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Non-invasive respiratory support for infants in low- and middle-income countries

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SUMMARY

The overwhelming majority of neonatal deaths worldwide occur in low- and middle-income countries. Most of these deaths are attributable to respiratory illnesses and complications of preterm birth. The available data suggest that non-invasive continuous positive airway pressure (CPAP) is a safe and cost-effective therapy to reduce neonatal morbidity and mortality in these settings. Bubble CPAP compared to mechanical ventilator-generated CPAP reduces the need for subsequent invasive ventilation in newborn infants. There are limited data on the safety and efficacy of high-flow nasal cannulae in low- and middle-income countries, requiring further study prior to widespread implementation.

1. Introduction

Advances in newborn care over the past 75 years led to substantial reductions in neonatal mortality in high-income countries. In the USA, the neonatal mortality rate (NMR, defined as the number of deaths that occur within the first 28 days of life) decreased from 28.8 deaths per 1000 live births in 1940 to 4.0 in 2013, a decline of ~3% per year [1,2]. Other high-income nations recorded more impressive gains during that time [2]. Unfortunately there is a stark disparity in neonatal outcomes between high-income and low- and middle-income countries. Among the >2.6 million neonatal deaths that occur worldwide each year, 98% occur in low- and middle-income nations [3]. A recent estimate from the United Nations and World Health Organization (WHO) suggests that the overall NMR in low- and middle-income countries is 19 deaths per 1000 live births. Rates in sub-Saharan Africa are as high as 29 deaths per 1000 live births, and in southern Asia 32 deaths per 1000 live births [3]. Many countries in these regions report even higher NMR, and within individual countries NMRs may vary two- to three-fold across different geographical regions and socio-economic groups [3–5]. In 2015, world leaders agreed on a series of Sustainable Development Goals and called for an end to "preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births" by 2030 [6].

Complications of preterm birth and pneumonia are the leading causes of under-5 mortality worldwide and together account for >1.8 million deaths per year (Table 1) [7]. Neonatal respiratory distress syndrome (RDS) and hypoxic respiratory failure secondary to infection and birth asphyxia are additional preventable or treatable causes of neonatal and early childhood death in low- and middle-income countries [8,9]. Although invasive mechanical ventilation (MV) is one effective therapy for the treatment of these conditions, it carries a high cost and significant practical (e.g. reliable electricity) and technical skill requirements that make it unsuitable for many resource-poor settings [10]. Even when administered in resource-rich environments, outcomes may be suboptimal; MV is associated with multiple short- and long-term sequelae that now lead many clinicians to strive to avoid this therapy [11–13]. By contrast, non-invasive continuous positive airway pressure (CPAP) is a relatively low-cost therapy shown to improve neonatal and infant outcomes across a wide range of health care settings [14–19]. Among other health interventions, wider dissemination of CPAP in low- and middle-income countries is highlighted as one effective means for reducing infant morbidity and mortality [20–22].

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Table 1
Estimated number of deaths worldwide by cause in 2013.[a]

Cause	Estimated number in millions (95% CI)
Neonates aged 0–27 days	
Preterm birth complications	0.965 (0.615–1.537)
Intrapartum complications	0.662 (0.421–1.054)
Sepsis	0.421 (0.269–0.688)
Congenital abnormalities	0.276 (0.175–0.438)
Pneumonia	0.136 (0.084–0.219)
Tetanus	0.049 (0.032–0.079)
Diarrhea	0.020 (0.012–0.033)
Children aged 1–59 months	
Pneumonia	0.800 (0.681–1.134)
Diarrhea	0.558 (0.429–0.731)
Malaria	0.456 (0.351–0.546)
Injury	0.324 (0.258–0.391)
Meningitis	0.151 (0.125–0.185)
AIDS	0.103 (0.076–0.142)
Measles	0.102 (0.074–0.166)
Pertussis	0.060 (0.043–0.094)

AIDS, acquired immune deficiency syndrome.
[a] Adapted from Liu et al. [7].

In this article, we summarize the epidemiology of neonatal and infant respiratory diseases in low- and middle-income countries, then discuss the current evidence in support of the use of non-invasive respiratory therapies, and finally we highlight important technical aspects of CPAP use and the barriers that limit widespread implementation in low- and middle-income countries.

