Neonatal–perinatal medicine in a transitional period in China

Bo Sun,1,2 Xiaomei Shao,1,2 Yun Cao,1,2 Shiwen Xia,3 Hongni Yue4

ABSTRACT
With an annual birth rate of 12%, or 16 millions, of all population (1.34 billions), and an implementation of universal healthcare policy for all rural residents in recent years, China is undergoing a dramatic and profound transition in perinatal and neonatal healthcare as a part of the global campaign for reduction in mortality of children under 5 years old. This review describes recent development in neonatal–perinatal medicine, with special emphasis on general neonatal–perinatal care, respiratory and intensive care, neurological and infectious diseases, for a comprehensive view of the trend and challenge in relation with problems and solutions of the field.

GENERAL STATUS OF NEONATAL–PERINATAL CARE
China has the largest birth population, hence it is the burden and challenge in maternal, fetal and neonatal healthcare in the global perspective.1 Efforts have been made in recent years by perinatal–neonatal and paediatric communities, leading to considerable reduction in maternal, neonatal and infant mortality and morbidity.2 3 The emphasis has now been put on infrastructure improvement for better prenatal care and delivery, clinical management and outcome in high-risk and preterm newborn infants,4 5 and genetically associated birth defects and disorders with high social and economic burdens. However, problems remain as inequity of healthcare resources and diversity in regional development, as approximately 50% are living in rural, mountainous and remote regions, by contrast with urban residents whose perinatal care is more effectively provided for. In 2010, the total population in China reached 1 340 000 000,6 and a nationwide healthcare insurance policy, the ‘New Rural Cooperative Medical Scheme’, was launched to benefit almost all the rural residents by covering the cost of medical care during hospitalisation up to 4–6 times the equivalent of the regional annual family income, with 80% subsidised by national and provincial public healthcare finance, whereas, each family paid annual premium fees at 100–300 Chinese Yuan (CNY, 6.3=US$1) per head according to local economics.

In the first decade of this century, there has been achievement in reduction of mortality of children under 5 years old, with >50% being neonates and infants.1–5 This was attributed greatly by hospital delivery and control of infectious diseases. Neonatal special care nursery (SCN, including intensive and intermediate care) in China was initially established in the early 1990s. It took more than 10 years for modern concepts for perinatal–neonatal care through regional perinatal network and SCNs to be widely adopted and implemented by provincial and subprovincial (prefectural) tertiary hospitals, through which each regional perinatal–neonatal network system serves populations varying at 2–6 millions.7 8 This has also been followed since 2010 by the health insurance coverage in most of the neonatal diseases for up to 50% of the costs at county hospitals, which significantly accelerated community infrastructure development. Current annual total births are estimated at around 16 millions, corresponding to 12% birth rate in the country’s population, with neonatal mortality varying at 3–5 times from newly industrialised to remote agricultural regions.5

In our recent survey,9 based on a complete birth population of more than 61 000 birth registries (total birth rate 11.3‰) in Huai’an, Jiangsu province in 2010, we found a perinatal mortality of 7.7‰, a neonatal mortality of 4.4‰ in all live births, a preterm rate of 3.72‰ with 7.61‰ mortality, and a low birth weight (LBW) of 2.8‰ with 8.83‰ mortality. Table 1 shows birth population and estimated vital statistics in China in 2010. Domestically, definition of the perinatal period is from 28 weeks of gestational age (GA) to 7 days of postnatal life, though very few neonates born before 28 weeks of GA may be included in the local birth registry for vital statistics. In practice, before 28 weeks of GA, some live births that died immediately after birth would be later reported as abortions, and those of fetal deaths before 28 weeks GA be treated as miscarriages. Therapeutic abortion is not counted as fetal deaths nor as stillbirths, hence is not included in the total birth registry. As the

Table 1 Basic information of birth population and estimated vital statistics in China in 2010

