Advances in neonatal critical care: pushing at the boundaries and connecting to long-term outcomes

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The care of newborn infants has evolved over the past 50 years from essentially simple, anecdotal and empirical processes to evidence-based, high technology, intensive care medicine, accompanied by a dramatic decline in mortality and increasing intact survival of many fragile extremely preterm infants and improving outcomes for infants exposed to perinatal asphyxia. Many factors have been responsible for these improved outcomes, but they all stem from the development of Neonatology and Maternal-Fetal Medicine as clinical specialties in their own right. Through these organizational disciplines, physicians, nurses, and allied health professionals have developed as teams, formalizing training, quality control, and simulation programs to provide high quality, standardized, state-of-the-art care. However, despite the huge advances in knowledge, care for newborn babies still represents a very careful balance between benefit and harm.

Around the time that the Society of Critical Care Medicine and Journal were being formed in 1971, care for newborn babies was usually carried out as part of the woman's maternity care and interest in the newborn was only slowly awakening. Many early attempts to improve care had floundered when unexpected complications ensued (**Table 1**). Despite this, dramatic falls in neonatal mortality had occurred over the 20th century associated with the introduction of better population nutrition and antisepsis (10). The seeds for the informed development of neonatal care had been sown, but recognizable Neonatal Critical Care emerged around this time with the recognition that the application of good science and the use of clinical trials could safely proceed.

Prior to 1970, there was little consensus as to how to best care for the newborn in the minutes and hours after birth and little understanding of the importance of thermal control. Indeed, supplemental oxygen apart, there was no understanding of how to support respiration when hyaline membrane disease occurred. Infants often had all feeding and fluids withheld until their respiratory symptoms settled, and there was uncertainty over the use of antibiotics, which seemed to cause disastrous complications, and fear over complications of the use of pain relief. Where pioneers had started to develop intensive care practices, there was criticism of the cost of neonatal care in terms of the high rate of disability among survivors. By 1970, there had been one trial of "intensive care"—use of oxygen and a glucose-bicarbonate infusion—and few attempts to understand the potential neurologic and neurocognitive outcomes that are currently monitored prospectively. Even more starkly, parents were

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TABLE 1.
Examples of Early Disastrous Interventions and Adverse Effects in Different Epochs (1950s–1970s)

Epochs	Interventions	Adverse Effects
1950s	Bloxsom air lock	Ineffective at resuscitation or ventilation (1)
1950s	High oxygen concentrations in primitive incubators for premature infants	Retrolental fibroplasia (retinopathy of prematurity), blindness (2)
1950s–1960s	Chloramphenicol prophylaxis	Gray baby syndrome and death (3, 4)
1960s	Starvation and food and fluids in immature infants	Bad neurologic outcome, increased mortality (2)
1960s	Ventilation with adult ventilators (no continuous flow and end-expiratory pressure) in larger preterm and term infants with respiratory distress syndrome	Bad respiratory outcome, high mortality (5)
1960s–1970s	Prophylactic ampicillin and sulfonamides	Kernicterus and death (6)
1960s–1970s	Hexachlorophene baths as prophylaxis for *Staphylococcus aureus*	Irreversible brain lesions and spongiform myelinopathy (3, 7)
1970s	Restrictions of inspired fraction of oxygen	Sixteen deaths per case of blindness prevented (8)
1970s	Hyperventilation and alkalosis for treating pulmonary hypertension	Severe lung injury and brain injury (9)

usually not welcome visitors on neonatal units and "viewing corridors" were commonplace. Furthermore, there was debate as to whether there were important long-term effects following preterm birth. Studies showed conflicting results and demonstrated the confounding effects of socio-environmental causes of low birth weight (11).

During the 1960s, as the terms "neonatology" and "neonatologists" began to appear, a whole range of developments occurred to set the foundations for modern critical care. Critical scientific enquiry underpinned much of this work. Understanding the physiology of the transition from fetus to neonate, how to assess a baby immediately after birth, what interventions were likely to be effective, and the critical nature of temperature control in preventing worsening neonatal illness were all developed in the 15 years prior to 1970. The recognition of the importance of a continuous distending airway pressure led to the development of the now widely used continuous positive airway pressure (CPAP) and early principles for the ventilation of babies with respiratory distress syndrome (RDS); these in turn promoted in the early 1970s the development of specific miniaturized technologies for the measurement of blood gas tensions, noninvasive oxygen tensions—through transcutaneous measures to saturation monitoring—with accurate vital sign monitors and infusion pumps that reliably delivered low volumes. In parallel, IV feeding became possible, and a better understanding of the use of antibiotics, including monitoring of levels, started to produce appropriate anti-infective strategies. Thus by 1971, neonatal care was on the threshold of blossoming into a full intensive care discipline. However, many problems and therapeutic strategies still needed to be overcome and the culture of benign neglect and disastrous interventions still prevailed across most of the world.

This article describes how the care of critically ill newborns has progressed over the past 50 years, through state-of-art of clinical care, and ending with future perspectives, placing special emphasis on extremely premature babies. To this end, we concentrate on topics considered among the most challenging for neonatologists, notably care at birth, respiratory support, nutrition, sepsis, and neurodevelopmental outcome, which have been and remain key subjects since the beginning of neonatal intensive care.

