serious problems of inequality and affordability for low-income families in access to health care, which likely affect quality of regional neonatal care, as reflected by key outcome statistics.

We conducted a study to evaluate NICU function by investigating diagnosis, management, and outcome of NRF. The objectives of this study were to determine the incidence and mortality of NRF, categorize the use of technology and resources of respiratory support, evaluate risk factors that are associated with death and disease burden, and explore regional variations in outcomes.

PEDIATRICS Vol. 121 No. 5 May 2008, pp. e1115-e1124 (doi:10.1542/peds.2006-2426)
Liling Qian, MD[a], Cuiqing Liu, MD[b], Wanzhu Zhuang, MD[c], Yunxia Guo, MD[d], Jialin Yu, MD[e], Hanqiang Chen, MD[f], Sannan Wang, MD[g], Zhenlang Lin, MD[h], Shiwen Xia, MD[i], Liming Ni, MD[j], Xiaohong Liu, MD[k], Chao Chen, MD[a], Bo Sun, MD, PhD[a] and the Chinese Collaborative Study Group for Neonatal Respiratory Diseases

METHODS

Participating Hospitals

We established a collaborative study group. Twenty-three NICUs in tertiary maternity and children's hospitals from major cities of 10 provinces and 2 municipalities (Shanghai and Chongqing) in the southeastern (*n* = 15) and midwestern regions (*n* = 8; Table 1, Fig 5, which is published as supporting information on www.pediatrics.org/content/full/121/5/e1115) participated. Data collection for this study was approved by the ethics committee of Children's Hospital of Fudan University and adopted by each center according to Chinese regulations. The NICUs were based in 11 children's hospitals (enrolling only outborn infants) and 12 maternity hospitals or women's and children's health centers (enrolling both outborn and inborn infants). Nine NICUs enrolled patients for pediatric surgery and 3 for cardiothoracic surgery. In total, there were 255 NICU beds (median: 10; range: 4–20). Coordination for this study was based at Children's Hospital of Fudan University.

TABLE 1 Profile of Participating Hospitals From Municipalities and Provincial Cities

Hospital	NICU Beds	Inborn/Outborn	PS	CS
Children's Hospital of Fudan University (Shanghai)	20	O	Y	N
Shanghai First Maternity Hospital (Shanghai)	5	I/O	N	N
Maternity Hospital of Fudan University (Shanghai)	5	I	N	N
Nanjing Children's Hospital (Nanjing, Jiangsu)	10	O	Y	N
Nanjing Maternity and Child Health Hospital (Nanjing, Jiangsu)	10	I/O	Y	N
Children's Hospital of Suzhou University (Suzhou, Jiangsu)	8	O	Y	N
Suzhou Women and Children's Health Center (Suzhou, Jiangsu)	10	I/O	N	N
Changzhou Children's Hospital (Changzhou, Jiangsu)	6	O	N	N
Yuying Children's Hospital of Wenzhou Medical College (Wenzhou, Zhejiang)	10	I/O	N	N
Shaoxing Maternity Hospital (Shaoxing, Zhejiang)	10	I/O	N	N
Jiaxing Maternity Hospital (Jiaxing, Zhejiang)	4	I/O	N	N
Guangzhou Children's Hospital (Guangzhou, Guangdong)	12	O	N	N
Shenzhen Children's Hospital (Shenzhen, Guangdong)	12	O	Y	Y
Provincial Maternity Hospital (Fuzhou, Fujian)	15	I/O	N	N
Quanzhou Women and Children's Hospital (Quanzhou, Fujian)	12	I/O	Y	Y
Children's Hospital of Chongqing Medical University (Chongqing)	20	O	N	N
Zhenzhou Children's Hospital (Zhenzhou, Henan)	10	O	N	N
Provincial Children's Hospital (Shijiazhuang, Hebei)	15	O	Y	N
Provincial Maternity Hospital (Wuhan, Hubei)	10	I/O	Y	N

Provincial Maternity Hospital (Xi'An, Shaanxi)	15	I/O	N	N
Xi'An Children's Hospital (Xi'An, Shaanxi)	20	O	Y	Y
Chengdu Children's Hospital (Chengdu, Sichuan)	8	O	N	N
Provincial Maternity Hospital (Lanzhou, Gansu)	8	I/O	N	N

The first 13 hospitals are in southeastern, and the last 8 are in midwestern region. I/O indicates inborn/outborn; PS, pediatric surgery; CS, cardiothoracic surgery.

Study Subjects

In this study, neonates with NRF were defined as follows:

1. neonates who were admitted to the NICU during the 12-month period from March 1, 2004, to February 28, 2005, and required any respiratory support during the first 7 days of life (including conventional mechanical ventilation [CMV], high-frequency ventilation [HFV], and/or nasal continuous positive airway pressure [nCPAP]);
2. neonates who at minimum received respiratory support for 24 hours; or
3. neonates who died within 24 hours of assisted and/or mandatory ventilation.

All NICU admissions were screened using a guideline for admission and discharge policies, defined by consensus of all participating sites. An admission was defined as infants with a stay in the NICU for at least 24 hours or infants who died within 24 hours of admission to the NICU. When an infant was transferred to a referral hospital within 24 hours, the admission was counted as a single admission. Both withdrawal of treatment by decision of parents/guardians and transfer to another NICU within 24 hours of admission were also included.

Data Collection

Prospective data were collected by trained staff using a standard case report form, which included demographic characteristics; antenatal history; pregnant history of mother; mode of delivery; health status and problems at birth; Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II)[8]; primary disease diagnosis; selected NICU practice and procedures; use of technology and resources, especially application of respiratory support; and outcome. Patients who were transferred to any 1 of the collaborative units were tracked until the completed case record form was submitted to the coordinating center within 30 days. The coordinating center established a standard central database based on Microsoft Access 2000 and an Internet Web site (www.shlung.com/neonet) for data submission, topic discussion, and information and resource sharing. Data collection by research staff in each unit was supervised by the NICU director, who was responsible for quality assurance. The coordinating center staff ensured local review and correction of incomplete or ineligible records.

Definitions Used

Gestational age (GA) was estimated first by attending obstetric staff before delivery, unless the postnatal pediatric estimate of gestation by using the Dubowitz score differed from the obstetric estimate by 2 weeks postnatally.[9] Preterm was defined as a GA of <37 weeks. Birth weight, body length, and head circumference were recorded within 24 hours of birth. Prenatal care was defined as receiving pregnancy-related care from a physician on at least 1 occasion during pregnancy. Application of antenatal steroids was regarded as "incomplete" when delivery occurred <24 hours after the first dose of corticosteroids.

A standardized list of definitions was compiled for major disorders that lead to respiratory failure and complications.[5,10,11] Chronic lung disease (CLD) was defined as a requirement of supplement oxygen to maintain adequate oxygenation after 28 days of life for an infant of ≥32 weeks' GA, or 36 weeks' corrected GA for an infant who was born at < 32 weeks' GA.[12] Retinopathy of prematurity (ROP) was diagnosed according to the International Classification of Retinopathy of Prematurity.[13]

Statistical Analysis

All statistical analyses were performed by using SPSS 11.0 software (SPSS, Chicago, IL). The primary goal of this study was to provide descriptive statistics of the patient population. Continuous variables are presented as means and SD or medians and range or quartile range (25th to 75th percentile), categorical variables as counts or rates, and odds ratio with 95% confidence intervals (CI). Comparison between continuous variables was made by using a Mann-Whitney test. Univariate analyses on categorical data were performed by using a 2-tailed Pearson χ^2 or Fisher's exact test wherever appropriate.

Univariate and multivariate analyses were performed separately by using logistic regression to analyze the risk factors of death in preterm, term, and postterm infants. GA, gender, prenatal care, multiple versus singleton birth, delivery mode, fetal distress status, born with appropriate hospital care, presence of a major anomaly, presence of a major hemorrhage, NICU location, and SNAPPE-II were included in the analysis. Small for GA status, 5-minute Apgar score, and Pa_{O_2}/fraction of inspired oxygen, etc, were not included in the analyses because they were already included in SNAPPE-II. Because birth weight and GA are highly correlated (r = 0.840 in our data set), only GA was included. We chose this because GA is more closely linked to lung maturation. A forward stepwise regression analysis was first used to determine significant independent variables associated with an increased risk for death ($P \leq .05$ for model entry, $P \geq .10$ for model exit). The independent variables that were found to be significant in the stepwise procedure were then investigated further for development of a final model for all factors retained in the multivariate logistic regression model. The overall fit of the model was checked with a Hosmer-Lemeshow test. $P < .05$ was considered statistically significant.

RESULTS

Incidence of NRF in NICU

During a 12-month period, there were 13070 NICU admissions. Of these, a total of 1722 were classified as NRF, corresponding to 13.2% (95% CI: 12.6%–13.8%) of NICU admissions. The incidence of NRF was found to differ between the southeastern and midwestern regions (11.6% vs 16.4%; $P < .001$). There was a higher incidence of NRF in June (15.3%) compared with December (10.7%), but this difference was not statistically significant.

Patient Characteristics and Perinatal Risks

Of 1722 NRF infants, 1644 (95.5%) were admitted to the NICU within 3 days of postnatal age, and the median age of infants with NRF on admission to NICU was 3 (quartile range: 1–12) hours. Of all infants with NRF, ~19.6% were inborn, 74.1% were outborn (born at other hospitals), and only 6.3% were homeborn. There was a male preponderance (75.5%). Moreover, the percentage of male infants was higher in the outborn (77.4%) and in the homeborn (78.7%) than in the inborn (68%). Mean GA was 34.9 ± 4.1 weeks (range: 24.7–44.0), and 63.3% were preterm. Mean birth weight was 2309 ± 832 g (range: 650–6075), and 59.8% were < 2500 g (1.9% < 1000 g, 15.3% 1000–1499 g, 42.5% 1500–2499 g, 38.3% 2500–4000 g, and 1.9% > 4000 g). Congenital anomalies were found in 146 (8.5%) patients, mainly congenital heart diseases ($n = 75$) but also diaphragmatic hernia ($n = 13$), laryngomalacia ($n = 10$), and tracheoesophageal fistula ($n = 10$). The age of mothers of all infants with NRF averaged 27.8 ± 4.8 years, and 53.1% of them had experienced spontaneous labor initiation. The patient characteristics and perinatal risks by GA and different disorders are shown in Tables 2 and 3, respectively. Of infants whose GA was ≤34 weeks, 31.7% received antenatal steroids. In the delivery room, of all infants with NRF, 55.9% received various resuscitations with oxygen supplement (49.1%), bag-mask ventilation (19.5%), endotracheal intubation (15.2%), chest compression (7.1%), epinephrine (2.8%), naloxone (3.7%), and sodium bicarbonate (2.1%).

