

# Development of Neonatal Respiratory and Intensive Care: Chinese Perspectives

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## Key Words

Neonatology · Prematurity · Respiratory distress syndrome · Respiratory failure · Respiratory therapy

## Abstract

Recent economic improvements in China have allowed the development of perinatal-neonatal care in sub-provincial regions. However, variations in neonatal respiratory and intensive care exist, especially in regions with limited resources. We conducted a series of collaborative clinical investigations into neonatal hypoxemic respiratory failure (NRF). In the study period from 2004 to 2005, this nationwide study found an incidence of NRF of 13.4% of total admissions to neonatal intensive care units (NICUs), with a mortality of 32%. Fewer than 30% of infants with respiratory distress syndrome (RDS) received surfactant treatment. Most cases of NRF had birth weights (BW) of 1,000–1,500 g. Approximately 60% of deaths were due to withdrawal of respiratory support because of economic restraints despite initial response to therapy. Extremely low BW or gestational age accounted for less than 2% of all NRF cases, and their survival rate was less than 50%. A prospective clinical epidemiologic study of NRF in 14 NICUs, mainly sub-provincial centers, in Hebei province was undertaken in the study period from 2007 to 2008. NRF made up 16.9% of total NICU admissions, with in-

creased use of surfactant (>50%) and continuous positive airway pressure (>80%) in this study. However, mortality due to RDS, meconium aspiration syndrome and pulmonary infection/sepsis remained higher than 30%, in part affected by socioeconomic factors. With measures to assist hospitalized neonates from low income families in urban areas, as well as the 'new rural cooperative health care program' to subsidize families from rural areas, the quality and affordability of NICU services may be improved in the forthcoming years.

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## Background of the Perinatal-Neonatal Care System

With the dramatic economic growth of the past decade, health care for women and children in China has emerged and developed to higher levels, as reflected by reductions in maternal deaths during childbirth to 48.5 per 100,000 and neonatal tetanus to 9 per 100,000 live births in 2006, and deaths of children under 5 years old to 20 per 1,000 in 2006–2007, along with infant and neonatal deaths to <15 and <10 per 1,000, respectively, with

This study was presented at the 25th International Workshop on Surfactant Replacement, Moscow (Russia), June 10–12, 2010.

regional variations of 3- to 5-fold between the urban and rural areas or between the coastal and remote regions, respectively. In the late 1990s, the leading causes of death in children under 5 years were prematurity and low birth weight (BW) and gestational age (GA), birth asphyxia, pneumonia, congenital heart diseases and asphyxia [1]. At that time, the average nationwide neonatal death rate was above 20 per 1,000 live births. Special neonatal care was mainly confined to major provincial hospitals, where the capacity and quality of neonatal intensive care units (NICUs) were low, qualified specialists were few and experience in respiratory support and intensive care was very limited. This was evidenced by a 40% death rate among term neonates with severe meconium aspiration syndrome (MAS) in children's hospitals in major cities [2]. For premature infants with respiratory distress syndrome (RDS), mortality in the whole country was probably above 50%. Even in Beijing, surfactant treatment for RDS resulted in approximately 65% survival at 28 days of age, with rates of major complications ranging from 7–79% [3]. Nowadays, perinatal-neonatal care in coastal provinces and municipalities, such as Shanghai, Beijing, Tianjin, Guangdong, Zhejiang, Jiangsu and Fujian, is well advanced, whereas in most of the northern and mid-eastern provinces, standards of care are variable. In the northeastern, southwestern and northwestern provinces and autonomous regions, the quality of care is low, especially at county level. In all these regions, provincial and sub-provincial levels of care are mainly supported by local public health care systems and funds, and these regions are characterized by high birth rates and a large patient population with limited service capacity and quality as well as affordability.