THE EVOLUTION OF NEONATAL CRITICAL CARE

Although clinical care has evolved in detail as shown below, other factors have prompted the rapid improvements we have seen in mortality and morbidity over 50 years. Central to this have been two major developmental threads. First, the inclusion of obstetric

medicine with neonatology in making decisions about perinatal care. In the early 70s, the first randomized trial of antenatal steroid treatment to improve neonatal outcomes was reported (12). This seminal article was the first acknowledgment that management of the mother might affect the outcomes for the baby but was not universally implemented until 1994 (13). Since then, several important advances have occurred, including the screening and treating of maternal infection, the use of magnesium sulphate infusion to reduce the rate of cerebral palsy in the infant, and the evaluation of the growth-restricted infant using Doppler ultrasound to evaluate fetal health and guide delivery. Second, the recognition that intensive care is a specialist discipline and that high-risk pregnancies and sick newborns need to be born and cared for in specialist centers. Mothers and babies who deliver at extremely low gestational ages both have high morbidity, and balancing the risk to both makes for challenging decisions (14). Finally, one of the most important differences that have developed over the past 50 years is our attitude to and engagement of parents in decision-making for their infant, and a recognition that neonatology should care for the baby within its family if the best outcomes are to be anticipated.

CARE AROUND THE TIME OF DELIVERY

Resuscitation for babies who do not immediately commence respiration has been attempted since antiquity, being well documented in several entertaining descriptions about techniques and devices (15, 16). Following the seminal work of Geoffrey Dawes and others in defining the physiology of neonatal transition, the modern history of neonatal resuscitation began in the 1970s, with reports of measurements of the pressure and volumes generated with initial aeration at birth (17). In the 1980s, as training in neonatal resuscitation became a national priority, the Resuscitation of the Newborn Task Force was established in the United States, building on the National Institutes of Health Neonatal Education Program (18). These initiatives codified an approach to neonatal resuscitation that was almost entirely based on customary practice and expert opinion and further developed by the American Academy of Pediatrics and the American Heart Association in the Neonatal Resuscitation Program (NRP) textbook in 1987 (19). In 1992, The International Liaison Committee on Resuscitation became the international consensus focus for all standards related to resuscitation, including a consensus approach to neonatal resuscitation, such as the NRP. The remarkable result of these initiatives has been extensive research targeted to the unknowns surrounding neonatal transition and resuscitation. Much of that research stemmed from the work of Colin Morley from 1998 to date, who developed a neonatal training program with physicians from around the world, that broke down neonatal resuscitation into its basic elements, seeking evidence about each element (20).

Initially, the standard gas used during neonatal resuscitation was 100% oxygen. In 1993, Saugstad et al (21) challenged the use of high oxygen concentrations because of his concerns about oxidant injury, demonstrating in randomized trials that 21% oxygen was preferable for term infants; high oxygen concentrations in blood can suppress respiratory drive and cause any reperfusion injury. It remains less clear how preterm babies should be managed. At birth, many preterm infants still require some supplemental oxygen to achieve stable oxygenation by 5 to 10 minutes of age. However, safe and reproducible techniques to transition the preterm lungs remain elusive and challenging to study with randomized controlled trials. The current recommendation is to titrate oxygen use based on oxygen saturation monitoring of the infant during resuscitation, beginning with about 30% oxygen (22).

The most important intervention in neonatal resuscitation is initiating successful aeration of the fluid-filled fetal lung. In the early ’70s, the only reliable method was by the insertion of an endotracheal tube and using positive pressure to inflate the lungs. At that time, other measures were considered ineffective and did not provide an opportunity to inspect and clear the airway. In 1981, building on the success of CPAP to treat RDS, a Laerdal infant resuscitator was modified at Johns Hopkins Hospital, to permit simple delivery of CPAP and successfully used for ventilation of infants with respiratory distress in the delivery room (23). By 1985, face mask use rather than intubation during resuscitation of newborn infants became more popular as better fitting interfaces were available (24).

Research has demonstrated that ventilatory support at birth is both difficult and frequently performed inefficiently (25). To achieve an increasing functional

residual capacity (FRC) in the nonbreathing infant requires effective delivery of pressure, usually via a mask, but it is recognized that clinical assessments of tidal volume may be quite inaccurate (26). The T-piece resuscitator has been a substantial improvement over self-inflating anesthesia bags or bags requiring a gas flow, as even an inexperienced rescuer can deliver consistent peak pressures and CPAP more reliably (27). However, some infants develop glottic closure that obstructs the airway and will prevent resuscitative efforts, regardless of ventilatory technique [28]). Of note, in low resource environments, infant mortality mostly results from the ineffective use of simple maneuvers to stimulate the breathing transition, such as drying, tactile stimulation and simple mask-bag ventilation whenever needed. Programs developed by the World Health Organization and the American Academy of Pediatrics—such as "Helping Babies Breathe" (29), focus on the basic elements to initiate ventilation only.

The concept of using sustained inflations to deliver a constant peak pressure to recruit FRC more effectively was developed in animal models (30). Early trials adopting initial sustained inflations of 5 to 15 seconds were encouraging (31), but a subsequent large trial was stopped because of an increased rate of early deaths following a 15 seconds sustained inflation (32). Recent studies in preterm sheep models demonstrate that achieving uniform inflation may best be done by ramped increases in CPAP (33). However, use of CPAP in the delivery room is not harmless. A large epidemiological study identified that indiscriminate use of CPAP in the delivery room increased symptomatic pneumothorax, which increased risk with advancing gestation and in infants not requiring oxygen (34).