TABLE 2 GA Distribution of Patient Profile and Perinatal Risks of Neonatal Respiratory Failure

	GA, wk					
Parameter, %	<28	28.0 to 32.9	33.0 to 36.9	37 to 42	>42	Total
No. of infants with NRF	45 (2.6)	552 (32.4)	482 (28.3)	602 (35.3)	23 (1.3)	1704
Male	64.4	76.6	73.7	76.9	78.3	75.5
Congenital anomalies	2.2	2.7	6.0	16.3	13.0	8.5
No prenatal care	15.4	19.0	11.9	15.8	23.5	16.0
Fetal distress	10.8	17.2	24.8	45.7	73.7	30.3
Cesarean section	15.5	27.5	52.0	54.7	52.2	43.8
Multiple births	31.1	25.2	13.1	2.7	0.0	13.6
Apgar score of <7 at 5 min	21.9	17.5	14.7	30.6	55.6	21.0

Gestational hypertension	4.4	7.6	11.2	5.0	4.3	7.5
Placenta previa	4.4	7.6	7.1	1.2	0.0	5.0
Premature rupture of placenta >24 h	13.3	8.9	5.0	1.3	4.3	5.1
Gestational diabetes	2.2	1.1	2.1	1.8	0.0	1.6

TABLE 3 Patient Profile in Different Disorders

	Disorders					
Parameter	RDS	Pneumonia/Sepsis	MAS	AAF	TT	HIE
No. of infants (%)	602	316	163	163	129	107
GA, mean ± SD, wk	31.8 ± 2.7	36.0 ± 3.5	39.9 ± 1.9	35.8 ± 3.1	36.0 ± 2.8	38.4 ± 3.4
Birth weight, mean ± SD, g	1751 ± 553	2460 ± 729	3321 ± 560	2480 ± 722	2463 ± 674	2909 ± 772
Male, %	74.8	80.4	71.2	74.2	69.0	83.2
Cesarean section, %	37.5	45.7	52.1	47.3	79.0	31.2
Surfactant use, %	36.0	11.1	1.8	5.5	6.2	0.0
Only nCPAP, %	36.4	39.2	16.6	59.5	68.2	13.1
Mortality, %	33.8	26.0	39.3	13.5	10.9	62.6
LOV, mean ± SD (median), h[a]	110 ± 114 (82)	97 ± 113 (70)	89 ± 57 (72)	63 ± 35 (52)	62 ± 52 (51)	83 ± 61 (65)
LOS in NICU, mean ± SD (median), d[a]	14.8 ± 12.3 (11.0)	10.6 ± 7.9 (8.0)	8.5 ± 4.1 (7.5)	8.1 ± 5.5 (7.0)	7.7 ± 4.8 (6.3)	9.0 ± 6.9 (8.0)
Cost of NICU, mean ± SD (median), x10^3 CNY[a]	17.6 ± 14.4 (13.5)	11.6 ± 8.6 (9.0)	10.8 ± 8.7 (8.3)	6.8 ± 4.5 (5.4)	6.9 ± 4.1 (5.8)	8.9 ± 8.7 (7.1)

AAF indicates aspiration of amniotic fluid; HIE, hypoxic-ischemic encephalopathy.

[a] Analyzed for infants who survived until discharge in recovery or in convalescence.

Neonatal Conditions Prompting Respiratory Support

Of 1722 cases of NRF in total, respiratory distress syndrome (RDS; n = 602, 35.0%) was the most common cause for mechanical ventilation. Other causes included pneumonia/sepsis (18.4%), meconium aspiration syndrome (MAS; 9.5%), aspiration of amniotic fluid (9.5%), transient tachypnea (TT, 7.5%), hypoxic-ischemic encephalopathy (6.2%), apnea of prematurity (4.5%), persistent pulmonary hypertension (1.3%), pulmonary hemorrhage (1.3%), major congenital anomalies (3.0%, including 27 congenital heart diseases, 13 diaphragmatic hernia, and 12 with other anomalies), surgical support (0.8%), and intraventricular hemorrhage (0.8%).

Surfactant Therapy

Of all infants with NRF, 285 (16.6%) received surfactant, 44 of whom received ≥2 doses. Prophylactic surfactant at delivery room was given to 9.9% of the infants who had NRF and were of GA < 30 weeks and 14.4% who had birth weight < 1200 g. When used in a prophylactic manner, the use of surfactant in male infants heavily outweighed that in female infants. The median age on receiving the first dose of surfactant in NICU was 6 hours (quartile range: 3–14). Among all the surfactant-treated infants, 76.1% (n = 217) had RDS, corresponding to 36.0% of all those with RDS (n = 602; Table 3). The use of surfactant decreased with increasing GA (Table 4). In the infants with GA < 35 weeks, 75% survived when they received surfactant (n = 238), and 67% survived when they had not received surfactant (n = 639; $P < .05$).

TABLE 4 Outcome and Costs of NRF

	GA, wk					
Parameter	<28	28.0 to 32.9	33.0 to 36.9	37 to 42	>42	Total
No. of infants (%)	45 (2.6)	552 (32.4)	482 (28.3)	602 (35.3)	23 (1.3)	1704
SNAPPE-II, mean ± SD (median)	34.3 ± 21.0 (27)	24.9 ± 18.1 (20)	23.4 ± 16.8 (20)	28.9 ± 20.3 (23)	39.7 ± 22.7 (42)	26.2 ± 18.8 (21)
Mortality, %	62.2	33.5	21.6	35.0	65.2	32.1
Complication, %						

Pneumonia/sepsis	40.0	21.6	14.3	14.0	13.0	17.1
Air leak	4.4	1.8	2.1	2.8	13.0	2.3
IVH	6.7	4.7	5.2	1.5	4.3	3.5
LOV, mean ± SD (median), h[a]	204 ± 188 (124)	112 ± 135 (82)	79 ± 59 (64)	83 ± 63 (65)	75 ± 41 (72)	92 ± 96 (70)
Surfactant use, %	53.3	28.2	15.6	2.6	4.2	16.6
LOS in NICU, mean ± SD (median), d[a]	35.1 ± 17.3 (34.0)	15.4 ± 12.9 (11.0)	9.1 ± 5.6 (8.0)	8.3 ± 4.6 (7.0)	10.1 ± 6.0 (8.0)	11.3 ± 9.6 (8.0)
Cost of NICU, mean ± SD (median), x10^3 CNY[a]	33.3 ± 17.9 (29.0)	15.8 ± 14.4 (10.8)	10.7 ± 9.0 (7.6)	9.7 ± 9.1 (7.3)	8.3 ± 4.2 (9.1)	12.3 ± 11.8 (8.4)
LOS in hospital, mean ± SD (median), d[a]	45.9 ± 25.8 (42.0)	26.6 ± 18.4 (22.0)	16.3 ± 8.9 (15.0)	14.1 ± 9.7 (13.0)	12.6 ± 7.6 (12.5)	19.2 ± 14.6 (15.0)
Cost of hospital, mean ± SD (median), x10^3 CNY[a]	37.0 ± 19.5 (31.3)	19.8 ± 17.6 (14.4)	13.2 ± 10.3 (9.6)	11.3 ± 8.5 (9.1)	12.7 ± 4.4 (11.3)	15.0 ± 13.5 (10.5)

IVH indicates intraventricular hemorrhage.

[a] Analyzed for infants who survived until discharge in recovery or in convalescence.

Mechanical Ventilation

The median age of all infants with NRF at the time of initiation of assisted ventilation was 9 hours (quartile range: 3–42). Length of ventilation (LOV) was analyzed for infants who survived until discharge. The longest median LOV was seen for infants with RDS (Table 3) and for infants at GA < 28 weeks (Table 4). nCPAP was used in 905 (52.6%), CMV in 1007 (58.5%), and HFV in 47 (2.7%) infants. Of 905 infants who received nCPAP, 664 (73.4%) received only nCPAP, 82 (9.1%) were after weaning from CMV and/or HFV, and 159 (17.6%) were with CMV/HFV after the failure of nCPAP. Nasal intermittent positive pressure ventilation was not used. The proportion in different GA category of infants who required CMV/HFV and/or nCPAP is presented in Fig 1. The use of nCPAP or together with CMV/HFV was greater among the preterm infants. The infants who received CMV/HFV only increased steadily from 36.2% among the youngest preterm infants to 62.7% among the term and postterm infants. nCPAP only was commonly applied for transient tachypnea (68.2%) among different disorders (Table 3).