<table>
<thead>
<tr>
<th>Total population*</th>
<th>1 340 000 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total annual birth rate†, n (‰)</td>
<td>16 000 000 (11.8)</td>
</tr>
<tr>
<td>Preterm birth rate, n (‰)</td>
<td>640 000–800 000 (4–5)</td>
</tr>
<tr>
<td>Preterm death rate, n (‰)</td>
<td>58 000–80 000 (9–10)</td>
</tr>
<tr>
<td>Low birth weight, n (‰)</td>
<td>480 000–560 000 (30–35)</td>
</tr>
<tr>
<td>Very low birth weight, n (‰)</td>
<td>24 000–42 000 (15–25)</td>
</tr>
<tr>
<td>Extremely low birth weight, n (‰)</td>
<td>16 000–20 000 (1–1.3)</td>
</tr>
<tr>
<td>Fetal death and stillbirth, n (‰)</td>
<td>64 000–80 000 (4–5)</td>
</tr>
<tr>
<td>Perinatal death rate, n (‰)</td>
<td>128 000–144 000 (8–9)</td>
</tr>
<tr>
<td>Neonatal death rate†, n (‰)</td>
<td>80 000–96 000 (5–6)</td>
</tr>
</tbody>
</table>

*Based on the 6th national census in 2010.5
†Based on the 2010 Huai’an complete birth population data file corrected by total births.9
§Based on the nationwide maternal-infant information surveillance data file.2
§Corrected by total live births.9

'one child family' policy has been in effect for more than three decades, domestic rules and practice applied for perinatal and neonatal care may have ethical and legal differences compared with that of the industrialised countries and other developing countries in Asia.

The domestic system classifies the provincial and subprovincial levels III and II hospital into four categories (A and B for each level) by national hospital administration, but there is no specific standard yet to classify and define SCN settings, staff, function, volume and quality. Most SCNs at provincial city children’s and maternity hospitals are newly designed and well equipped for service quality and capacity upgraded to match dynamic growing demand. Table 2 outlines hospital levels, types and facilities for child delivery and SCN settings. So far, most of the newborns (90–99%) are delivered in regional levels I–III hospitals, with majority in levels I (>50%) and II (>30%) as normal or moderately abnormal, and approximately 10–20% in level III hospitals with high proportion of pregnant complications or delivery-associated adverse events. Newborns at high risk of death or complication are usually attended by paediatricians or neonatologists at delivery, and hospitalised in a SCN. A nationwide survey of 109 hospital SCNs (mostly levels III and II in A and B classes) in 200910 revealed 36 beds per unit on average (maximum 300), and physician-to-patient or nurse-to-patient ratio at 1:3.24 or 1:1.43, respectively. A province-wide SCN network study11 reveals that a nurse-to-bed ratio at >:1 and <:1 was associated with a doubled case fatality rate in the neonatal patients with respiratory failure. Thus, quality of care in most of SCNs is less than optimal, as survival rates of very or extremely LBW (VLBW, ELBW) infants is below 85% and 50%, respectively, though average hospitalised neonatal mortality was extremely LBW (VLBW, ELBW) infants is below 85% and 50%, respectively, though average hospitalised neonatal mortality was 0.76 to 0.34 per 1000 deliveries. From 2010, NRP has been promoted in all provinces, mainly targeted at birth attendants and neonatal care providers at county and subcounty (levels II and I) hospitals for dissemination of standard of perinatal care.

Domestic management of asphyxia-related brain injury or hypoxic-ischemic encephalopathy (HIE) is based on perinatal history and clinical diagnosis, biochemistry and sonographic assessment, and MRI for evidence of severe intracranial injury, haemorrhage and chronic impairment. Many provincial and subprovincial maternity and children’s hospitals established a neonatal follow-up programme, and rehabilitation clinics, especially for those recovering from initial brain injury by means of physical and mental development intervention and assessment, including individualised developmental care, and integrated traditional Chinese medicines, such as acupuncture and massage. Oxygen use in preterm infants is controlled to prevent iatrogenic adverse events,16 such as early diagnosis and intervention for retinopathy of prematurity, available mainly at provincial centres.

