Etiologies of NICU Deaths
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BACKGROUND AND OBJECTIVES: Infant mortality is an indicator of overall societal health, and a significant proportion of infant deaths occur in NICUs. The objectives were to identify causes of death and to define potentially preventable factors associated with death as areas for quality improvement efforts in the NICU.

METHODS: In a prospectively defined study, the principal investigator in 46 level III NICUs agreed to review health care records of infants who died. For each infant, the principal investigator reviewed the medical record to identify the primary cause of death and to look for preventable factors associated with the infant’s death. Infants born at ≥22 weeks estimated gestational age who were born alive were included. Stillborn infants were excluded.

RESULTS: Data were collected on 641 infants who died. At lower gestational ages, mortality was most commonly due to extreme prematurity and the complications of premature birth (respiratory distress progressing to respiratory failure, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis). With increasing gestational age, the etiology of mortality shifted to hypoxic–ischemic encephalopathy and genetic or structural anomalies. Reviewers of clinical care identified 197 (31%) infants with potentially modifiable factors that may have contributed to their deaths.

CONCLUSIONS: The factors associated with death in infants admitted for intensive care are multifactorial and diverse, and they change with gestational age. In 31% of the deaths, potentially modifiable factors were identified, and these factors suggest important targets for reducing infant mortality.

WHAT’S KNOWN ON THIS SUBJECT: Infant mortality is an important indicator of societal health, and approximately two-thirds of all infant deaths occur during the neonatal period and in neonatal intensive care units.

WHAT THIS STUDY ADDS: We report detailed information on the cause of death in infants admitted for intensive care. Factors associated with death are multifactorial, diverse, and change with gestational age. Potentially modifiable factors were identified in 31%.
Infant mortality is a sensitive indicator of overall societal health that is divided into 2 age periods: neonatal (birth–28 days) and postneonatal (29–364 days).\(^1\) Approximately two-thirds of all infant deaths occur during the neonatal period and are caused by complications arising from preterm births, birth defects, maternal health conditions, complications of labor and delivery, and lack of access to appropriate care at the time of delivery.\(^1\) A proportion of postneonatal deaths in NICUs can be attributed to factors arising from the neonatal period. Deaths occurring in NICUs have a major impact on infant mortality. Understanding the causes of death in NICUs and the modifiable factors associated with death has the potential to reduce infant mortality.

Public health policies to improve neonatal and infant survival rates must be informed by a thorough understanding of the factors contributing to neonatal and infant mortality rates.\(^2\) Prematurity is a major cause of infant death, but standard ways of categorizing the cause of death do not fully capture modifiable factors that contribute to the death.\(^3,4\) Infants born prematurely, especially at earlier gestational ages, unless they are considered preivable and not offered care, may die of specific preventable diseases.

The goal of this study was to better understand the factors associated with mortality and identify potentially preventable causes of death in infants who die during NICU care. As a result, an improved classification system may help define strategies to decrease neonatal and infant mortality.

**METHODS**

**Prospective Study**

We included infants who were $\geq 22$ weeks estimated gestational age (EGA) born alive and for whom health care was provided. Stillborn infants were excluded. We included only infants who died before discharge from the hospital. Enrollment began in November 2010 and was completed in October 2012. The protocol was approved and a waiver of consent was obtained from each site's institutional review board. The study was conducted in compliance with the Health Information and Accountability Portability Act (HIPAA) Privacy Rule regarding the use of a decedent’s health record.

**Primary Causes of Death**

The site’s principal investigator reviewed the medical record, completed a root cause analysis to identify the primary cause of death, and looked for potentially preventable causes associated with each infant’s death. The investigators selected from a predefined list of potential causes and modifiable factors associated with death. Acquired bowel disease was defined as a subgroup of infants with necrotizing enterocolitis (NEC) or spontaneous intestinal perforation. Text input was allowed to report factors not provided on the lists and to provide details of events surrounding an infant’s death. Those responses were reviewed and are summarized in the results.

**Review of Pediatrix Clinical Data Warehouse**

To evaluate the generalizability of our findings we retrospectively reviewed data on all deaths included in the Pediatrix Data Warehouse that occurred between 2010 and 2012 (the time our study was enrolling infants). This evaluation of outcome data were performed under a waiver from the Western Institutional Review Board for use of deidentified, HIPAA-compliant infant information within the Pediatrix Medical Group Clinical Data Warehouse (CDW). CDW data are captured prospectively from admission to discharge in daily progress notes generated by clinicians using a computer-assisted EMR.