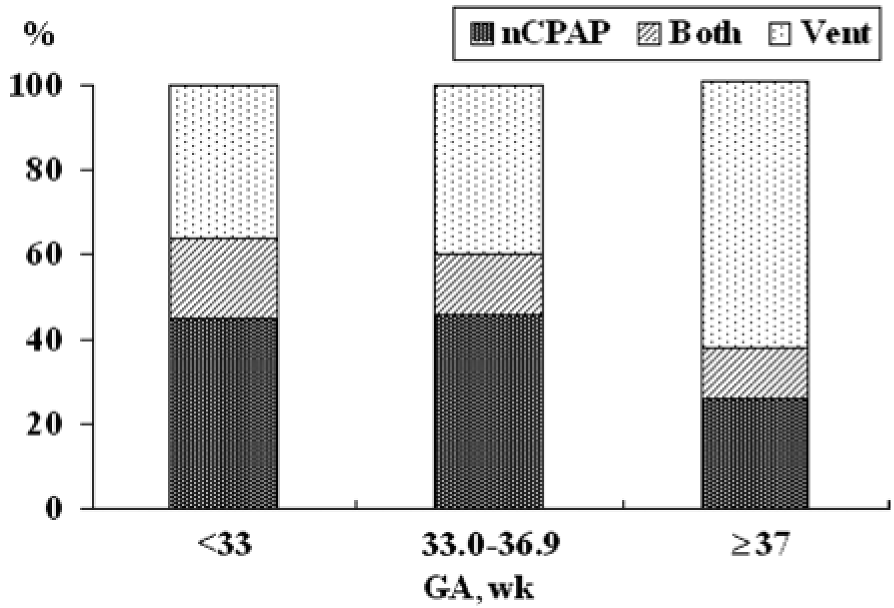

FIGURE 1 Use of different modes of assisted and/or mandatory ventilation categorized by GA. Vent indicates endotracheally intubated and mechanically ventilated.

Other Therapies

The mean duration of oxygen supplement was 143 ± 156 hours (median: 106; quartile range: 48–184) for all infants with NRF and 179 ± 162 hours (median: 142; quartile range: 90–215) for the survivors. Nitric oxide inhalation was used for hypoxemic respiratory failure in 58 infants in 5 hospitals, corresponding to 3.4% of infants with NRF. The underlying major cause of NRF in these cases was persistent pulmonary hypertension (58.6%), followed by RDS and lung infection. At this time, extracorporeal life support was not established in any site in China.

Mortality and Risk Factors

Of the total 1722 patients with NRF, 553 died, giving an overall mortality of 32.1% (95% CI: 29.9%–34.4%). In total, 67.1% (n = 1155) of infants with NRF survived to live discharge. These survivors included 47.7% (n = 821) discharged from the hospital without oxygen dependence, who had a full recovery, and 19.4% (n = 334) in convalescence who were transferred to community hospitals. The major causes of death included progressive and intractable respiratory failure (n = 330; 59.7%), circulatory failure (n = 91; 16.5%), and sepsis (n = 45; 8.1%). The highest mortality was seen in infants with MAS (Table 3) and in infants at GA > 42 weeks (Table 4). Infants with major congenital anomaly had significantly higher mortality than those without (52.4% vs 31.3%; P < .001). Major bleeding, including intracranial hemorrhage and pulmonary hemorrhage, was also associated with higher mortality as compared with infants without (45.9% vs 31.1%; P = .001).

We explored several potential factors in relation to survival. The incidence of congenital anomaly and SNAPPE-II were higher in male than in female infants, but mortality was the same between both genders.

The place of birth was related to variable mortality (inborn: 22.2%; outborn: 33.2%; home: 50.0%; $P < .001$). The mortality increased with increasing SNAPPE-II, although there were fewer infants at higher score categories (Fig 2). Place of birth was associated with increases of the mean (median) SNAPPE-II among the inborn (23.6 ± 17.2 [19.0]), outborn (26.5 ± 19.1 [21.0]), and home-born (33.1 ± 20.3 [29.0]; $P < .001$). The mortality in the midwestern region was significantly higher than in the southeastern region (Table 5). This was accompanied by higher fetal distress, cesarean section rate, and SNAPPE-II and lower rate of surfactant treatment.

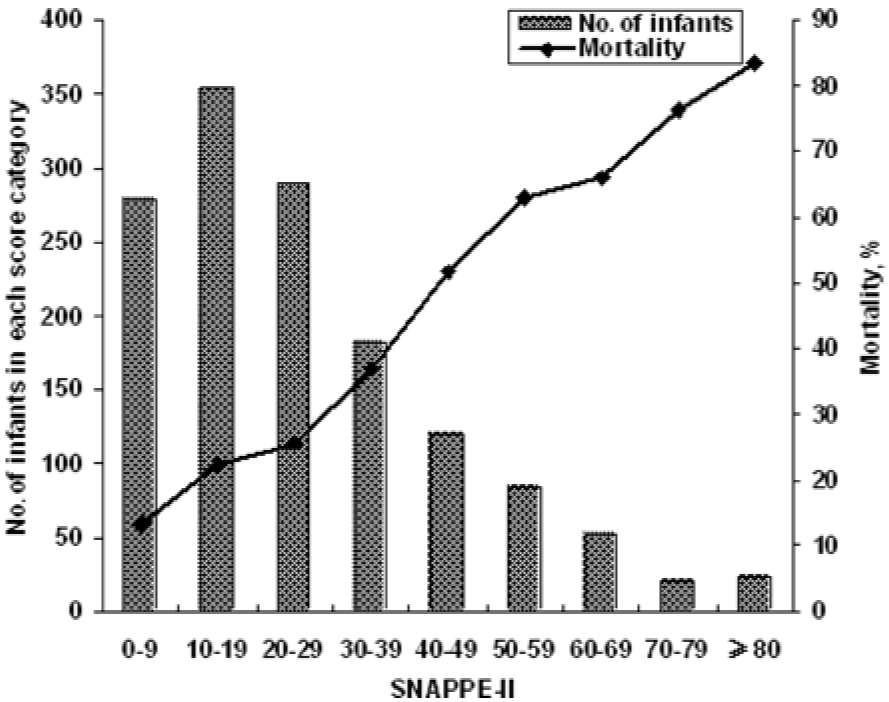

FIGURE 2 Mortality of neonatal respiratory failure related to the SNAPPE-II score on admission day.

TABLE 5 Comparison of Demographic Data, Perinatally Related Risk Factors, and Costs Between the NICUs From Southeastern and Midwestern Regions of China

Parameter	Southeastern	Midwestern	*P*
Male/total (%)	767/1019 (75.3)	533/703 (75.8)	>.050
GA, mean ± SD (median), wk	34.4 ± 4.1 (34.0)	35.6 ± 4.0 (35.8)	.000
Birth weight, mean ± SD (median), g	2244 ± 858 (2100)	2408 ± 781 (2350)	.000
SGA, %	4.8	5.9	>.050

Home birth, %	6.2	6.4	>.050
Congenital anomalies, %	7.2	10.4	.018
Fetal distress, %	25.5	37.1	.000
Cesarean section, %	41.5	47.2	.019
Apgar score of <7 at 5 min, %	20.2	24.0	>.050
SNAPPE-II, mean ± SD (median)	25.2 ± 18.7 (20.0)	28.0 ± 19.1 (23.0)	.001
Mortality, %	28.9	36.7	.001
LOV, mean ± SD (median), h[a]	97 ± 107 (72)	83 ± 69 (65)	.015
Surfactant use, %	21.8	9.0	.000
LOS in NICU, mean ± SD (median), d[a]	12.4 ± 10.5 (9.0)	9.5 ± 7.6 (8.0)	.000
Cost of NICU, mean ± SD (median), x10^3 CNY[a]	14.2 ± 12.4 (9.6)	9.4 ± 10.1 (6.9)	.000
LOS in hospital, mean ± SD (median), d[a]	21.9 ± 16.4 (17.0)	14.8 ± 9.6 (13.0)	.000
Cost of hospital, mean ± SD (median), x10^3 CNY[a]	17.7 ± 15.0 (12.3)	10.9 ± 9.4 (8.5)	.000

For hospital allocation, see Table 1. SGA indicates small for gestational age.

[a] Analyzed in infants survived until discharge in recovery or in convalescence.

Univariate and Multivariate Logistic Regression Analysis for Death Risk
Univariate and multivariate analyses were performed separately to analyze the risk factors of death in preterm, term, and postterm infants. For preterm infants, univariate logistic regression revealed the following statistically significant risk factors for death: low GA, vaginal delivery, lack of prenatal care, fetal distress, born out of hospital, presence of a major anomaly, presence of a major hemorrhage, born in the midwestern regions, and high SNAPPE-II (Table 6, which is published as supporting information on www.pediatrics.org/content/full/121/5/e1115). Male gender and multiple births were not significant risk factors for death in preterm infants by univariate analysis. In both term and postterm infants, increasing GA, vaginal delivery, nonprenatal care, NICU of the midwestern regions, and high SNAPPE-II were statistically significant for higher risk for death (Table 7, which is published as supporting information on www.pediatrics.org/content/full/121/5/e1115).

We next performed a multivariate logistic regression. Factors that were independently associated with an increased risk for death in preterm infants, in ascending order of significance, were low GA (OR: 1.158; 95% CI: 1.072–1.252; *P* < .001), high SNAPPE-II (OR: 1.511; 95% CI: 1.361–1.681; *P* < .001), fetal distress before delivery (OR: 2.002; 95% CI: 1.253–3.199; *P* = .004), vaginal delivery (OR: 2.248; 95% CI: 1.444–3.500; *P* < .001), and the presence of a major anomaly (OR: 7.813; 95% CI: 2.232–27.027; *P* = .001). Overall, the discrepancy between the observed and the predicted mortality of this model was very small, as was demonstrated by the Hosmer-Lemeshow goodness-of-fit test (*P* = .732). The factors that were associated independently with an increased risk for death in both term and postterm infants were a high SNAPPE-II (OR: 1.686; 95% CI: 1.686–1.946; *P* < .001) and the presence of a major anomaly (OR: 7.407; 95% CI: 2.639–20.833; *P* < .001). The goodness-of-fit test result of this model indicated that the observed and predicted mortality was not statistically different (*P* = .588).

Morbidity

Of all 1722 infants with NRF, 294 had complicated pneumonia/sepsis, 64 had intraventricular hemorrhage (grades 1–2: *n* = 54; grade 3–4: *n* = 10), 43 had air leak, and 22 had pulmonary hemorrhage. CLD was present in 26 cases (1.5% of infants with NRF) and accounted for 2.4% of preterm infants (< 37 weeks) with NRF and 8.9% of infants with a birth weight of <1500 g. ROP was found in 17 cases (1% of infants with NRF) and accounted for 1.6% of preterm infants and 5.8% of infants with birth weight < 1500 g. Complicated pneumonia/sepsis was the most prevalent in infants at GA < 28 weeks, and the highest incidence of air leak was seen in postterm infants (Table 4).