Among these efforts, selective hypothermia, or head cooling, was reported to be effective in moderate HIE, as the follow-up results at 18 months revealed significant reduction in

### Table 2 Hospital types and facilities for child delivery and neonatal special care

<table>
<thead>
<tr>
<th>Hospital levels</th>
<th>Location</th>
<th>Delivery volume %</th>
<th>Neonatal ward</th>
<th>High-risk pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Township</td>
<td>50–60</td>
<td>No</td>
<td>Variable</td>
</tr>
<tr>
<td>Level II</td>
<td>County or city district</td>
<td>20–30</td>
<td>Yes/No</td>
<td>Intermediate to high</td>
</tr>
<tr>
<td>Level III</td>
<td>Prefectural city</td>
<td>10–20 or variable</td>
<td>Yes</td>
<td>Centralised with high proportion</td>
</tr>
<tr>
<td></td>
<td>Provincial city</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metropolis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital types</th>
<th>Level</th>
<th>Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetrics and neonatology in general hospital:</td>
<td>II–III</td>
<td>Delivery/neonatal care</td>
</tr>
<tr>
<td>Maternity (women and children’s) hospital:</td>
<td>II–III</td>
<td>Delivery/neonatal care, neonatal special care</td>
</tr>
<tr>
<td>Children’s hospital:</td>
<td>III</td>
<td>Neonatal special care, neonatal surgery and cardiac surgery</td>
</tr>
</tbody>
</table>

Facilities and function of neonatal special care service (level III): Ventilators (continuous positive airway pressure devices, conventional and high-frequency ventilators); automated blood gas analyser; incubators, resuscitation bed, life-sign monitors, bedside x-ray apparatus, B-mode ultrasound, transport team with incubator and portable ventilator and life-sign monitor; spaces for staff, therapy, isolation, logistic and storage; visiting clinical fellowship and continuing education programme.

PREVENTION OF BIRTH ASPHYXIA AND BRAIN INJURY

Neonatal asphyxia has long been one of the leading causes of death in perinatal and neonatal mortality in the past two decades.2 3 In the 1960s, Dr Shuzhong Shi, from Shanghai First Maternity Hospital and one of the pioneer neonatologists, first initiated resuscitation at the delivery room, and his efforts persisted for more than three decades and is widely recognised and appreciated. In 2004, Neonatal Resuscitation Program (NRP) initiated by both American Academy of Pediatrics and American Heart Association was introduced into the Chinese perinatal community. A Chinese version of NRP was introduced into 20 provinces through the Chinese Perinatal Society.14 In 322 hospitals enrolled under NRP,15 the incidence of neonatal asphyxia in 2003–2008 was reduced from 6.3% to 2.9%, its death rate from 0.76 to 0.34 per 1000 deliveries. From 2010, NRP has been promoted in all provinces, mainly targeted at birth attendants and neonatal care providers at county and subcounty (levels II and I) hospitals for dissemination of standard of perinatal care.
death and severe disabilities between the cooling and control groups (31/100 vs 46/94, p<0.01). This therapy is currently used by more than 30 SCNs. Other efforts also showed variable effects such as systemic erythropoietin trial in moderate HIE that resulted in significant reduction of neurodevelopmental disability at 18 months between the treated and controls (25% vs 44%, p=0.017). More studies were conducted in the early diagnosis and management of HIE-associated brain injury and pathogenesis, ranging from amplitude-integrated electroencephalography, positron emission tomography, to hypoglycaemia, or cerebral infarction. Since the early 1990s, hyperbaric oxygen therapy was also used in some regions for term infants with moderate to severe HIE after asphyxia by short (30–60 min) pure oxygen exposure in a 1.5 atmospheric pressurised chamber, once daily for 1–2 weeks postnatally, with variable effects reported only in domestic literature in the 1990s. In general, incidences of birth asphyxia and severe HIE are declining with steady improvement of perinatal and neonatal care in regions with functioning systems. In a multicentre study from 33 tertiary hospitals in 2009, 348 term newborns with hyperbilirubinemia were associated with bilirubin encephalopathy, whose underlying disorders were bacterial infection (52.6%), blood type incompatibility in ABO (29.9%) or Rh (6%) haemolysis, asphyxia (10.1%) and glucose-6-phosphatase deficiency (G-6-PD), and more than 16% died. Incidence of G-6-PD is more commonly seen in southern China provinces, and especially among the ethnic minorities.