For many years, the timing of the clamping of the umbilical cord was considered an obstetric/midwifery issue, despite issues with neonatal hypotension and the frequent need for volume expansion. More recently, the importance of allowing the blood volumes to equilibrate between baby and placenta has been shown and deferring of cord clamping for a variety of times has been proposed, leading to reduced neonatal mortality in very preterm infants, among other benefits. Recent work in preclinical models indicates substantial benefits in cardiopulmonary transition with delayed cord clamping until respiration has commenced, even among infants who are apneic at birth (35).

The original NRP algorithm included the use of an opioid antagonist, and bicarbonate and calcium boluses, along with epinephrine. As the care has become more evidence-based, apart from the use of epinephrine, the use of drugs for neonatal resuscitation has stopped (36).

POSTNATAL RESPIRATORY SUPPORT

Respiratory support for infants initially evolved from attempts to breathe for alive but apneic newborns at delivery (37). By the 1960s, a number of newly created neonatal ICUs (NICUs) were attempting to ventilate larger preterm infants and term infants primarily with adult ventilators, without continuous flow and end-expiratory pressure (e.g., the Bird Mark VIII), with only modest success. In general, the indication was for moribund infants with severe RDS, as described by Delivoria-Papadopoulos et al (5) in 1965, where only seven of 20 survived and the only survivors were infants who needed positive pressure support after 28 hours of age. Indeed, early severe respiratory failure was uniformly fatal or with unfavorable outcome (38). Initial attempts to salvage infants with severe respiratory failure were considered futile by many, as it was for adults.

By 1970, continuous positive pressure breathing was known to improve oxygenation, but disadvantages were thought to be alveolar rupture and the need to measure cardiac output to avoid over pressurizing the chest and inhibiting heart function, as shown in adult patients (39).

In 1968, Harrison et al (40) from South Africa noted that intubation of infants with RDS stopped their grunting and decreased their oxygenation, and when extubated their oxygenation improved. In 1971, Gregory et al (41) read the article from South Africa and applied the concept of CPAP to 20 infants with RDS with apnea or on 100% oxygen; 16 survived using an anesthesia bag with continuous flow. These two critical concepts of continuous flow and positive end-expiratory pressure (PEEP) were incorporated into the Baby Bird Neonatal Ventilator design, which became the first effective and versatile neonatal ventilator (42). Indeed, the critical observation that transformed neonatal ventilation was the recognition of the need for PEEP. Over the next 10 years, there were innovations as to how to apply CPAP and to use PEEP, which became standard

of care as many lung problems in infants include airspace collapse and loss of FRC. These innovations included continuous negative pressure ventilation, nasal CPAP, high flow, and multiple other reports of various ways to use CPAP noninvasively (43). CPAP lost favor in the late 1970s as the primary care strategy for RDS, with the wide availability of several neonatal ventilators as an easier way to manage RDS. However, in 1967 Northway et al (44) first described bronchopulmonary dysplasia (BPD) in relatively large premature infants exposed to mechanical ventilation with high amounts of oxygen and no PEEP. The growing recognition that oxygen and mechanical ventilation in combination could cause severe progressive lung injury with lifetime consequences became a major problem for neonatal respiratory care (45), leading to increased support for avoiding ventilation and prompting clinical trials that supported CPAP as the initial respiratory management in most preterm infants (46). Indeed, the American Academy of Pediatrics recommends that CPAP should be considered as an alternative to intubation, even in extremely preterm infants (47).

Of note, in 1992, Sinclair and Bracken (48) published the first meta-analysis of infant mechanical ventilation, providing information on elements of mechanical ventilation such as neuromuscular paralysis and long versus short inspiratory times. Concomitantly, multiple innovations to support respiratory failure, both invasively and noninvasively, have been explored. For example, high-frequency oscillatory ventilation (HFOV) appeared to be a promising tool in preterm infants with respiratory failure. However, systematic reviews assessing elective HFOV versus conventional ventilation in these patients did not reveal significant differences in terms of death or BPD (49).

Ventilators for infants have evolved from simple continuous flow pressure limited devices to complex ventilators with patient synchronization, volume targeted ventilation modes, pressure support modes, monitoring using pulmonary waveforms, and graphics, which allow caregivers to fine-tune the respiratory support in almost infinite ways, to optimize ventilation and decrease injury (50). High-frequency oscillatory or jet ventilation is used in selected circumstances to rescue infants with respiratory failure on conventional ventilation or with severe air leaks. Some clinicians may use them as a primary respiratory support strategy, even though large meta-analyses demonstrate few differences in outcome (49, 51). Recent trials suggest that low tidal volume, targeted low-pressure ventilation may be of benefit for decreasing BPD (52).

The availability of surfactant treatments to treat RDS is another success story for neonatal respiratory care. In 1959, Avery and Mead (53) identified surfactant deficiency with RDS as the developmental abnormality that caused the severe atelectasis and low compliance of the lungs of infants with RDS. By the early 1970s, Enhörning and Robertson (54) had demonstrated that airway instillation of surfactants from animal lungs could improve the lung mechanics of preterm rabbits. In 1980, Fujiwara et al (55) treated ten infants with RDS with a bovine lung lipid extract, with large improvements in oxygenation. Several surfactants were developed and tested with Food and Drug Administration approval of two surfactants to treat RDS in 1990. Since that time, the use of surfactant has become universal in neonatal intensive care. Surfactant preparations are best administered early in the course of the disease and have been shown in multiple studies to effectively reduce acute lung disease and minimize mortality, but they did not decrease BPD.