Since 2005, the development of perinatal-neonatal medicine at sub-provincial tertiary centers (level III) has been advancing in the most populated provinces and regions in China, mainly in the mid-southern and mid-eastern regions, such as Hebei, Shandong, Henan, Hubei and Hunan provinces, each with populations ranging from 50–90 million. This was followed by provinces with relatively low economic development in the eastern, northern, northeastern and mid-western regions, such as Anhui, Jiangxi, Liaoning, Jilin, Guangxi, Shaanxi, Shanxi and Sichuan provinces. Many sub-provincial regional cities have established or are establishing perinatal-neonatal centers in either maternity and children's hospitals or regional general hospitals, each serving populations of 1–5 million, corresponding to 10,000–60,000 annual deliveries, through a network linking to 30–100 local hospitals (level I–II). Such organization has led to a steadily

growing workload to meet the demand of special care, reduction in perinatal death rates, quality of survival and affordability for hospitalized newborns. In the study period from 2008 to 2009, a jointly funded government health care insurance system, termed the 'new rural cooperative health care program', was introduced [4]. This program covers 60–80% of the total health care expenditure, or up to 4–6 times the amount of the annual disposable income of most rural families [national average from 2008 to 2009 was CNY 4,500–5,000 (USD 650–700) equivalent per person], which allows rural families to obtain essential health care at very low cost. Implementation of this program may directly or indirectly affect the organization of perinatal-neonatal care in both rural and urban regions.

With urbanization and industrialization, more than a hundred million (8% of the total population of 1.3 billion by 2010) migrant workers from rural areas moved to Beijing, Shanghai and major cities in southeastern (coastal) provinces and regions to take part in construction and manufacturing. This contributed to 30–50% of admissions to local neonatal wards, many requiring respiratory support and intensive care. In recent years, measures were taken in these regions to enable migrant families to share essentially local perinatal-neonatal care. These include local funds to subsidize costs of hospital delivery and hospitalized neonatal care. Another solution was to cover the costs with the 'new rural cooperative health care program' [4] from their original regions of residence. In most neonatal special care services, there are hospital funds to meet unpaid hospital costs for those from very low income families.

In a retrospective survey, the Subspecialty Group of Neonatology of the Pediatric Society of the Chinese Medical Association [5] reported the clinical characteristics of 43,289 hospitalized neonates from 86 hospitals in 47 cities in 20 provinces during 12 consecutive months in 2005. In these infants, the male-to-female ratio was 1.73:1 and the prematurity rate was 26.2%, with 16.4% born late preterm (34–36 weeks' gestation). Major reasons for hospitalization were asphyxia, pneumonia and hypoxic-ischemic encephalopathy (HIE). Among those with respiratory disorders, 46.2% had pneumonia, 17.1% asphyxia, 3.6% MAS, 3.0% apnea and only 2.5% RDS. HIE was found in 18.1% of the neonates, with mild, moderate and severe types accounting for 52, 40 and 8%, respectively. Overall, 63.9% of neonates recovered, 27.3% improved but did not recover, 7.6% requested own discharge (or withdrawal) and 1.2% were clinical deaths. Most deaths occurred in the first 3 days, with only 26.9% of deaths oc-

curing after that period. The major causes of neonatal death were respiratory (66.1%), cardiac (12.2%) and renal (4.6%) failure. Of the nonsurvivors, 49.2% had asphyxia, in contrast to 15.9% of the survivors. Maternal pregnancy-induced hypertension was significantly associated with neonatal asphyxia, small for GA, wet lung, RDS, pulmonary hemorrhage, MAS and HIE. Kang et al. [6], from Zhengzhou, Henan province, reported that the major causes of death in NICUs were RDS, sepsis and sclerema in preterm infants, whereas sepsis, asphyxia and pneumonia were commonest in term infants.

### **A Nationwide Neonatal Network for Respiratory Diseases**

Between 2000 and 2003, most of the provincial perinatal-neonatal centers established NICUs with mechanical ventilation as a major means of life support. Surfactant treatment was also introduced for premature infants with RDS. Since then, we have conducted collaborative clinical investigations in three phases through a nationwide collaboration as a neonatal network for severe respiratory diseases, mainly targeted to neonatal hypoxemic respiratory failure (NRF) [7]. We speculated that, in resource-limited regions, it would be possible to improve the standard of NICUs by improving knowledge of clinical epidemiology and respiratory support. In the first phase, a multicenter randomized trial of surfactant (Curosurf®) for treatment of MAS was undertaken in selected provincial NICUs [8]. The results revealed some efficacy of surfactant therapy and relatively low mortality (<10%) for MAS. This study enabled specialists from major city NICUs to cooperate in solving critical care problems by adopting international criteria and methodology. In the second phase, from 2004 to 2005, a prospective survey was undertaken in 23 NICUs at provincial level, 15 from southeastern (coastal) and 8 from mid-western areas [9]. This study showed that the incidence and mortality of NRF were 13.4% (of total admissions of critically ill neonates) and 32%, respectively. Fewer than 30% of preterm babies with RDS received surfactant. The majority of problems in preterm neonates occurred in those with a BW of 1,000–1,500 g or a GA of 28–32 weeks. About 60% of deaths were due to withdrawal from aggressive respiratory support. Neonates with an extremely low BW or GA accounted for less than 2% of this special NICU-based population. The mortality and cost of NRF differed significantly between NICUs in mid-western and southeastern regions, mainly associated with the or-