### ADVANCED NETWORK FOR NEONATAL RESPIRATORY AND INTENSIVE CARE

Since 2001, we have established a collaborative study group among different regions of development for neonatal respiratory diseases through a special project sponsored by the China Medical Board of New York and domestic funds, focusing on reduction of death in neonatal hypoxic respiratory failure (NRF). The efforts have paid off with concrete progression as outlined in table 3, where a clear trend of enlarged NICU service capacity, more admission of NRF, increased use of assisted ventilation and surfactant, lowered overall death rate can be found. However, the death rate in VLBW patients remained high (>50%), and 50% survival rate may be found in surfactant-treated respiratory distress syndrome (RDS) with GA at 27–28 weeks, which underscores the efficiency of respiratory and intensive care in the transitional period. In these studies, clinical burden of NRF was 10 000–15 000 Yuan for term and later preterm, 20 000–30 000 Yuan for VLBW infants, on average, corresponding to 1–2 years of urban resident income. There is also 8.5% net increase in survival rate (63.5% vs 72%), between the two nationwide studies, in those of RDS as VLBW not treated by surfactant, suggesting steady improvement of overall respiratory and intensive care over time, the evidence is particularly encouraging for paediatric services starting SCNs in underdeveloped regions. Inhaled nitric oxide for treatment of NRF in term neonates with persistent pulmonary hypertension is confined to investigational use, whereas, extracorporeal life support is just established in a few SCNs. Parent-requested termination of intensive care for extremely immature infants (<28 weeks GA) are seen more in regions under optimal SCN service. In the non-survivors of NRF, withdrawal of care by parents accounted for 2/3 to 3/4, with VLBW, female and low family income being at higher prevalence before the era of ‘New Rural Cooperative Medical Scheme’, implying the low in-hospital neonatal death rate may be biased by reporting criteria.

In recent years, more and more bronchopulmonary dysplasia (BPD) is being reported from SCNs. In the western countries, BPD is mainly contributed by ELBW infants, whereas in China, BPD is seen more in VLBW, as ELBW constitutes only 1% of total live births, with >50% mortality. A retrospective survey of BPD in 10 hospitals in 2006–2008 reported an incidence of 1.26% of SCN-admitted premature infants (<37 weeks GA), with median GA of 30 weeks and BW 1300 g. We recently found 1.8% with established BPD in 11 000 preterm infants (<35 weeks) admitted to SCNs, and overall survivals are seen more in those with BW 1000–1500 g (Sun B, unpublished data). In the preterm infants (<35 weeks) developing RDS, only 1/4 received antenatal corticosteroids (11, 25; table 3). Postnatal corticosteroid use in preterm infants is restricted to evolving and established BPD with intractable lung inflammation damage.