The availability of surfactant treatments simplified the respiratory care of the smaller and more immature infants but did not decrease BPD, presumably because of increased survival of infants who otherwise would have died of their lung disease (56). Surfactants purified from animal lungs are predominantly used worldwide, but novel synthetic products, so-called second generation, protein-containing synthetic surfactants, may become alternative to natural surfactants in the future (57). Current interest is focused into how surfactant can be given less invasive or by noninvasive methods of surfactant administration, for example, without intubation of the airways and in conjunction with CPAP to avoid any lung injury and decrease BPD (58).

Clinical neonatal care was substantially simplified by the use of methylxanthines to treat apnea of prematurity (59) and to assist in weaning from mechanical ventilation. In 2006, Schmidt et al (60) demonstrated that caffeine was safe and effective for reducing apnea of prematurity and that it incidentally decreased BPD without impacting long-term neurodevelopmental outcomes.

Other ancillary therapies have changed clinical respiratory management. Antenatal corticosteroids, first

proposed by Liggins and Howie (12), became widely used by 1994 to mature the fetal lungs and decrease RDS-related mortality. In animal models, antenatal steroids and surfactant have synergistic effects on the preterm lung to improve function (61). Curiously, low-grade antenatal inflammation also induces lung maturation and augments antenatal corticosteroid benefits (62).

At present, neonatal intensivists have an effective armamentarium to virtually prevent infant deaths from RDS, except at extremely low gestational ages or when other pathologies such as lung infection and pulmonary hypoplasia complicate RDS (63). The goals of oxygen supplementation have been explored with collaborative oxygen targeting trials, which provide guidance for oxygen use (64). Over the past 50 years, the combination of antenatal steroids and early lung maturation induced by pregnancy-related abnormalities (inflammation) (62), surfactant treatment, noninvasive ventilatory support, and good nutrition has markedly improved survival of newborn infants with RDS (**Fig. 1**) (65). Unfortunately, most marginal infants may end up with severe BPD, which remains the major respiratory care challenge as more and more very immature infants survive with interdisciplinary care needs (66). These infants may have a spectrum of lung injuries that includes large airway injury requiring long-term tracheotomy, small airway disease categorized as an asthma phenotype and parenchymal lung disease with decreased gas exchange ability, and chronic pulmonary vascular disease, causing pulmonary hypertension (67). Optimizing their care and outcomes remains an ongoing challenge. Importantly, these functional abnormalities persist through to adult life and are associated with reduced lung function test results, alongside vascular problems such as higher blood pressure and reduced vascular compliance (68) and a unique cardiac phenotype with an impaired response to stress (69). Improved neonatal outcomes may have very long-term consequences.

One green apple that has not ripened for neonatal respiratory care was liquid ventilation with perfluorocarbons, which are chemically inert compounds with a high affinity for oxygen (70).

There have been other ventilation misadventures over the years. The management of infants with meconium aspiration and pulmonary hypertension focused on achieving pulmonary vasodilation by causing alkalosis with hyperventilation, which often was transiently beneficial. The price was severe lung injury and brain injury (71). Things improved with the obstetric approach to avoid late term deliveries and severe meconium aspiration, the acceptance that infants could be managed with lower oxygen saturations, as well as the availability of inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO). Interestingly, the first successful case of neonatal ECMO was in 1975, when Bartlett et al (72) successfully used prolonged venoarterial extracorporeal support for life-threatening respiratory failure. Simultaneously, a National Institutes of Health-sponsored multicenter prospective randomized trial of ECMO for adult patients with acute respiratory distress syndrome was terminated for futility, as mortality was 90% in both the ECMO and control patients, thus discouraging research on ECMO for adult respiratory failure for at least 2 decades. In contrast, as

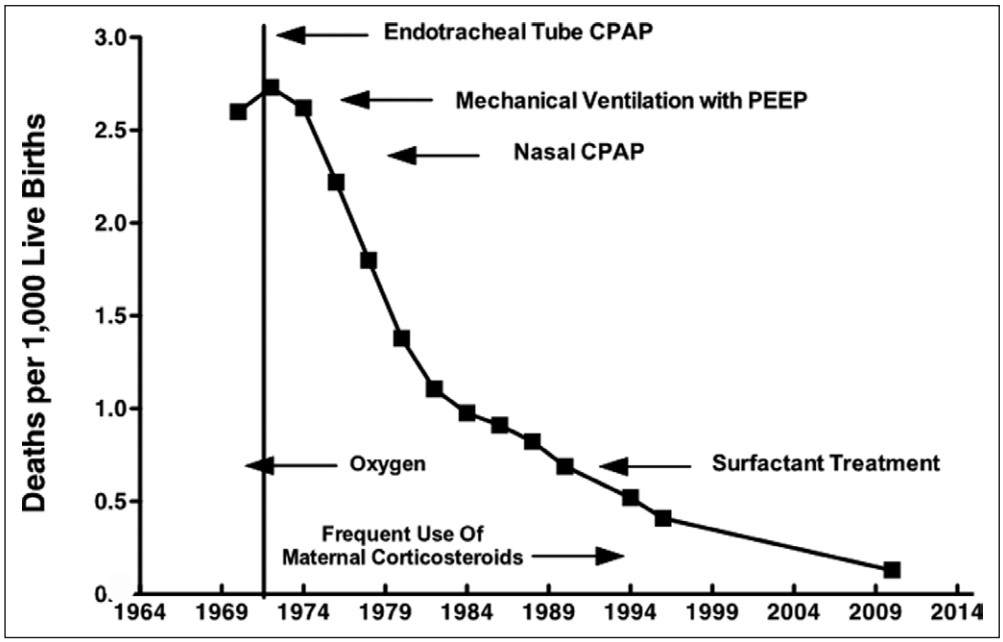

Figure 1. Mortality of infants from respiratory distress syndrome in U.S. population since 1970. Deaths per total live births (65). CPAP = continuous positive airway pressure, PEEP = positive end-expiratory pressure.