NICU Stay Days and Costs of Care

The median length of stay (LOS) in NICU was prolonged ~5 times for infants < 28 weeks' GA (34 days) as compared with 7 days for term infants (Table 4, Fig 3). The NICU cost rose from 7276 Yuan for term infants to 29036 Yuan for infants at GA < 28 weeks, a fourfold increase (Table 4, Fig 4). Costs of stay included nursing and physician work time entailed per service item for the infant undergoing NRF. There was significant difference in the costs of NICU stay between NICUs located in the southeastern and midwestern regions. The cost of LOS in NICU and hospital were higher and LOV and LOS in NICU and hospital were longer in male than in female infants. Geographically, the LOV and LOS were significantly shorter and costs for LOS in NICU and hospital were significantly lower in the NICUs from midwestern than those in the southeastern regions (Table 5).

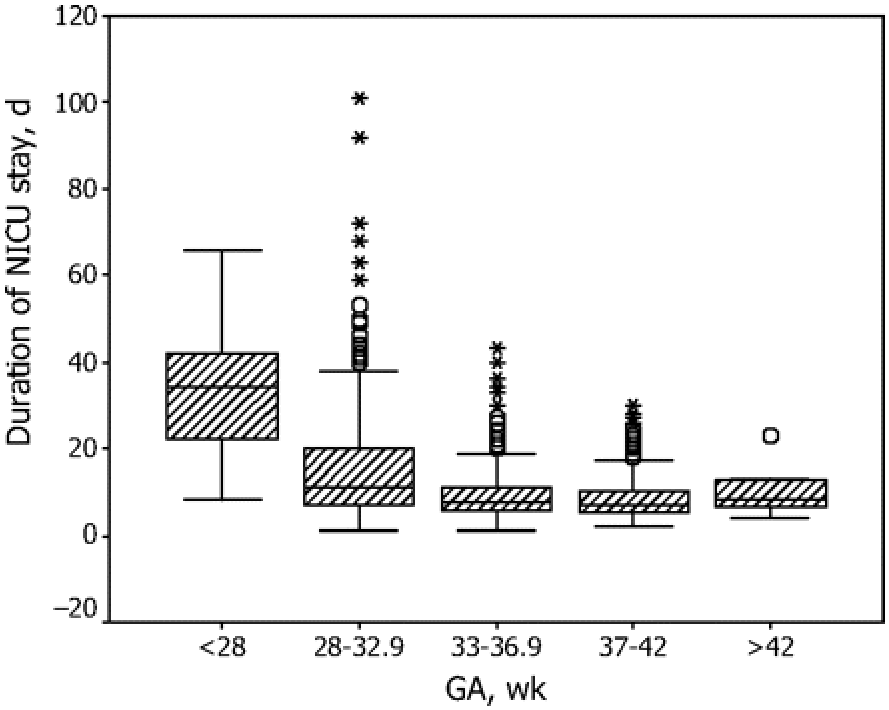

FIGURE 3 Duration of NICU stay of survivors categorized by GA. Values in boxplot are expressed as median and quartile (midline, upper and lower limit of the box) and 1.5 times of the difference of the quartiles (upper and low ticks). Circles (○) or asterisks (*) represent outliers or extreme values, respectively.

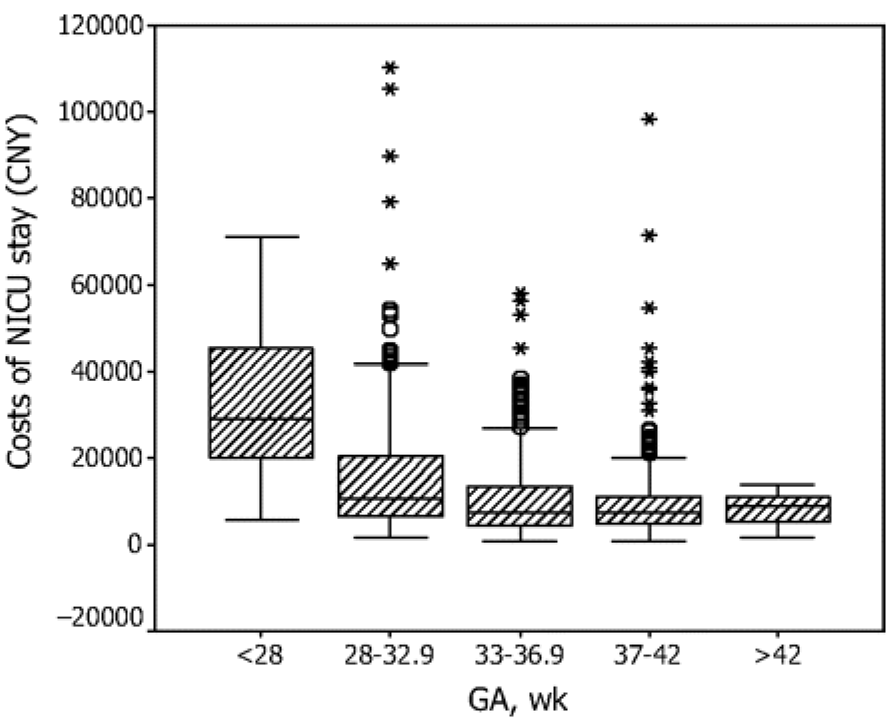

FIGURE 4 The costs (in Chinese Yuan [CNY]) of NICU stay of survivors categorized by GA. Values in boxplot are expressed as median and quartile (midline, upper, and low limit of the box) and 1.5 times of the difference of the quartiles (upper and low ticks) Circles (○) or asterisks (*) represent outliers or extreme values, respectively.

DISCUSSION

This report provides the first prospective and detailed clinical profile of NRF in Chinese NICUs in the current era (2004–2005), forming a base for longitudinal comparisons. Previous reports relied on retrospective data and informed us only of overall GA demographics.[14] Until the present time in China, both national and regional vital statistics lacked a detailed picture of perinatal and neonatal care. We believe that this report reflects the status and limitations of neonatal respiratory and intensive care in the provincial cities of China. A drawback of this study is that our study design did not account for all births, and our data were confined to births of infants who were treated with NICU care. We acknowledge that this introduces a selection bias in our data set; however, it is likely that these missing data would only accentuate our findings. It is estimated in recent years that China has an annual birth rate of ~20 million. Evidently, respiratory failure remains one of the major causes of death in neonates and infants. In discussing Chinese data, it should be recalled that respiratory care standards of industrialized countries may not form the most appropriate comparison.

Our data reflect some potential goals for China over the next 20 years. We reported a 32.1% in-hospital mortality of infants with NRF, much higher than 14.6% in Italy[3] and 11.1% in the United States[4] in the early 1990s. Because respiratory therapy requires both costly training and expertise and an initial outlay for equipment, it may not be equitably distributed. The cost of the treatment is likely to affect the decision of treatment and clinical outcome. In the participating cities in this study, there is a large population of low-income families, largely residents with a transient background, who have only limited or no health insurance. According to a national statistical report (www.stats.gov.cn/tjsj/ndsj/2005/indexch/htm), average values of gross domestic product of the corresponding provinces and municipalities involved in this study were estimated at 18395 ± 12466 Yuan (median: 12850; range: 7232–52378). Corresponding annual income of urban resident (per head) in these regions were 10892 ± 4121 Yuan (median: 8622; range: 6806–16683). Angus et al[4] reported that mean LOS in hospital and cost of caring for an infant who had NRF and survived until discharge from the hospital were 31.1 days and $51700 in the United States. Although average hospital cost of an infant with NRF in our study is much lower in contrast to that in the United States, it is at least as high as the total of an average 1-year family income in China. It is quite possible that in level I and II neonatal special care, the actual mortality of NRF might be even higher and the shortage in NICU resource and ability of families to pay for care more prominent, especially for extremely low birth weight (ELBW) and very low birth weight (VLBW) infants. Both low income and lack of public health coverage may at least in part account for the higher mortality of infants with NRF in this study.

These averaged figures cannot easily pinpoint intervention targets. In contrast, the geographic variation that we found suggests some therapeutic program goals.

The discrepancy in mortality between the two regions may be associated with resource use in perinatal-neonatal care. Our findings demonstrated that in the midwestern regions, there were less access to perinatal care, less use of surfactant, shorter LOV and LOS in NICU, and lower costs of NICU and hospital stay, which suggested that service level and affordability of resources were limited compared with those in the southeastern regions. This was confirmed to be a significant predictive factor for mortality in the univariate logistic regression models. Similarly, Cifuentes et al[15] reported a correlation between the rescue facilities and death of VLBW infants in hospitals with limited rescue means. The background social issues may explain the variation in the regional outcomes. In the midwestern regions, more families are likely to be unable to afford expensive therapies (eg, intensive care, surfactant) and may have withdrawn care more frequently because of economic embarrassment. Although all participating hospitals are tertiary, there are differences in medical facility levels, evidenced by, for example, allocation of modern equipments and facilities, introduction of advanced therapies and technology, and staff allocation, as a result of different economic development. This was corroborated by the major data comparison between the midwestern and southeastern regions, where gross domestic products were 29978 ± 13045 Yuan (range: 18476–52378) and 10149 ± 2387 Yuan (range: 7232–14858), and corresponding annual incomes of urban resident (per head) were 15183 ± 3267 Yuan (range: 11175–16683) and 7827 ± 738 Yuan (range: 6806–9221), respectively.

Another important program goal is indicated by one cultural factor reflected in our gender data. It seemed that more male infants with NRF in western countries were reported[3,4]; however, we found an even higher rate of admitted male infants with NRF. Despite this, our mortality showed no gender difference. Although male infants are more vulnerable to lung disease, there are likely social reasons underlying such a higher admission rate for male infants. There is in China a high male-to-female gender ratio at birth, especially in rural areas. With the high rural immigration into cities, demographics in the cities have changed. For transient residents in Shanghai, the male-to-female gender ratio was 110.6 to 100 (as reported in the fifth population census in 2000), whereas for registered permanent residents, the male-to-female ratio was only 102 to 100. The imbalance of gender ratio of birth population in Shanghai resulted from the higher male-to-female ratio of the city's immigrant population at birth.[16] We have become aware that families tend to give more aggressive treatment to male infants, reflecting socioeconomic and cultural factors in China. Our results suggest that more male infants should have been transported to NICUs for aggressive treatment by family decision. Because both NICU service charge and surfactant are the two major costs for NRF in these data, which are not paid for by the public health insurance, this will be differentially distributed.