ganization of perinatal care, NICU facility and staff competence, health insurance coverage and socioeconomic and cultural complexity [9–11]. In the third phase, during 2007–2010, we conducted several multicenter studies, either as a province-wide network or nationwide, employing interventional protocols for improvement of respiratory support and registration of NRF [12, 13].

### **Neonatal Network in Hebei NICUs**

In 2007, we conducted a clinical epidemiologic study of NRF in 14 provincial and sub-provincial NICUs in Hebei province [12] using the same study protocol [9]. This province was in the mid-range of economic development, representative of ten provinces in northern and mid-eastern China. Prospectively collected data on neonatal NRF reflected approximately 75% of level III NICU capacity in the whole province, before the ‘new rural cooperative health care program’ was implemented (2008–2010). During the study period, neonatal in-hospital costs were almost fully borne by the parents.

For 11,100 NICU admissions during 12 consecutive months, the incidence of NRF was 16.9% ( $n = 1,875$ ), with more than 60% having a BW <2,500 g and 2% <1,000 g. More than 40% of NRF cases were due to RDS, and 58.3% received surfactant therapy. In those requiring respiratory support, continuous positive airway pressure (CPAP) was used more than conventional ventilation. The mortality due to NRF (31.4%) was similar to that found in the nationwide study in the period from 2004 to 2005, and the mortality due to NRF with RDS, MAS and pneumonia was 30% or higher (table 1). Of nonsurvivors, 1 in 4 was reported as a ‘failure of aggressive rescue’, which means 3 in 4 deaths followed from the parental decision to withdraw care due to financial problems and/or concerns about poor prognosis. The mortality rate of NRF varied across the regions by up to 7-fold. The male-to-female ratio of NRF was 2.6:1, and more male infants received surfactant than females [12]. Surfactant use in RDS in both studies achieved a nearly 15% net increment in survival (table 1), demonstrating its cost-effectiveness in these NICUs in the two study periods. The capacity and utilization of major respiratory therapies in the Hebei study tended to be the same as, or even better than, in the nationwide one, with similar outcome.

Moreover, analysis of the in-hospital data from the Hebei study showed the incidence of NRF to be 14.8 per 1,000 live births (557/37,635), for which RDS, MAS and pneumonia/sepsis were diagnosed in 0.9, 0.024 and

**Table 1.** Comparison of NRF data from nationwide and Hebei province network studies

Variables	Ref. No.:	Nationwide [9–11]	Hebei province [12]
Study period		2004–2005	2007–2008
Provinces, n		14	1
NICUs, n		23	14
NICU admissions, n		13,070	11,100
NRF, n		1,722	1,875
Incidence of NRF, %		13.2	16.9
GA, weeks		35.2 ± 4	35.0 ± 4
BW, g		2,316 ± 831	2,267 ± 804
Male, %		75.5	72.3
Survival, %		67.9	68.6
RDS, n		602 (35)	881 (47)
Survival, %		66.2	67.3
Surfactant use, %		36	58.3
Survival <sup>1</sup> , %		78.8	73.7
No surfactant use, %		64	41.7
Survival <sup>1</sup> , %		63.5	58.6
MAS, n		163 (9.5)	146 (7.8)
Survival, %		60.7	66.9
Pneumonia/sepsis, n		316 (18.4)	469 (25.1)
Survival, %		74	68

Figures in parentheses represent percentages of NRF cases.

<sup>1</sup> Figures provided by personal communication.