survival was about 50% in newborns with severe respiratory failure (73), following further trials, ECMO has been used to treat a broad group of sick newborn infants, although its use remains contra-indicated for small preterm infants and is mainly used to support infants with pulmonary hypertension, resistant other modalities. Meanwhile, it has also become progressively used in adults.

NUTRITIONAL CARE

Initially, neonatologists were fearful of feeding newborns enterally because of the risk of aspiration, worsening respiratory condition, and of the emerging disease necrotizing enterocolitis. Small immature babies were initially starved of food and fluid, and few received human milk, resulting in low-birth-weight infants often weighing below the tenth percentile at the time of discharge (74). Infants appropriately grown in utero were rendered small for gestational age. The negative impact of this on long-term growth and neurologic outcome was immense, and only in the 1970s was total parenteral nutrition added but cautiously because of fears about the effects of lipid on physiology and following pathologic findings of lipid in lungs and brain at post mortem. At the same time, important trials of calorie-rich formulae were enacted—many of which are still under follow-up. Since the early 1980s, the introduction of whey-predominant formulas for the preterm infant, early parenteral nutrition with protein and lipid supplementation, trophic feeds (minimal enteral nutrition), the use of feeding protocols, and, more recently, exclusive use of colostrum and human milk have progressively improved nutrition, while decreasing overall morbidity from cholestasis, necrotizing enterocolitis, and sepsis (6, 75). Neonatologists are now keenly aware of the nutritional needs of the newborn.

SEPSIS

Neonatal infections have always been important determinants of outcome, particularly in extremely premature newborns. Early therapeutic misadventure through the use of anti-infective agents has been replaced with well-understood regimes, but the lessons of unexpected complications of drug therapies remain and have led to cautious drug development and use. Success in intrapartum screening and prophylaxis has minimized the occurrence of early-onset "perinatal" infections, mainly with group B Streptococcus, which appeared in the early 1070s as an important pathogen. However, there is increasing anxiety about the role of infective agents in the causation of preterm birth and its effect on the baby but, as yet, there are no successful trials or formal treatment recommendations. Despite the development of multiple generations of antibiotics, neonatal intensive care is frequently complicated by infections. In one study, as survival of extremely preterm infants increased, mortality from sepsis increased in prevalence and later acquired infection became the major cause of death (76). Attempts to reduce sepsis rates through the use of probiotics, colostrum, and exclusive human milk feeding, together with optimizing nutritional intake and minimizing periods of undernutrition, have yet to demonstrate conclusively benefit.

OUTCOMES FOLLOWING PRETERM BIRTH

Since the early seventies, neonatal mortality has decreased steadily. Between 1970 and 1988, neonatal mortality fell in the United States from 14.0 to 7.0 deaths per 1,000 live births, falling by 5.6% per year. This trend has continued steadily in the United States (2018: 5.9/10^3 live births) and other countries (United Kingdom 2019: 2.9/10^3 live births; Sweden 2019: 1.5/10^3 live births). One of the challenges is that as survival at lower gestational ages increases, the babies who die tend to be the most immature and form the bulk of neonatal deaths, to some extent hiding the improvement in survival for more mature infants (**Fig. 2**). Survival for infants born before 27 weeks has increased steadily over the past 20 years as attitudes to providing such care and the quality of care improve (**Fig. 3**). Current survival rates based on reports where active survival-focused care is provided at birth are similar across reported studies.

In the early 1970s, seminal work from Cecil Mary Drillien showed that there was indeed an association between poor developmental or cognitive performance and prematurity. Concerns were even raised by other investigators about a higher prevalence of sociopathy (77). In a landmark article, Stewart et al (78) produced one of the first systematic reviews in the area, demonstrating that in quinquennia from 1945, there had been a steady improvement in survival and survival without handicap for births under 1,500 g and under 1,000 g. However, there appeared to be an irreducible