### NEONATAL INFECTION AND SEPSIS

There are domestic guidelines and recommendations for neonatal sepsis. In a nationwide, population sampling-based survey, Liang et al reported that pulmonary infection...
(pneumonia) had the highest case mortality rate (80%), and was prominent even in the remote areas. The relative risk of neonatal infection-related death is 2–6 times higher in the inland and remote regions than in the coastal regions (1, 2.6, 0.3 per 1000 live births, respectively). In 2003–2008, neonatal mortality was reduced from 10 to 6.4 per 1000 live births, neonatal infection-associated mortality reduced from 1.4 to 0.9 per 1000 live births, however, constitution of the neonatal infection-associated mortality almost remained unchanged at 14% of the total neonatal deaths. We anticipate this trend to persist and lead to a neonatal mortality close to 5 per 1000 live births, with neonatal infection-associated mortality around 10% of the total neonatal deaths in a nationwide perspective. In another study involving 4 SCNs in China, Malaysia, Hong Kong (Macau) and Thailand in 2006–2009, overall incidence of neonatal sepsis was 26 per 1000 admissions, whereas, that of early (EOS) and later onset sepsis (LOS) was 0.6 and 5 per 1000 live births, or 5 or 21 per 1000 admissions, with 7% and 16% case-fatality rates, respectively. The incidence of group B streptococcus sepsis was low, but remained the most common single pathogen of EOS. Klebsiella tended to be the most common Gram-negative pathogen in LOS, along with high levels of antibiotic resistance to all Gram-negative pathogens, especially to the third-generation cephalosporins and gentamicin. These are corroborated by our (Cao Y, unpublished) data in 2003–2012 in which major pathogens in 162 EOS consist of coagulase-negative staphylococcus (CONS, 35.8%), group B streptococcus (11.7%) and Escherichia coli (11.1%) by contrast with 287 nosocomial LOS with Gram-negative bacilli (48.1%), Gram-positive bacteria (39.0%), and fungi (12.9%), with CONS (22.6%), Klebsiella pneumoniae (18.5%) and E. coli (9.4%) being the most common pathogens.

Efforts were made for the identification of regional pathogen spectra and also the biomarkers that may predict sepsis in neonatal settings. As outbreak of severe sepsis is one of the most compelling challenges in SCNs of different regions, standardised neonatal ward management to prevent nosocomial infections is now mandatory and becoming a routine measure which requires well-controlled sterilisation facilities, hand hygiene, isolation space, restricted use of antibiotics, among other things, implemented as part of the hospital quality assurance. Umbilical vascular-accessed and peripheral-inserted central catheterisation are being more and more used for VLBW infants with restricted length of indwelling to prevent nosocomial infection in SCNs. Other pathogen-related infections are also encountered in daily service, ranging from hepatitis B virus and HIV to mycoplasma, chlamydia and syphilis. Rooming-in in SCNs is becoming more acceptable for those with modest to moderate illness, especially during recovery. Fortified formula milk for immature infants is widely used in most SCNs, whereas, very few units use human milk to feed preterm infants. Application of human milk fortification is recently considered in a few SCN, for investigational purposes. There is no human milk bank service, the reasons being a lack of initiation and finance, maternal source, sterilisation and storage, and so on. Most SCNs do not have rooming-in for mothers of preterm patients requiring assisted ventilation and intensive care, therefore, the infant’s own mother’s breast milk supply for preterm patients staying at the SCN is a complex issue.

In summary, the information we present here reflects several aspects of recent advances and transition of neonatal–perinatal care in China. The Chinese perinatal–neonatal community should contribute much more to the world maternal and infant healthcare with its own characteristic development and experience, and be an active part of international collaboration in areas, such as quality assurance of SCNs, network-based registry of rare diseases, new diagnostic and intervention methodologies and therapies, infection control and nutrition, relevant at home and abroad to many developing and emerging countries and regions.

**Contributors** BS, drafted sections of the general status of neonatal–perinatal care and advanced network for neonatal respiratory and intensive care, did all communication with all coauthors and completed the final version. XS, drafted the section of the protection of birth asphyxia and brain injury, reviewed literature and revised the manuscript. YC, drafted the section of the neonatal infection and sepsis, provided unpublished data, reviewed literature and revised the manuscript. SX, drafted the sections of the protection of birth asphyxia and brain injury and the neonatal infection and sepsis and revised the manuscript. HY, drafted the section of the general status of neonatal–perinatal care, provided unpublished data and revised the manuscript.

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