0.04%, respectively. This suggests that delivery at regional perinatal centers should have a remarkable impact on mortality due to NRF, occurrence of MAS and pulmonary infection. Assuming that the in-hospital live births in these participating hospitals accounted for 4.7% of the whole provincial deliveries (estimated at 800,000 a year) and that NRF cases from those deliveries accounted for 10% of all NRF cases, it would derive 10 times the total NRF cases (estimated at 5,570 a year), which should be equivalent to 3 times the total number of NRF cases in this study population. Therefore, the total number of NRF cases eligible for respiratory support in NICUs should be tripled (5,500–5,600 cases a year). Assuming an annual neonatal mortality of 7 per 1,000, or 5,600, in Hebei, the estimated death toll from NRF (583 × 3) may account for more than 30% of the total neonatal deaths in Hebei in that period. Should 30% of these fatal cases of NRF be treated successfully, i.e. mortality of NRF be reduced to 20%, this may lead to a reduction of neonatal mortality in this province of approximately 10%.

## Related Studies in Guangdong

In Shenzhen, Guangdong province, a neonatal network was established in 2006 aimed at raising the standard of respiratory support and intensive care and reducing NRF-related mortality. More than 18 neonatal units participated in the 12-month study, covering a total population of 12 million and 90,000 annual deliveries. Approximately 3% of admissions for neonatal special care suffered from NRF, of which about 30% were preterm. Mortality due to NRF was below 30%, with RDS and MAS comprising 50 and 9%, respectively. With an ‘aggressive rescue effort’, the survival rate of RDS and MAS in this survey was close to 80 and 70%, respectively, reflecting the quality of respiratory support and intensive care. In this region, prophylactic surfactant was given to 13% of preterm infants below 30 weeks’ gestation, and rescue surfactant was given to 75% of patients with RDS, the highest level in China. Han et al. [14] from the Guangdong Provincial Maternity Hospital reported that, between 2001 and 2006, the use of surfactant (Curosurf) significantly reduced the occurrence of RDS by 43–58% in those neonates less than 30 weeks of age and 30–31 weeks compared to nontreated controls. The study also revealed better outcome in the treatment group as regards 7-day mortality, length of ventilation, length of oxygen therapy and major complications. However, length of hospital stay was not significantly different.

## Estimation and Management of Premature Delivery

Previously, another nationwide retrospective survey revealed a premature birth rate of about 8% in 80 urban hospitals [15]. Our recent study in an agricultural county (in Hebei province) with a population of more than 400,000 revealed a rate of 4.5% in a 12-month period [16]. Our ongoing study in Huai’an (in Jiangsu province), with a population of 5 million, also revealed a premature delivery rate of 4% (unpublished data), suggesting a nationwide average rate of about 5–6% of all the deliveries by weighted sum in rural and urban populations, corresponding to 0.9–1 million premature births. Our data on NRF in the Hebei NICU network was mainly in very low BW infants (<1,500 g) and term and near-term neonates. It is different from the data in North America and European countries, where in the late 1980s–1990s, care for very low BW and extremely low BW infants accounted for the major workload in NICUs [17–19], and since then early postnatal intervention for NRF and prevention of

chronic lung disease (bronchopulmonary dysplasia) have been the major objectives. We anticipate that this will occur in the next decade in the Chinese urban neonatal population when perinatal-neonatal care will have fully developed and health insurance will cover much more than at present.

Cesarean section is now the major mode of delivery in many urban obstetric clinics, accounting for 50–70% of births in some areas or hospitals. The high cesarean section rate in urban hospitals results in substantial numbers of late preterm and term newborns with RDS, as reported in another retrospective survey by Chen et al. [20] from Quanzhou, Fujian province. In 196 out of 508 late preterm infants, 43 (26.5%) developed RDS, 59 (30.1%) transient tachypnea, 6 (3.1%) MAS and 27 (13.7%) pneumonia, whereas in term infants these incidences were 6.6, 14.5, 15.2 and 38.1%, respectively. In late preterm infants with RDS, CPAP, conventional ventilation and surfactant were used in 26.5, 18.4 and 15.3% compared to 4.9, 10.9, and 3.6%, respectively, in term infants. The overall survival rate in those infants with and without NRF was 91 and 95%, respectively, along with incomplete (withdrawal from) treatment or death in 9 and 5%, respectively. The cesarean section rate in an agricultural county hospital was around 30% in the period between 2007 and 2008 [16], and RDS in late preterm and term infants was not so prominent. In a recent controlled multicenter study of inhaled nitric oxide therapy, mortality due to NRF was reduced to 11–15% in 200 term and near-term infants whose initial oxygenation index was  $\geq 15$  and 70% of whom were delivered by cesarean section [13].