**Data Collection and Monitoring in the Prospective Study**

An electronic system assigned unique study codes and collected deidentified data on each subject. Clinical research associates monitored each site for protocol adherence and data accuracy and ensured that the site’s conduct was in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and HIPAA regulations. We determined data accuracy by reviewing data collected in the electronic case report form against the medical record.

**Statistics and Sample Size Considerations**

The project’s unifying goal was to define potentially preventable causes of death in infants who received NICU care. Based on the assumption that 10% of neonatal deaths might be preventable and that 60 deaths due to preventable causes would provide an adequate sample to identify the most common causes of preventable death, we chose a sample size of 600 infants. This was a descriptive study, and we report our observations. No special statistics were needed.

**RESULTS**

**Demographics**

We identified 641 unique infants who were provided care in 46 different NICUs; all were level III NICUs (III, $n = 6$; IIIB, $n = 34$; and IIIC, $n = 6$). Infants who died were predominantly male and white; 36% of the infants were $<25$ weeks’ EGA (Fig 1); 59% died within 7 days of birth, and 85% died within 28 days after birth (Fig 2). Fifteen percent of the infants died in the postneonatal period. The 641 infants identified and included in our prospective study were also among 4418 infants that were reviewed using our CDW; the 2 groups were similar with respect to demographic characteristics, EGA distribution, and age at death (Figs 1 and 2 and Table 1).
Primary Causes of Death

The most common cause of death was extreme prematurity or low birth weight \((n = 89, 14\% \text{ of studied infants})\) (Fig 3). The second and third most common causes of death were sepsis \((79, 12\%\) and acquired bowel disease \((70, 11\%\). Other primary causes of death \((n, \%)\) in descending order of occurrence included lung hypoplasia \((61, 9.5\%\), intraventricular hemorrhage \((IVH)\) or intracranial hemorrhage \((60, 9.4\%\), respiratory distress syndrome \((RDS)\) \((51, 8.0\%\), lethal anomaly \((49, 7.6\%\), hypoxic–ischemic encephalopathy \((HIE)\) \((39, 6.1\%\), genetic syndrome \((32, 5.0\%\), major heart defects \((22, 3.4\%\), bronchopulmonary dysplasia \((18, 2.8\%\), hemorrhagic shock or profound anemia \((14, 2.2\%\), pulmonary hemorrhage \((13, 2.0\%\), renal failure \((13, 2.0\%\), congenital diaphragmatic hernia \((11, 1.7\%\), air leak syndrome \((4, 0.6\%\), and pulmonary hypertension \((4, 0.6\%\).

At lower gestational ages, mortality was most commonly caused by extreme prematurity and the complications of premature birth \((RDS, IVH, NEC, \text{ and sepsis})\). With increasing gestational age, the etiology of mortality shifted to HIE and genetic or structural anomalies \((Table 2)\).

Confounding Factors Associated With Death

The 89 infants with extreme prematurity or low birth weight were either <25 weeks \((79 \text{ out of } 89, 89\%)\) or <750 g \((85 \text{ out of } 89, 96\%)\) at birth. Nineteen \((21\%)\), all of whom were born alive, were considered nonviable and offered comfort care alone. Ten \((11\%)\) of the 89 infants were born at level II or lower units; 3 \((3.4\%)\) were unplanned deliveries that occurred at home. Six \((6.7\%)\) of the 89 mothers who delivered extremely preterm infants had received no prenatal care, and only 50 \((56\%)\) mothers had a previous consultation with a maternal–fetal medicine specialist. Thirteen \((15\%)\) were conceived using artificial reproductive technology, 8 from in vitro fertilization. Fifty \((56\%)\) died within 24 hours, and 79 \((89\%)\) died within 7 days of birth.

Sepsis as a cause of death occurred after 7 days of life \((48 \text{ out of } 641, 7.5\%)\ more commonly than sepsis causing death on or before day 7 \((31 \text{ out of } 641, 4.8\%)\). Thirty-nine percent of infants who died of sepsis were born at <25 weeks’ gestational age. The 2 most commonly acquired gastrointestinal causes of death were NEC \((63, 9.8\%)\) and spontaneous intestinal perforation \((7, 1.1\%)\). Of the 63 infants with NEC, 21 \((33\%)\) had total bowel necrosis, 19 \((30\%)\) were born at <25 weeks’ gestation, and 3 \((4.8\%)\) had major anomalies \((gastrochisis, atroventricular canal, and tracheoesophageal fistula)\).