The GA and birth weight distributions of infants with NRF seemed to be a significantly lower proportion of the extremely immature infants (23–25 weeks) in contrast with industrialized countries.[3,4,17] This difference suggested either that there were fewer deliveries of ELBW infants or that fewer ELBW infants were referred to the NICU, in preference to VLBW infants. These data corroborated a nationwide retrospective study of 77 hospitals,[14] which found an incidence of 7.8% of preterm infants in live birth in 2002–2003. In 6179 prematurely born infants hospitalized both GA < 28 weeks and birth weight < 1000 g were ~1.1%, and those with GA 28 to 32 weeks were 12% and birth weight 1000 to 1499 g were 8%, respectively. Hospitalized VLBW infants were 32.3%, and male/female at 1.67:1.

This survey only looked at rates of prematurity; our study, in contrast, examined in much more detail the contribution of NRF to the overall picture of prematurity in China.

Similar to the western data, the leading underlying causes of NRF were RDS and other major respiratory disorders, nearly 80% of the total in our study. In Italy,[5] RDS was 43%, TT was 40.7%, MAS was 3.8%, and pulmonary infection was 4.4%. In the United States,[18] RDS was 42.9%, MAS was 9.7%, pneumonia/sepsis was 8.3%, and TT was 3.9%. Our data showed a relatively higher incidence of severe respiratory disorders related to the level of perinatal intervention (prenatal and intrapartum lung infection and MAS), whereas the relatively low proportion of RDS might be attributable to fewer VLBW and ELBW infants. Other differences from the Western data include a high rate of cesarean section and a low rate of antenatal corticosteroids. The rate of cesarean section has been increasing since the 1970s and was up to 40% to 50% in the 1990s.[19] A study published in 2006[20] reported that social factors have an important impact on the high rate of cesarean section and accounted for 20% of the causes of cesarean section. Our study reflects this changing trend in rates of cesarean section in China.

The surfactant use in this report was relatively low in the infants with birth weight < 1500 g or with RDS. Horbar et al[1] found that there was an increase of surfactant use for VLBW infants who weighed < 1500 g in NICU from 53% in 1991 to 62% in 1999. In our study, the data of LOV resembled that of the western data.[18,21] In general, nCPAP was often used for preterm infants with NRF in contrast to CMV in the term and near-term infants. This was also similar to the west, where the use of nCPAP increased from 34.1% in 1991 to 55.2% in 1999, in contrast to a decrease of CMV from 80.8% to 71.6%.[1] Inhaled nitric oxide was mainly for investigational use in hypoxemic respiratory failure with persistent pulmonary hypertension. In Clark's report,[18] use of this therapy occurred for 17% of infants who had NRF and were born at an estimated GA of ≥ 34 weeks. So far, there is no report of extracorporeal life support in NICU in China. Strategies such as prenatal care and extensively skilled resuscitation at delivery are among the most cost-effective means to reduce neonatal mortality; however the implementation of appropriate respiratory therapies in NICU in the provincial city hospitals is also vital. That mortality remained high in our patient population; even for aspiration of amniotic fluid and TT, the mortalities were higher than expected, reflects inadequate management of moderate to severe NRF in the participating centers.

The low incidences of CLD and ROP in our study were probably attributable to a very low admittance rate of ELBW infants, although low ascertainment for ROP might also be a problem. Clark[18] reported that for infants who had NRF and GA ≥34 weeks, the incidence of CLD was 11%. Kirchner et al[22] reported that, in 1994–2002 in infants with birth weight < 1500 g, 14% to 32% developed CLD, whereas Horbar et al[1] reported that 27% to 39% of infants developed CLD. In Canada,[5] for those who had birth weight < 1500 g and were treated in NICU and survivors of corrected GA of 36 weeks, 26% had CLD and 50% had eye examinations for ROP before discharge, 43% of whom had ROP. We did not have a follow-up in the protocol, and, therefore, no neuromotor development outcome was available, but an increasing burden of CLD and ROP is foreseeable because more ELBW and VLBW infants will survive in NICU, which will necessitate screening and triage for therapy.

Adam et al[23] indicated that in developing countries, preventive interventions at the community level for newborn infants and at the primary care level for mothers and newborn infants are extremely cost-effective. Our data from NICU do not directly evaluate these aspects, but, in summary, we have characterized the incidence, management, outcome, and death risks of NRF in a Chinese NICU network and analyzed cost of the treatment. The data reflect current neonatal intensive care status in Chinese municipal and provincial cities and suggest that our perinatal care service should be improved. Inequality as a result of reform in the health care system affecting low-income families has been one of the major obstacles to overcome. It is warranted to conduct a more in-depth investigation in our neonatal care program to enhance the use of technologies based on advanced respiratory care and clinical epidemiology for reduction of mortality of NRF.

What This Study Adds

This article reports, from total NICU admissions in a multicenter prospective study, incidence, causes, management, outcome and death-related risk factors of respiratory failure, in different regions of China. A high mortality of respiratory failure is associated with multiple factors characteristic of perinatal-neonatal care.

REFERENCES

1. Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants 1991–1999. *Pediatrics.* 2002;110 (1 pt 1):143 –151[Abstract/Free Full Text]

2. Markestad T, Kaaresen PI, Ronnestad A, et al. Early death, morbidity, and need of treatment among extremely premature infants. *Pediatrics.* 2005;115 (5):1289 –1298[Abstract/Free Full Text]

3. Rubaltelli FF, Bonafe L, Tangucci M, Spagnolo A, Dani C. Epidemiology of neonatal acute respiratory disorders: a multicenter study on incidence and fatality rates of neonatal acute respiratory disorders according to gestational age, maternal age, pregnancy complications and type of delivery. Italian Group of Neonatal Pneumology. *Biol Neonate.* 1998;74 (1):7 –15[CrossRef][ISI][Medline]

4. Angus DC, Linde-Zwirble WT, Clermont G, Griffin MF, Clark RH. Epidemiology of neonatal respiratory failure in the United States: projections from California and New York. *Am J Respir Crit Care Med.* 2001;164 (7):1154 –1160[Abstract/Free Full Text]

5. Lee SK, McMillan DD, Ohlsson A, et al. Variation in practice and outcome in the Canadian network: 1996–1997. *Pediatrics.* 2000;106 (5):1070 –1079[Abstract/Free Full Text]

6. Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. *Pediatrics.* 1999;103 (1 Suppl E):350 –359[Medline]

7. Bennett CC, Johnson A, Field DJ. A comparison of clinical variables that predict adverse outcome in term infants with severe respiratory failure randomised to a policy of extracorporeal membrane oxygenation or to conventional neonatal intensive care. *J Perinat Med.* 2002;30 (3):225 –230[CrossRef][ISI][Medline]

8. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. *J Pediatr.* 2001;138 (1):92 –100[CrossRef][ISI][Medline]

9. Dubowitz LMS, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr.* 1970;77 (1):1 –10[CrossRef][ISI][Medline]

10. Taeusch HW, Ballard RA. *Avery's Diseases of the Newborn*. 7th ed. Philadelphia, PA: WB Saunders; 1998

11. Rubaltelli FF, Dani C, Reali MF, et al. Acute neonatal respiratory distress in Italy: a one-year prospective study. Italian Group of Neonatal Pneumology. *Acta Paediatr.* 1998;87 (12):1261 –1268[CrossRef][ISI][Medline]

12. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163 (7):1723 –1729[Free Full Text]

13. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An international classification of retinopathy of prematurity: II—the classification of retinal detachment. *Arch Ophthalmol.* 1987;105 (7):906 –912[ISI][Medline]

14. The Subspecialty Group of Neonatology, Chinese Pediatric Society. An initial epidemiologic investigation of preterm infants in cities of China. *Zhongguo Dang Dai Er Ke Za Zhi.* 2005;7 (1):25 –28

15. Cifuentes J, Bronstein J, Phibbs CS, Phibbs RH, Schmitt SK, Carlo WA. Mortality in low birth weight infants according to level of neonatal care at hospital of birth. *Pediatrics.* 2002;109 (5):745 –751[Abstract/Free Full Text]

16. Jiao YB. The effect of immigrant population on the sex ratio of birth population in Shanghai. *Nanjing Ren Kou Guan Li Gan Bu Xue Yuan Xue Bao.* 2005;21 (4):15 –17

17. Subhedar NV, Tan AT, Sweeney EM, Shaw NJ. A comparison of indices of respiratory failure in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2000;83 (2):F97 –F100[Abstract/Free Full Text]

18. Clark RJ. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. *J Perinatol.* 2005;25 (4):251 –257[CrossRef][Medline]

19. Zheng P, Huang XH, Wang SZ. The changing trend of cesarean section rates in 35 years. *Zhonghua Fu Chan Ke Za Zhi.* 1996;31 (3):142 –145[Medline]

20. Wang XM. The analysis of causes for high cesarean section rates. *J Bethune Mil Med Coll.* 2006;4 :209 –210

21. Wilson A, Gardner MN, Armstrong MA, Folck BF, Escobar GJ. Neonatal assisted ventilation: predictors, frequency, and duration in a mature managed care organization. *Pediatrics.* 2000;105 (4 pt 1):822 –830[Abstract/Free Full Text]

22. Kirchner L, Weninger M, Unterasinger L, et al. Is the use of early nasal CPAP associated with lower rates of chronic lung disease and retinopathy of prematurity? Nine years of experience with the Vermont Oxford Neonatal Network. *J Perinat Med.* 2005;33 (1):60 –66[CrossRef][ISI][Medline]

23. Adam T, Lim SS, Mehta S, et al. Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. *BMJ.* 2005;331 (7525):1107[Abstract/Free Full Text]

Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomized trial

Peter Stutchfield, *consultant paediatrician*[1], **Rhiannon Whitaker**, *trial statistician*[2], **Ian Russell**, *director*[2], on behalf of the Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team

[1] Conwy and Denbighshire NHS Trust, Glan Clwyd Hospital, Rhyl, Denbighshire LL18 5UJ, [2] Institute of Medical and Social Care Research, University of Wales Bangor LL572PX

Abstract

Objective To test whether steroids reduce respiratory distress in babies born by elective caesarean section at term.
Design Multicentre pragmatic randomized trial.