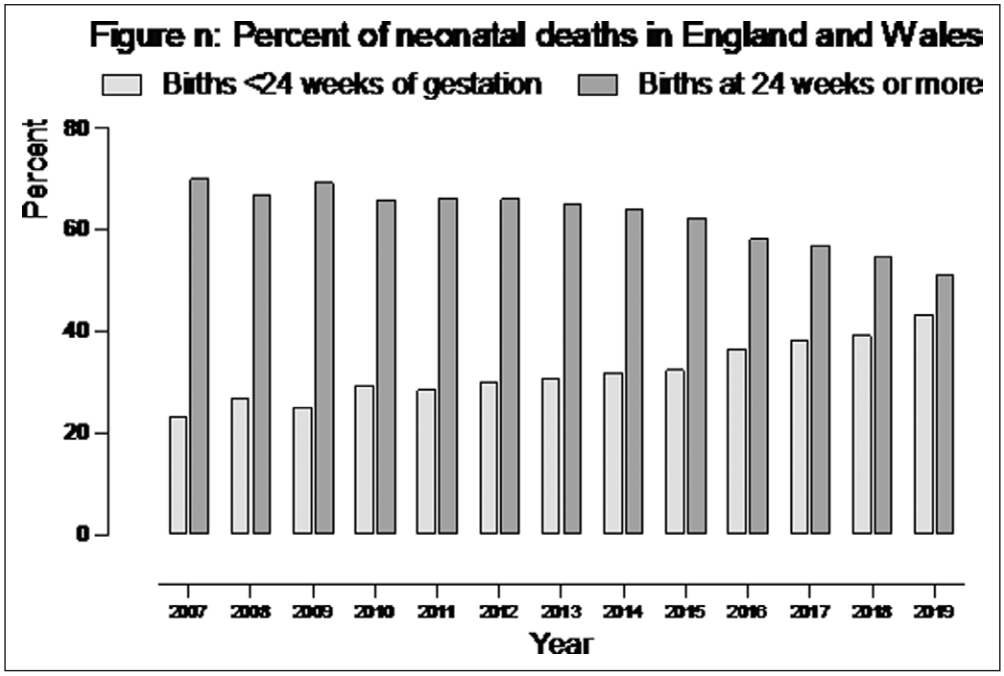

Figure 2. Percent of neonatal deaths in England and Wales in the period from 2007 to 2019, considering infants born less than 24 wk of gestation and infants born at 24 wk or more.

proportion of live births (about 6–8%) who survived with disability (78).

These findings refuted the proposition that neonatal care for small premature infants was associated with increasing proportions of children with disability in the population. Indeed, the balance and loss for neonatal care have always shown in favor of providing care (79). As more extremely premature births survive, a significant proportion of them have neurodevelopmental disability, defined as cerebral palsy (CP), behavioral and neurodevelopmental impairment, and visual or hearing deficits. Indeed, one of the first consequences of providing intensive care at increasingly lower gestation may be to actually increase the risk of impairment, presumably by saving infants at high risk (80). Over time, the rates of CP have subsequently fallen as expertise and care have improved (81). As survival now extends to babies born at 22–23 weeks, these arguments are advanced again, but survival rates are similar across different studies (**Fig. 4**).

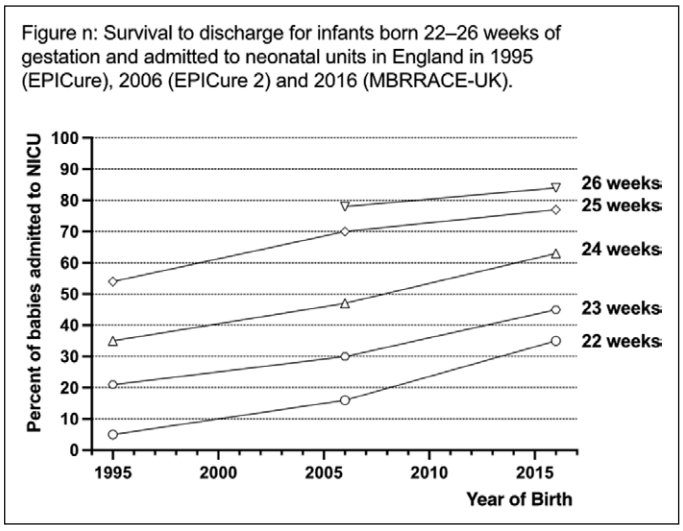

Figure 3. Survival to discharge for infants born 22–26 wk of gestation and admitted to neonatal units in England in 1995 (EPICure study), 2006 (EPICure 2 study), and 2016 (MBRRACE-UK study). NICU = neonatal ICU.

Among premature infants, serious disability is associated with the occurrence of germinal matrix hemorrhage and ischemic injury to the periventricular tissues. Detection primarily using ultrasound allowed the development of interest in prevention, which until the 1980s was poorly understood. Since that time, there has been a reduction in the prevalence of lesions based mainly on better attention to care around the time of birth, avoidance of swings in blood pressure and hypotension. This has contributed to the slow but steady decline in the rate of cerebral palsy among survivors.

Today, postdischarge follow-up of high-risk infants is the yardstick by which the quality of care is measured. Neonatal units, networks, and countries report survival and outcome data on a regular basis. The key outcomes of concern are currently those of cognitive impairment with associated behavioral and socialization problems (82). There is good evidence for a gestational age-dependent relationship with all neurocognitive outcomes, including impaired cognition, behavioral problems, and educational performance. This relationship seems almost exponential such that there is a rapid rise in the need, for example, for special educational support in children born before 28 weeks (83). Understanding the etiology of these problems is essential before we can intervene effectively to prevent