### Estimation of NICU Resources and Function

The perinatal-neonatal care system in the north- and southwestern provinces/autonomous regions of China, such as Shaanxi, Ningxia, Gansu, Xinjiang, Qinghai, Tibet, Chongqing, Sichuan, Yunnan, Guizhou and Guangxi, regions which have lower gross domestic products, is under-developed with regard to both facilities and health care cost coverage. At the Hunan Provincial Children's Hospital, there were 33 physicians and 100 nurses for 200 beds in the neonatal department with 3 wards. Total admissions in 2009 were 5,778, and about 25% required intensive care. There were 60 beds in the NICU, half for intensive and half for intermediate care, with 33 nurses and 16 physicians. In that province, this hospital serves as a main pediatric and neonatal emergency center with an extensive transport team. Nearly 50% of admissions

were transferred from the regional hospital network through land transportation. For infants with a BW  $>1,000$  or  $<1,000$  g, the survival rate was 80 and 50%, respectively. Respiratory support with mechanical ventilation was given to 650 infants, and the survival rate was 70% in those with BW  $>1,000$  g, but in those with BW  $<1,000$  g, survival was below 30%. CPAP-treated infants had a 90% survival rate. In those treated with conventional and high-frequency ventilation, 70% recovered or were discharged, which was similar to the results of the nationwide and Hebei network studies [9, 12]. This province is located in mid-southern China, with a population of 69 million and 780,000 births in 2009. This neonatal department ranks as one of the largest in capacity, representative of a provincial children's hospital-based NICU with relatively well-equipped facilities for respiratory support, and may be classified as IIIc equivalent according to North American standards [21]. In the whole province, there are about 40 level II and III hospitals with neonatal wards and 1,200 beds. NICUs are mainly located in the 22 hospitals in major provincial and sub-provincial cities, rarely in county hospitals.

A similar situation was encountered in the maternity hospitals of the northwestern provinces. In the Shaanxi Provincial Maternity Hospital, there were 11,000–12,000 births annually between 2008 and 2009, many of which were high-risk. The hospital received 1,800 cases into neonatal special care, with half transferred through the provincial network from 50 level I–II hospitals within a radius of 100 km. The NICU was equipped with 4 conventional and 9 CPAP (Infant Flow System<sup>®</sup>) ventilators, a bedside blood gas analyzer, X-ray and ultrasound apparatus. There were 50 beds, 40 nurses and 18 physicians (7 senior, 5 attending and 6 residents). This hospital, along with others in major cities of the northwestern provinces, constitutes the mainstay for regional perinatal-neonatal care. However, the standard of neonatal special care at sub-provincial tertiary centers is low. We speculate that, to ensure good quality and adequate neonatal special care in resource-limited regions, a target of 1 NICU bed for every 2,000 live births should at least be achieved. In other words, for every 100,000 live births, provision of 50 NICU beds (or 5 NICUs, each with 10 beds on average), mainly IIIa–IIIb [21], should be considered in sub-provincial regions, along with an appropriate standard of care commensurate with the best available domestic conditions.

In summary, a nationwide NICU network for improvement of neonatal respiratory care is feasible and would be advantageous. The clinical investigations in

this patient population are relatively highly cost-effective based on daily service practice and relevant to the clinical situation where parents often have financial difficulties in maintaining 'rescue therapy'. The overall outcomes of NRF in both the nationwide and Hebei province studies show a clear trend of improvement in sub-provincial regional centers for neonatal special care. With further progress, this type of organization and experience should constitute a very important part of the neonatal community, linking developed and underdeveloped regions in China.

## Disclosure Statement

This work was supported by grants from the '211 Project (Phase III)', Ministry of Education, China-Canada Joint Health Research Program (National Natural Science Foundation of China-Canadian Institutes of Health Research, No. 30611120518), and the Program for Outstanding Medical Science Leader (No. LJ06038), Shanghai Municipal Department of Health.

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