Setting 10 maternity units.

Participants 998 consenting women randomised at decision to deliver by elective caesarean section; 503 randomised to treatment group.

Interventions The treatment group received two intramuscular doses of 12 mg betamethasone in the 48 hours before delivery. The control group received treatment as usual.

Outcome measures The primary outcome was admission to special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care in response.

Results Sex, birth weight, and gestation were not different between the two groups. Of the 35 babies admitted to special baby units with respiratory distress, 24 were in the control group and 11 in the intervention group (P = 0.02). The incidence of admission with respiratory distress was 0.051 in the control group and 0.024 in the treatment group (relative risk 0.46, 95% confidence interval 0.23 to 0.93). The incidence of transient tachypnea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12). The incidence of respiratory distress syndrome was 0.011 in the control group and 0.002 in the treatment group (0.21, 0.03 to 1.32).

Conclusions Antenatal betamethasone and delaying delivery until 39 weeks both reduce admissions to special care baby units with respiratory distress after elective caesarean section at term.

Introduction

The rate of caesarean section in England rose from 9% in 1980 to 22% in 2003 as a result of changing practice in the management of previous caesarean and breech presentation as well as increased choice for women.[1 2] This increase has included some women who opted for caesarean section at socially convenient times, without medical reasons.[3] One survey reported that 69% of consultant obstetricians in England and Wales agree to women's requests for section in the absence of obstetric indications.[4] Recent guidelines from the National Institute for Clinical Excellence (NICE, now National Institute for Health and Clinical Excellence) have recommended that a woman's request alone is not an indication for caesarean section.[5]

The consequences of elective caesarean section at term for the baby have received little attention. The incidence of respiratory distress is much higher than in vaginal delivery (0.036 *v* 0.0053).[6] Other risk factors for respiratory distress include gestational age, mode of delivery, male sex, fetal asphyxia, maternal asthma and diabetes, and type of anesthesia given during delivery (regional or general).[6-9] The development of respiratory distress leads to admission to a special care baby unit or neonatal intensive care unit, often at a distance, separation from the mother, and complications from invasive procedures including artificial ventilation.

Antenatal corticosteroids reduce the incidence of respiratory distress in preterm babies.[10] Guidance has long recommended their routine use when delivery is expected before 34 weeks' gestation.[11] [12] However, no trials have been conducted of antenatal corticosteroids in mothers delivered by elective caesarean section at term.

The antenatal steroids for term caesarean section (ASTECS) randomised trial therefore sought to evaluate whether giving the recommended two doses of betamethasone before delivery[13] reduces the incidence of respiratory distress in babies delivered by elective caesarean section at term. Five studies lasting between three and 20 years, with more than 1500 patients, have shown no adverse effects of a single course of antenatal corticosteroids, neither through infection of fetus or mother nor in long term neurological or cognitive effects.[10] [12]

Methods

In 1995 the ASTECS team submitted the protocol to the National Perinatal Trial Centre, started recruitment, and invited other obstetric units to participate. By November 1998, altogether 10 units were taking part.

Mothers were eligible for the trial if elective caesarean section was planned at 37 weeks' gestation or beyond. Exclusion criteria included severe maternal hypertension, history of peptic ulceration, severe fetal rhesus sensitization, and evidence of intrauterine infection. We used an algorithm from the Confidential Enquiry into Sudden Death in Infancy (CESDI) to calculate gestation from last menstrual period, expected date of delivery, and estimates from first ultrasound scan and at birth. Women who were eligible received an explanation of the study and an information sheet. In the 48 hours before elective caesarean section, women received either two intramuscular doses of 12 mg of betamethasone, separated by 24 hours, or treatment as usual, without antenatal steroids.

The trial centre in Rhyl held a list of treatment allocations derived from the random number generator in MS Excel but concealed from all participants. Midwives with signed consent from a mother phoned Rhyl and received the next allocation on the list. They informed the mother and recorded the allocation in her notes. As ASTECS was a pragmatic trial to estimate the effectiveness of betamethasone for caesarean section at term in routine clinical practice, blinding participants and professionals was neither desirable nor possible.

Outcome measures

The primary outcome was admission to a special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care needed.[14] To diagnose respiratory distress within 24 hours of birth needed tachypnea (more than 60 breaths per minute) with grunting, recession, or nasal flaring.

From reported arterial gases and oximetry measurements, we graded respiratory distress as mild if the baby received less than 30% oxygen, severe if it received more than 70% oxygen or ventilatory support, otherwise moderate. We asked for chest radiographs of babies admitted with respiratory distress. Two neonatal radiologists (David Pilling, consultant radiologist at Alder Hey Children's Hospital, and Alan Sprigg, consultant radiologist at Sheffield Children's Hospital) independently assessed these for the radiological features of transient tachypnea of the newborn or the reticular granular pattern of respiratory distress syndrome.[15]

Sample size and analysis

Recruiting 1100 mothers would have yielded 80% power of detecting a reduction in the percentage of babies admitted to special baby units with respiratory distress from 8% to 4% when a 5% significance level was used. Because antenatal steroids do not reduce respiratory distress syndrome in twin pregnancy,[16] we analyze only singleton deliveries. Analysis was by intention to treat, *t* test for normally distributed data, and χ^2 test for categorical data, using logistic regression to adjust for confounding variables.

Results

Recruitment began in Rhyl in February 1995 and another nine centers by November 1998. The last pregnant woman entered the trial in April 2002. Follow-up continued until December 2002, when all babies had left hospital. In all 998 women entered the study—313 from Bradford Royal Infirmary, 233 from Ipswich Hospital, 210 from Glan Clwyd Hospital, 135 from Southmead Hospital, and 107 from the remaining six centers.

Figure 1 shows the flow of participants through the trial. The trial centre received no data after randomization on 29 women. There were 20 sets of twins, and seven mothers gave birth before 37 weeks' gestation. Hence 942 babies were available for intention to treat analysis, 467 in the treatment group and 475 in the control group. These two groups were similar in mothers' age, asthma, and smoking, and in babies' sex and birth weight. Eighty six (9.1%) were born at 37 weeks' working gestation, 434 (46.1%) at 38 weeks, 357 (37.9%) at 39 weeks, 46 (4.9%) at 40 weeks, 13 (1.4%) at 41 weeks, and 6 (0.6%) at 42 or more weeks. Ten women (four in the treatment group) had diabetes: six had gestational diabetes that was controlled by diet, three had type 1 diabetes and one type 2 diabetes. None of their babies developed respiratory distress. In all, 51 women delivered by emergency section before random allocation came into effect.

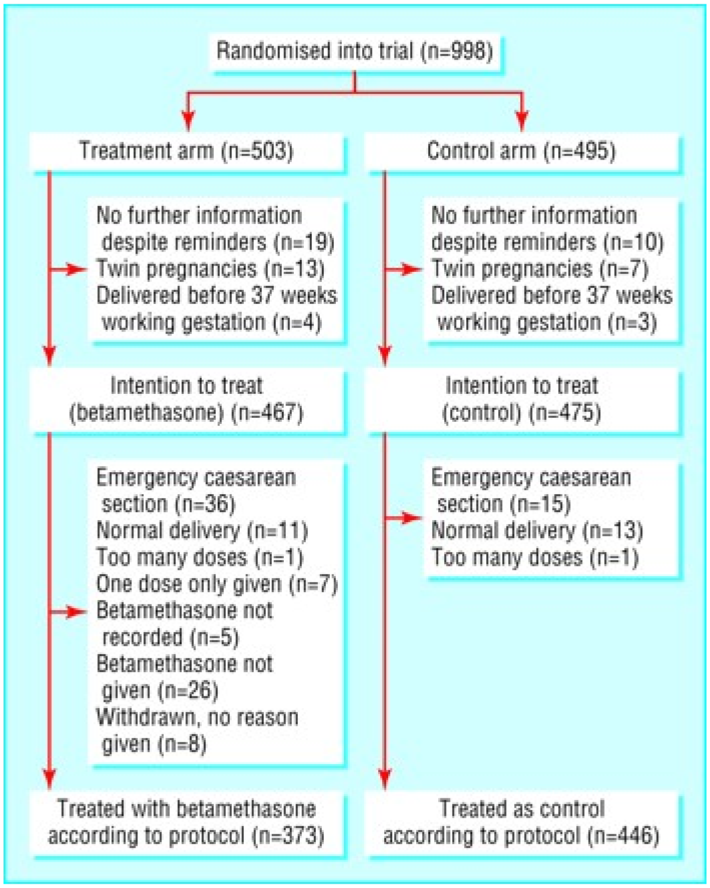

Fig 1 Flow of participants through the trial

Secondary outcomes

No mother of a control baby admitted to a special care baby unit received general anesthetic, compared with five (45%) in the treatment group (P < 0.001). Three (12%) of the control babies so admitted received neonatal resuscitation, compared with eight (73%) in the treatment group (P < 0.001). Four (36%) of these intervention babies also received ventilation through a mask, and two (18%) also received intubation, compared with none in the control group (P = 0.006 and P = 0.09, respectively). The two groups did, however, not differ significantly with regard to the sex, birth weight, or gestation of infants admitted to a special baby unit.

Table 3 shows that the severity of respiratory distress in babies admitted to special care baby unit was similar in both groups. We received radiographs relating to 22 of the 35 babies admitted with respiratory distress. The remaining 13 babies had diagnoses of transient tachypnea of the newborn on discharge. Nineteen control babies had transient tachypnea of the newborn and five had respiratory distress syndrome, compared with 10 treated babies with transient tachypnea and one with respiratory distress syndrome.