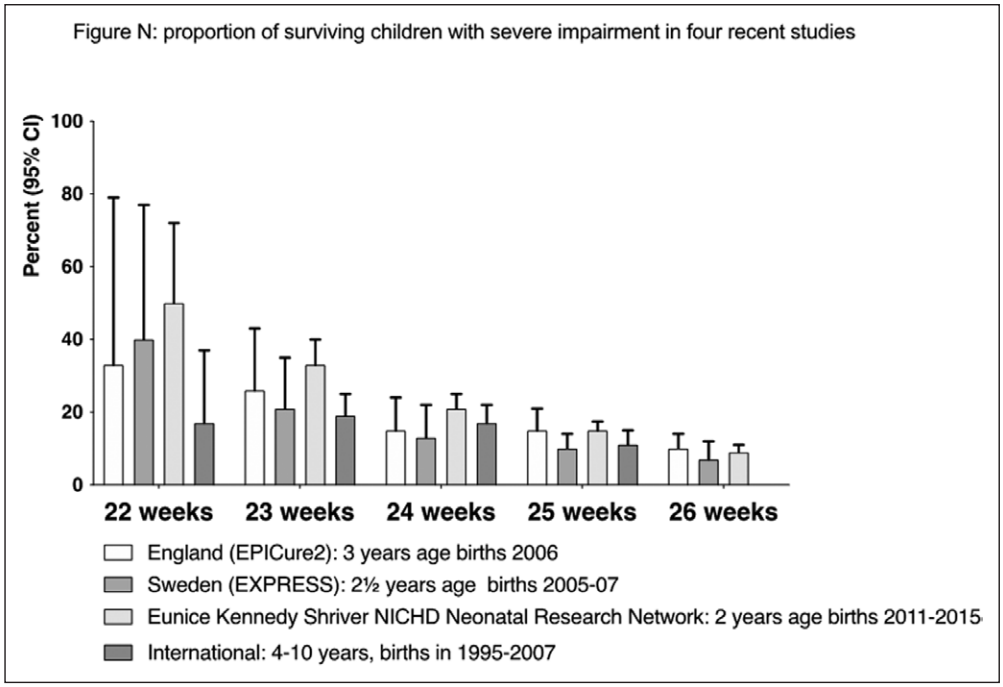

Figure 4. Proportion of extremely premature infants with severe impairment at 2–10 yr follow-up in four recent studies. EPICure2 = EPICure2 study, EXPRESS = Extremely Preterm Infant Study in Sweden, NICHD = National Institute of Child Health and Human Development.

them. Furthermore, understanding how these traits and disorders track into adult life is essential (84).

Following individuals from birth allows the evaluation of trajectories that might be amenable to intervention. Studies from the United Kingdom show that trajectories of cognitive development and behavior are somewhat fixed from school age through 19 years (85). However, identifying effective interventions remains a major challenge, and it is as yet unclear which is the most effective time and how to attempt intervention (86). What is clear is that developmental outcomes are influenced by many factors, including male sex, social, genetic, and biological risks. For children of extremely low gestational age, neonatal risk factors tend to predominate. Chorioamnionitis, birth asphyxia, BPD, intraventricular hemorrhage, sepsis, technology dependence, and nutritional failure may all dramatically influence outcome. Neonatal care outcomes are the aggregation of marginal gains from constantly improving the quality of care and treatments with regard to the potential to cause harm. Neonatal teams are becoming more confident at caring for extremely immature infants, including those born before 23 weeks of gestation. It is unclear whether we are seeing true improvements yet in the longer term outcome for these groups, and some have reported no improvement (87). To date, only one study has reported outcomes in the fourth decade, although several have done so in early adult life (88), so it is difficult to be sure how the wealth of findings in childhood, adolescence and young adult life will translate in the longer term.

TREATING BRAIN INJURY IN FULL TERM INFANTS

Term and near-term babies with perinatal asphyxia may develop severe hypoxic-ischemic encephalopathy (HIE) and permanent neurologic impairment. In these patients, the brain injury is secondary to both the hypoxic-ischemic event and the reoxygenation-reperfusion following resuscitation. Currently, therapeutic hypothermia is the only established treatment in the subacute phase of asphyxia-induced brain injury for babies with moderate/severe HIE and is increasingly used for mild encephalopathy (89).

Despite the advent of therapeutic hypothermia, a large proportion of treated infants still suffer severe neurologic consequences. Thus, various therapies, including erythropoietin, allopurinol, xenon, argon, cannabinoids, topiramate, and stem cells, are currently under investigation in conjunction with therapeutic hypothermia, to improve long-term neurodevelopmental outcomes further. To date, both erythropoietin and melatonin appear to carry some benefit, but the results of large, randomized trials with neurodevelopmental outcomes are awaited with interest.

FUTURE PERSPECTIVES

Advances in neonatal care have progressively extended the boundaries of care, in a way certainly not predictable 50 years ago. At present, infants with a gestational

age of 22 or even 21 weeks now survive in several centers with reasonable reported outcomes (14, 90) in contrast to rare survival at 28 weeks and under in 1970. The anxiety about outcomes for this new generation of survivors reflects continuing concern for those at the margins of what can be achieved. Yet, there is much greater knowledge of the range of pervasive effects that prematurity has on development in all organ systems, as described above. The moral and ethical dilemmas of working at this advancing interface remain very important. Prevention of severe preterm birth thus remains a fundamental priority, in parallel to developing new effective therapies for preventing and treating consequences of neonatal illness and a focus on minimizing harm from interventions.

A range of exciting new opportunities are evolving, some examples of which are detailed below:

Avoidance of mechanical ventilation is a key plank of current practice. Researchers are developing new methods for supporting extremely preterm infants even without mechanical ventilation, which may avoid the lung injury and developmental changes that underpin BPD.

For example, artificial placenta-based systems aim to allow premature lungs to grow and develop enough to provide an adequate gas exchange to the neonate after birth. Through extracorporeal life support or pumpless circuits, gas exchange is maintained for days or weeks via oxygenators connected to the umbilical or other central vessels. In some animal models, the fetus is submerged in a bath of artificial amniotic fluid. Indeed, preclinical studies have shown remarkable results in experimental models (91, 92), suggesting a potential clinical utility of such technology for infants at extremely low gestational ages.