2. Terminology

Variable terms such as “developing,” “low-income,” and “non-industrialized” are used in the literature on health care in low-resource countries. In this article, we define countries using the World Bank classification of low-income, middle-income, and high-income. For the fiscal year of 2016, low-income countries are defined as those with a per-capita gross national income (GNI) of US$1,045 or less in 2014. Middle-income countries are those with per-capita GNI of US$1,046 to US$12,735, and high-income as those with a per-capita GNI of US$12,736 or more [23]. Over time, countries rise and fall in this classification as economies fluctuate and the GNI cutpoints change. Most global health statistics combine data for low- and middle-income countries. When possible we classify individual countries as low- or middle-income based on the year of data collection.

3. Epidemiology of neonatal and infant respiratory diseases in low- and middle-income countries

Accurate measurement of the incidence of neonatal and infant respiratory diseases in low- and middle-income countries is hindered by a number of factors. Most of these countries do not maintain well-functioning vital statistic registries, thus the majority of childhood deaths worldwide are not documented [3,24]. Household surveys such as the UNICEF-supported Multiple Indicator Cluster Survey are often the best source of data on infant disease and mortality, but sampling errors in these can be substantial [3]. Even when higher-level medical attention is provided and adequate documentation is available, the clinical and diagnostic evaluation may be inadequate to determine the etiology of the respiratory condition [24,25]. Finally, the incidence of respiratory illnesses may vary widely within individual countries depending on factors such as location (e.g. rural vs urban, high vs low altitude), rates of intrauterine growth restriction and preterm birth, and the perinatal and newborn care available to the local population [26].

3.1. Neonatal disorders

3.1.1. Neonatal respiratory distress syndrome

Worldwide, ~15 million babies (11% of all live births) are born preterm each year [27]. Complications of preterm birth are now the leading cause of neonatal and under-5-years mortality (Table 1) [7,9,27]. Survival among infants born <32 weeks of gestation in many low- and middle-income countries is <50%, the approximate rate of survival for most infants born at 24 weeks of gestation with access to neonatal intensive care in high-income countries [27].

Primary RDS from surfactant deficiency in the newborn lung is the most prevalent respiratory disorder among preterm infants [28]. For many of the reasons described earlier, the true incidence of RDS in low- and middle-income countries is difficult to determine and published rates vary widely (Table 2). RDS-specific mortality in low- and middle-income countries is high. Among infants born at eight hospitals in the Brazilian Network of Neonatal Research Centers, a diagnosis of RDS was the second highest risk factor for death (adjusted odds ratio 3.1, 95% confidence interval (CI) 1.4–6.6) after gestational age [36]. In eight NICUs in the Alexandria Governorate in Egypt, RDS was the most frequent cause of death [33]. In single-center studies conducted at large referral hospitals in Karachi (Pakistan) and Dar es Salaam (Tanzania), the rate of death from RDS was 41% and 52% respectively [13,38]. Over a five-year period at a regional teaching hospital in northwestern Ethiopia, the rate of death from RDS was a staggering 91% [39].

3.1.2. Meconium aspiration syndrome (MAS)

Meconium is a viscous, hyperosmolar substance that may cause severe respiratory distress and hypoxia when aspirated in utero or immediately after birth [40,41]. In high-income countries, meconium-stained fluid is present in ~10–15% of live births and significant respiratory compromise due to meconium aspiration occurs in 0.1–0.35% of live births [42,43]. Infants born in low- and middle-income countries suffer high rates of morbidity and mortality due to MAS. This is especially so where in-utero infection rates are high and where there is limited availability of fetal monitoring, birth attendants trained in neonatal resuscitation, and appropriate respiratory therapies [44–46]. Among liveborn infants cared for at 18 referral centers in India, 1.3% of inborn and 7.9% of outborn infants were diagnosed with MAS [29]. A recent randomized controlled trial (RCT) from a single center in New Dehli (India) examined the effect of intrapartum oropharyngeal suctioning in full-term infants born through meconium-stained fluid [47]. Among the 509 enrolled infants, 82 (16.1%) developed MAS [47]. Single-center reports from Karachi (Pakistan) and Kelantan (Malaysia) found, respectively, that 27.4% and 38.5% of meconium-stained infants developed MAS [48,49]. A prospective study in four administrative units in Latifabad (Pakistan) reported that 9.4% of infants born through meconium-stained fluid died within the first 28 days of life (relative risk (RR) of death 2.7, 95% CI 1.4–5.3) and, across 23 tertiary NICUs in southeastern and midwestern China, mortality among infants who required MV for MAS was 39.4% [50,51].

3.2. Neonatal and infant disorders

3.2.1. Pneumonia

Pneumonia is the second most frequent cause of childhood death and accounts for ~136,000 deaths per year among neonates aged 0–27 days and 935,000 deaths among children aged <5 years [7]. A recent systematic review estimated the incidence of