The incidence of respiratory distress syndrome was therefore 0.011 in the control group and 0.002 in the treatment group (relative risk 0.21, 0.03 to 1.32), and the incidence of transient tachypnea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12).

Table 3 Reason for admission to special care baby unit by group

Reason for admission	Betamethasone group	Control group
Respiratory distress by severity:		
Mild	4	9
Moderate	6	10
Severe	1	5
Respiratory distress by type:		
Transient tachypnea of the newborn	10	19
Respiratory distress syndrome	1	5
Total No of babies admitted	**26**	**32**
With respiratory distress (subtotal)	11	24

Other (without respiratory distress)	15	8

Only two intervention babies received intensive care—one at level 1 for one day and level 2 (high dependency) for three days, the other at level 2 for one day (fig 2). In contrast, 14 control babies received intensive care; three with respiratory distress syndrome required ventilation for between two and five days and stays of between 12 and 18 days. Antenatal betamethasone thus substantially reduced resource use in special baby units.

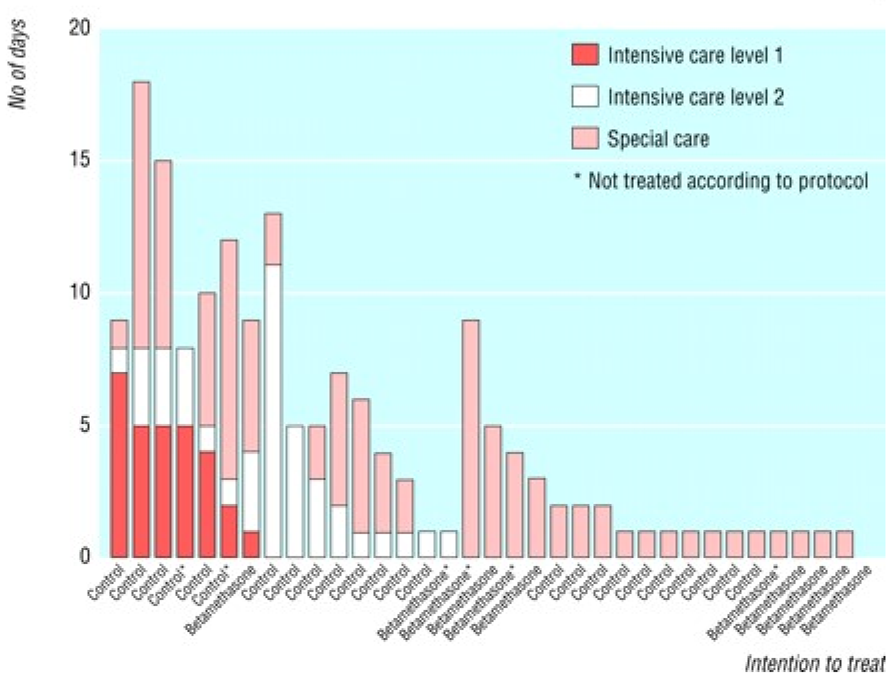

Fig 2 Babies admitted to a special care baby unit in descending order of intensity of care and of length of stay: intention to treat analysis

The logistic regression model in figure 3 predicts the probability of admission to special care baby unit with respiratory distress from the gestational age of the baby. The predicted probability of admission at 37 weeks was 11.4% in the control group and 5.2% in the treatment group, at 38 weeks it was 6.2% and 2.8%, respectively, and at 39 weeks it was 1.5% and 0.6%.

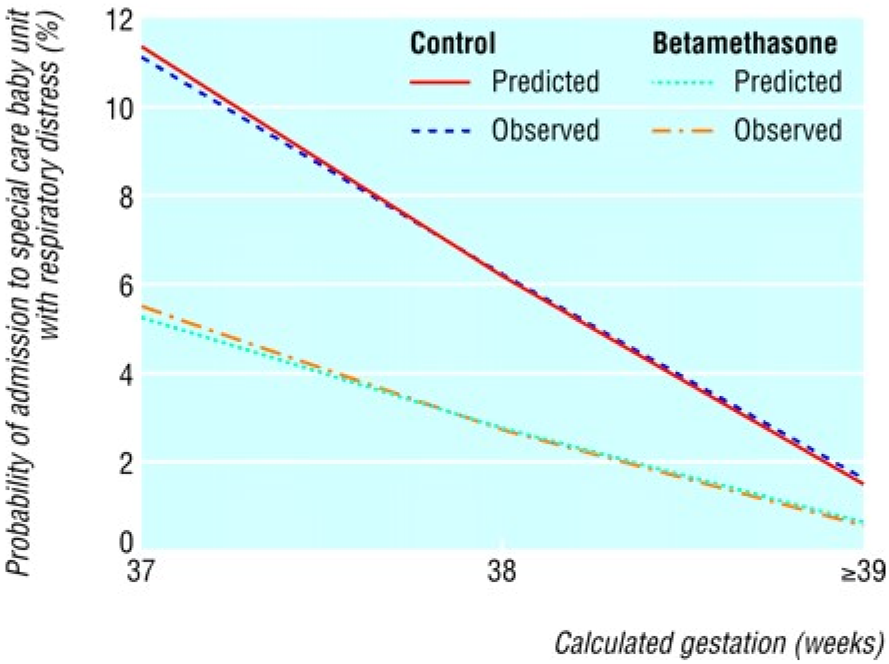

Fig 3 Probability of admission to special care baby unit with respiratory distress by gestation (observed and predicted by logistic model): intention to treat analysis. Logistic regression model: z=-5.034+2.139 (if baby is 37 weeks)+1.472 (if baby is 38 weeks)+0.840 (if mother was not randomised to receive betamethasone) where the default is randomised to receive betamethasone at 39 weeks. Predicted probability=exp(z)/[1+exp(z)]

Adverse effects

Reports of side effects came from seven mothers in the treatment group who had received two doses of betamethasone and one who had received only one. Five reported generalized flushing, one nausea, one tenderness at the injection site, and one increased energy with difficulty in sleeping. No such reports came from the control group. No reports were made of wound infection or neonatal sepsis.

Discussion

Betamethasone given immediately before elective caesarean section at term reduces respiratory distress and admission to a special care baby unit. The rate of such admission was 0.050 in the control group and 0.024 in the treatment group. This rate falls with increasing gestation, supporting the recommendation to delay elective caesarean section until the 39th week.[6] Nevertheless, the benefits of antenatal steroids persist until 39 weeks.

Strengths and weaknesses of the trial

We designed ASTECS as a pragmatic trial to estimate the effectiveness of betamethasone for caesarean section at term in routine practice in 10 diverse maternity units. Blinding participants and professionals was therefore neither desirable nor possible. Similarly the use of placebos was not practical. Furthermore the primary outcome, respiratory distress requiring admission to special care baby unit, is hardly susceptible to maternal influence.

To simplify, and thus increase, recruitment we did not stratify treatment allocation by gestation or centre; no imbalance in allocation resulted. The need to alter clinical practice to permit two injections in the 48 hours before delivery slowed recruitment to the trial, which finished before reaching its target; nevertheless, the trial detected significant differences between groups. Although race reportedly modifies the effect of antenatal steroids, the evidence is conflicting.[7,16] The trial lacked power to tackle this secondary issue.

Unanswered questions
Reducing the number of babies born by elective caesarean section before 39 weeks' gestation will reduce admissions with respiratory distress to special care baby units. However, many clinical factors influence the timing of elective caesareans. There may be uncertainty regarding gestation, medical indications for earlier delivery, and concerns about spontaneous onset of labor resulting in emergency caesareans with risks for mother and baby.[17] Social factors also influence timing.[4] Plans for changing clinical management should take all these factors into account.

Meaning of the study
Independent radiological review confirmed that antenatal betamethasone reduced the incidence of transient tachypnea of the newborn from 4% of elective caesarean sections to 2.1% and that of respiratory distress syndrome from 1.1% to 0.2%. To our knowledge this is the first report that antenatal steroids prevent transient tachypnea. During labor and at birth, the mature lung switches from active chloride and fluid secretion to active sodium and fluid absorption.[18-20] The reduced incidence of transient tachypnea in the steroid group is consistent with the hypothesis that corticosteroids, increased in mother and fetus through the stress of labor, encourage the expression of the epithelial channel gene and allow the lung to switch from fluid secretion to fluid absorption. Without another source of corticosteroid, elective caesarean section will disrupt this process. Thereafter admission with respiratory distress to a special unit separates mother and baby, potentially disrupting bonding, and increasing the cost of care and the risk of complications.[21,22] Furthermore, neonatal respiratory morbidity increases the risk of asthma in childhood.[23]

What is already known on this topic

Two antenatal doses of betamethasone reduce the incidence of respiratory distress syndrome by more than 50% in babies born before 34 weeks' gestation, thus reducing morbidity and mortality

Although this is now recommended practice, the treatment is considered of no benefit beyond this gestational age

The treatment's effect is thought to be mediated through increased surfactant production, a shortage of which leads to respiratory distress syndrome, which is common in preterm babies

Long term studies have shown no harmful effect of a single course of betamethasone

What this study adds

Babies born after 37 weeks by elective caesarean section also benefit from antenatal

betamethasone This reduces the incidence of respiratory distress by more than 50%, mainly by reducing transient tachypnea of the newborn These findings imply that antenatal steroids can aid the clearing of lung fluid after delivery When counseling a mother before elective caesarean section at term, the increased risk of admission with respiratory distress should be considered The likely benefits of antenatal betamethasone should be compared with those of delaying caesarean section until 39 weeks when possible

Conclusion
Antenatal betamethasone is effective in reducing admission to special care baby unit with respiratory distress after elective caesarean section at term. In planning elective caesareans, the risk of respiratory distress should be considered and the likely benefits of antenatal corticosteroids should be compared with those of delaying delivery until 39 weeks when possible.

A list of collaborators is on bmj.com
We thank all participants—patients, staff, and collaborators—for their contributions. For funding we thank the NHS: the Wales Office of Research and Development in health and social care (WORD) and Conwy and Denbighshire NHS Trust.