There remain important practical and ethical considerations necessary before human trials of such technology. The risk of infection, for example, is very high in early reports, but introduction may be on the horizon.

Despite advances in care, the prevalence of BPD in very preterm survivors has not changed over recent decades and may even have increased (93). New exciting strategies for preventing and treating BPD are forthcoming. Following encouraging preclinical results, mesenchymal stem cells (MSCs) therapy has been proposed in infants at high risk of severe BPD or with established BPD (94). Human amnion epithelial cells have been administered in small series of BPD patients, either intratracheally or IV, showing a good safety profile. However, due to concerns that MSC administration might induce tumor formation, researchers have been exploring the therapeutic role of extracellular vesicles in experimental models of BPD. Indeed, these appear to be an attractive therapeutic alternative to MSC, being cell-free and holding a great regenerative potential (95).

The high prevalence of neurodevelopmental impairments in extremely preterm infants is fueling the ongoing search for neuroprotective interventions, either to prevent brain injury or to enhance normal development and repair of the immature brain. The balance between destructive lesions (e.g., periventricular leukomalacia) and developmental disturbances, for example, in producing long-term deficits, is poorly understood (96). Rapid advances in computational MRI are leading our understanding of the effects of both these processes and provide the potential to act as bridging biomarkers to long-term effects. As therapeutic hypothermia is currently not recommended in premature infants (97), experimental and human studies of other neuromodulator agents have been attempted to improve long-term motor and cognitive outcome in later childhood (98). For example, recombinant human erythropoietin has shown promising but conflicting results regarding neuroprotection and trophic effects on the global brain connectivity of preterm infants (99). The involvement of parents and promotion of mother-infant bonding and feeding also shows great promise in reducing the human and neurobehavioral cost of neonatal care.

For full term infants, future directions include further investigating the mechanisms of neural injury to identify safer and more effective neuroprotective and rehabilitative interventions (100). Sophisticated monitoring systems, state-of-the-art computational imaging using conventional MRI and spectroscopy, and more accurate prognostic indicators, both for the acute and subacute phase of brain injury, will aid optimal treatment and facilitate individualized counseling and rehabilitation strategies. For example, thalamic proton magnetic resonance spectroscopy of N-acetylaspartate concentrations acquired within 14 days of birth in term neonates who also received therapeutic hypothermia provided the best accuracy for predicting neurodevelopment 2 years later (101).

Advances in technology will continue to fabricate miniaturized devices and sophisticated tools capable of providing key information and continuous monitoring of the respiratory and hemodynamic status, even in the tiniest patients, by new invasive and noninvasive methods (102). For example, the diaphragm's electrical impedance tomography and electromyography are noninvasive, bedside monitoring tools that promote more individualized optimization of invasive and noninvasive respiratory support, by evaluating regional changes in lung volume and ventilation alongside spontaneous breathing effort (103). Computational analysis of heart rate patterns characteristics shows great promise as an early indicator of infection, facilitating prompt commencement of treatments, and improved antibiotic husbandry strategies are being trialed to reduce the antibiotic-induced selection pressure in neonatal units.

Analysis of exhaled breath might provide useful prognostic information in preterm infants at risk for BPD. Among available technologies, the electronic nose analysis (eNose) enables real-time analyses of the patterns of selected volatile organic compounds in exhaled breath. A recent study in mechanically ventilated preterm infants suggested that the eNose could identify those developing BPD at an early age (104). As the eNose can be used at the bedside in infants treated both with invasive and noninvasive respiratory support, analysis of exhaled breath might predict BPD at an early stage of the disease, prompting clinicians to adopt individualized preventive strategies for BPD (104).

Near-infrared spectroscopy-based monitoring of regional tissue oxygenation is fast becoming a standard, noninvasive bedside technique in the NICU, again favoring personalization of care to improve short and long-term outcomes (105). Hi-tech imaging techniques, such as CT, MRI, and spectroscopy, may become available at the bedside, providing repeatable, high-quality anatomic and functional information while avoiding unnecessary transfers for unstable patients.

Finally, the application of the human genome and development of the science of "-omics"—genomics, proteomics, epi-genomics, and metabolomics—is essential for understanding the cause and personalized treatment, enabling earlier diagnosis and stratifying appropriate intervention, thus accelerating the path toward precision medicine in extremely premature infants.

THE PRETERM ADULT

The earliest survivors of modern neonatal care have now reached early adult life and outcomes have been reported for population-based births cohorts of very and extremely preterm individuals in Canada, United States, Australia, Germany, and the United Kingdom, among others. As a group, they have lower educational attainment, are less likely to graduate from college and enter adult life in less-skilled jobs (88). However, much of the disadvantage found in these cohorts as adults is due to the high proportion of individuals with neurosensory impairments. There is also evidence from population studies that mental health issues are found more frequently in preterm adults, and studies of trajectories over adolescence confirm that the preterm behavioral phenotype observed in childhood and adolescence persist. Despite these potential challenges, many preterm adults have good and worthwhile outcomes (106).

As neonatal care improves and more individuals enter adult life, the importance of the perinatal course increases when extremely preterm individuals are faced with medical problems (68). Adult physicians need to be aware of their increased risk for respiratory, cardiovascular, and renal problems, alongside the pattern of neurocognitive and neurobehavioral symptoms that follow on from the well-described childhood and adolescent phenotypes—a new generation of issues that must be addressed.

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