Contributors: Authors and other members of the ASTECS trial team contributed as follows. PS is consultant pediatrician at Glan Clwyd Hospital, which provides a neonatal intensive care service for North Wales. He developed the protocol, initiated and coordinated the trial, recruited other centers, supervised collection, validation and analysis of data, and drafted this paper. He guarantees its clinical content. Philip Banfield, consultant obstetrician at Glan Clwyd Hospital, recruited patients to the trial. Jeff Berry and James Satelle, information analysts at Glan Clwyd Hospital, developed and managed the trial database. Nigel Bickerton, consultant obstetrician at Glan Clwyd Hospital, contributed to the protocol and recruited patients to the trial. Duncan Cameron, consultant pedestrian and neonatologist at Glan Clwyd Hospital, contributed to the protocol, the newsletter for participating centers and data collection. Lesley Furneaux, personal secretary to PS, acted as research coordinator, randomizing patients, collating and entering data, and checking their completeness. David Pilling, consultant radiologist at Alder Hey Children's Hospital, and Alan Sprigg, consultant radiologist at Sheffield Children's Hospital, independently assessed the chest radiographs submitted. IR contributed to analyzing, interpreting, and writing this paper. He guarantees its statistical content. RW validated and analyzed data, and contributed to interpreting and writing this paper. Matouk Zbaeda, previously senior pediatric registrar at Glan Clwyd Hospital, reviewed elective caesarean sections at term, thus stimulating the trial, and contributed to the protocol.

Funding: Wales Office of Research and Development in health and social care (WORD) and Conwy and Denbighshire NHS Trust.

Competing interests: None declared.

Ethical approval: North West Multi-centre Research Ethics Committee and the 10 relevant local research ethics committees approved the trial protocol.

References

1. Royal College of Obstetricians and Gynecologists Clinical Effectiveness Unit. *The national sentinel caesarean section audit report*. London: RCOG Press, 2001.

2. Department of Health. *NHS maternity statistics, England: 2002-3*. London: DoH, 2004. (Bulletin 2004/10.)

3. Doctors told to curb "posh" caesareans. *Sunday Times* 2004 April 25: 14.

4. Cotzias CS, Paterson-Brown S, Fisk NM. Obstetricians say yes to maternal request for elective caesarean section: a survey of current opinion. *Eur J Obstet Gynaecol Reprod Biol* 2001;97: 15-6.[Medline]

5. National Collaborating Centre for Women and Children's Health. *Caesarean section clinical guideline*. London: RCOG Press, 2004.

6. Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol* 1995;102: 101-6.[ISI][Medline]

7. Robert ME, Neff RK, Hubbell JP, Taeusch HW, Avery ME. Association between maternal diabetes and the respiratory distress syndrome in the newborn. *N Engl J Med* 1976;294: 357-60.[Abstract]

8. Schatz M, Zeiger RS, Hoffman CP, Saunders BS, Harden KM, Forsythe AB. Increased transient tachypnea of the newborn in infants of asthmatic mothers. *Am J Dis Child* 1991;145: 156-8.[Abstract]

9. Demissie K, Marcella SW, Breckenridge MB, Rhoads GG. Maternal asthma and transient tachypnea of the newborn. *Pediatrics* 1998;102: 84-90.[Abstract/Free Full Text]

10. Crowley P. Prophylactic corticosteriods for preterm birth. *Cochrane Database Syst Rev* 2000;(2): CD000065.

11. Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1990;97: 11-25.[ISI][Medline]

12. Royal College of Obstetricians and Gynecologists Scientific Advisory Committee. *RCOG guidelines No 7: antenatal corticosteroids to prevent respiratory distress syndrome*. 2nd ed. London: RCOG Press, 2004: 1-9.

13. McCarthy M. Recommendations for antenatal corticosteroids. *Lancet* 1994;343: 726.

14. Report of working group of the British Association of Perinatal Medicine and Neonatal Nurses Association on categories of babies requiring neonatal care. *Arch Dis Child* 1992;67: 868-9.[Medline]

15. Avery ME, Gatewood OB, Brumley G. Transient tachypnea of newborn. *Am J Dis Child* 1966;111: 380-5.[Medline]

16. Quist-Therson EC, Myhr TL, Ohlsson A. Antenatal steroids to prevent respiratory distress syndrome; multiple gestation as an effect modifier. *Acta Obstet Gynecol Scand* 1999;78: 388-92.[Medline]

17. Hillan EM. Postoperative morbidity following caesarean delivery. *J Adv Nurs* 1995;22: 1035-42.[Medline]

18. Watlers DV, Oliver RE. The role of catecholamines in lung fluid absorption at birth. *Pediatr Res* 1978;12: 239-42.[ISI][Medline]

19. Rimmer S, Fawcitt J. Delayed clearance of pulmonary fluid in the neonate. *Arch Dis Child* 1982;57: 63-7.[Abstract]

20. O'Brodovich HM. Immature epithelial Na^+ channel expression is one of the pathogenetic mechanisms leading to human neonatal respiratory distress syndrome. *Proc Assoc Am Physicians* 1996;108: 345-55.[ISI][Medline]

21. Symanski ME. Maternal-infant bonding, practice issues for the 1990s. *J Nurs Midwifery* 1992;37: 2:67S-73S

22. Madar J, Richmond S, Hey E. Surfactant deficient respiratory distress after elective delivery at `term'. *Acta Paediatr* 1999;88: 1244-8.[Medline]

23. Smith GC, Wood AM, White IR, Pell JP, Cameron AD, Dobbie R. Neonatal respiratory morbidity at term and the risk of childhood asthma. *Arch Dis Child* 2004;89: 956-60.[Abstract/Free Full Text]

Neonatal respiratory failure Post-Test

Select the ***best*** answer to each of the following items. Mark your responses on the Answer form.

1. _______ is one of the most common, serious clinical problems and a major cause of death in newborn infants.

a. Sudden Infant Death Syndrome (SIDS)
b. Neonatal respiratory failure (NRF)
c. Low Birth Weight (LBW)
d. None of the above

2. In the past 2 decades, several factors have significantly reduced overall neonatal death, especially in extremely immature infants with NRF, in industrialized countries. These include _______.

a. agressive intervention at delivery
b. establishment of an NICU
c. development of advanced respiratory therapies
d. All of the above

3. In high-growth regions of China, there is a trend to centralize neonatal service in local maternity hospitals or medical center for women's and children's health. This has led to the availability of modern equipment and facilities in many NICUs at provincial and subprovincial pediatric and medical centers.

a. True
b. False

4. In the study reviewed in this course, prospective data were collected by trained staff using a standard case report form, which included _______.

a. demographic characteristics
b. antenatal history
c. pregnant history of mother
d. All of the above

5. In the study, prenatal care was defined as receiving pregnancy-related care from a physician on at least _____ occasion(s) during pregnancy.

a. one
b. two
c. three or more
d. none of the above

6. In the study reviewed in this course, chronic lung disease (CLD) was defined as a requirement of supplement oxygen to maintain adequate oxygenation after _____ days of life for an infant of ≥32 weeks' GA, or 36 weeks' corrected GA for an infant who was born at < 32 weeks' GA.

a. 10
b. 19
c. 28
d. None of the above

7. The primary goal of this study was to provide descriptive statistics of the patient population. Continuous variables are presented as means and SD or medians and range or quartile range (25th to 75th percentile), categorical variables as counts or rates, and odds ratio with 95% confidence intervals (CI).

a. True
b. False

8. In this study of neonatal conditions prompting respiratory support, of 1722 cases of NRF in total, respiratory distress syndrome (RDS; *n* = 602, 35.0%) was the most common cause for mechanical ventilation.

a. True
b. False

9. Prophylactic surfactant at delivery room was given to _______ of the infants who had NRF and were of GA < 30 weeks and 14.4% who had birth weight < 1200 g.

a. 5.5%
b. 9.9%
c. 15.9%
d. 26.5%

10. Among all the surfactant-treated infants, 76.1% (n = 217) had RDS.

a. True
b. False

11. The median age of all infants with NRF at the time of initiation of assisted ventilation was 9 hours (quartile range: 3–42). Length of ventilation (LOV) was analyzed for infants who survived until discharge.

a. True
b. False

12. Nitric oxide inhalation was used for hypoxemic respiratory failure in 58 infants in 5 hospitals, corresponding to 3.4% of infants with NRF.

a. True
b. False

13. In the study reviewed here in this course, of the total 1722 patients with NRF, 553 died, giving an overall mortality of 32.1% (95% CI: 29.9%–34.4%). In total, _______% (n = 1155) of infants with NRF survived to live discharge.

a. 49.8
b. 58.2
c. 67.1
d. 78.5

14. In the study reviewed in this course, the major causes of neonatal death included _______.

a. progressive and intractable respiratory failure
b. circulatory failure
c. sepsis
d. All of the above

15. According to the authors of this study, "Our data from NICU do not directly evaluate these aspects, but, in summary, we have characterized the incidence, management, outcome, and death risks of NRF in a Chinese NICU network and analyzed cost of the treatment. The data reflect current neonatal intensive care status in Chinese municipal and provincial cities and suggest that our perinatal care service should be improved."

a. True
b. False

MEDEDSYS
PO BOX 81831, San Diego, CA, 92138-3939
TOLL FREE 1-877-295-4719
FAX: 619-295-0252
info@mededsys.com
www.mededsys.com

How to Complete Your Test and Print Your Certificate Online

If you chose to receive your order by postal mail, you have been mailed the printed course material(s) and the printed test(s). To take a test, simply complete the mailed test and send it back. Upon successful completion of a test, a certificate will be mailed or faxed to you. If you don't wish to mail the test back, customers who chose to have the course material(s) mailed may also follow the steps below to complete a test and print a certificate online.

INSTRUCTIONS

1. Go to www.mededsys.com
2. Login and go to "My Account".
3. On the page that opens, select an option from the "My Courses" menu.
4. Select the test you wish to complete.
5. After completion of test, print your certificate online by clicking on the "Continue" button. Alternatively, you may return to the "My Courses" section and select the option to print a certificate.