In 61 infants with lung hypoplasia, the most common causes for hypoplasia were major renal anomalies \((n = 23, 38\%)\), prolonged rupture of membranes \((n = 20, 33\%)\), and hydrops \((n = 7, 11\%)\). Although lung hypoplasia was considered the primary cause of death in infants with renal anomalies, we suspect that the renal anomalies \((renal agenesis or Potter syndrome, n = 7; polycystic kidney disease, n = 5; posterior urethral valves or obstructive uropathy, n = 4; multicystic dysplastic kidney, n = 2; hydronephrosis or other, n = 5)\) were important contributing factors.

Fifty-one infants died of progressive respiratory failure from RDS; 25 \((49\%)\) were <25 weeks’ and 6 \((12\%)\) were ≥34 weeks’ EGA. All 51 infants were ventilated, 47 \((92\%)\) were treated with surfactant, and 19 \((37\%)\) received inhaled nitric oxide.

Of 49 infants with lethal anomalies, 22 \((45\%)\) had brain anomalies,
7 (14%) had renal agenesis and profound renal failure but not severe lung hypoplasia, 4 (8.2%) had thanatophoric dwarfism, and 8 (16%) had multiple anomalies but no defined syndrome or genetic disorder. The most common brain anomalies were anencephaly (n = 8) and severe hydrocephalus (n = 5). Other lethal anomalies were a large sacrococcygeal teratoma associated with severe hydrops, severe craniofacial banding and airway anomalies, lethal skeletal dysplasia, Pierre Robin anomaly with profound hypotonia and significant airway problems, scimitar syndrome, sirenomelia, surfactant protein B deficiency, and VACTERL association.

Of the 39 infants with HIE, 15 (38%) were born at <35 weeks’ EGA and did not receive hypothermia. Of the 24 infants born at ≥35 weeks’ EGA, 4 (17%) were not treated with hypothermia. Fifty-nine percent of infants with HIE were born at a level III center, 90% were intubated at birth, 62% had a neonatologist or a neonatal nurse practitioner in attendance, 72% received chest compressions, and 62% received epinephrine at delivery.

Thirty-two infants died of major genetic syndromes: trisomy 18 (n = 13, 41%), trisomy 13 (n = 5, 16%), Wolf–Hirschhorn syndrome (n = 2, 6.3%), and 1 each of trisomy 4, trisomy 20, 4P–, 12q24.21–q24.22, 22Q deletion, chromosome 15 deletion, congenital central hypoventilation syndrome, Klinefelter syndrome, myotonia congenita, myotonic dystrophy type 1, myotubular myopathy, Smith–Lemli–Opitz syndrome, and Zellweger syndrome. In 3 infants with trisomy 21, the deaths were not attributed to their genetic defect.

Of the infants with major heart defects, 20 (91%) were born at level III centers. Twelve infants did not fit into any predefined category. Their causes of death included gastroschisis or cardiac tamponade due to Broviac complication; congenital airway abnormalities that prevented intubation; omphalocele; severe perinatal depression but no hypoxemic–ischemic encephalopathy; ureaplasma pneumonia;
For the 641 infant deaths, the study reviewer identified 197 (31%) infants with potentially modifiable factors that may have contributed to the death; 75 out of 197 (38%) infants had >1 factor. The most common modifiable factor associated with mortality was delivery at a center without an appropriate level of support (n = 67, 10%) for the infant’s needs; 13 (2.0%) were born at home. One hundred forty-one (23%) infants needed transport. In 6 infants, transport was delayed, 2 each for weather, inadequate resources, and delay in consultation. Eight (1%) infants were difficult to intubate; 4 of these infants were born in hospitals without NICUs, and 4 were born in hospitals with NICUs and an attending neonatologist at the delivery.

Limited or no prenatal care (n = 57, 8.9%) was the second most common modifiable factor associated with mortality. In 35 out of 641 (5.5%) infants, the mother had no prenatal care, and in 22 out of 641 (3.4%) prenatal care was limited (=2 visits). Other perinatal modifiable risk factors included the following:

- Cardiovascular collapse: 3
- Cardiopulmonary arrest: 5
- Respiratory failure: 61
- Cardiopulmonary failure: 12
- Cardiac arrest: 8
- Cardiorespiratory failure: 5
- Progressive respiratory failure: 3
- Cardiovascular collapse: 3
- Cardiorespiratory collapse: 3
factors included the following: 101 (16%) mothers smoked tobacco during pregnancy, 47 (7.3%) used nonprescription drugs, and 28 (4%) had a history of alcohol abuse. Drug screens were positive in 41 (6.4%) mothers or their infants. Two mothers who used drugs left the hospital against medical advice, only to return and deliver precipitously. Sixty-nine (11%) mothers were <20 years old.

One hundred thirty-seven (27%) mothers of 501 infants born at <34 weeks’ EGA did not receive antenatal glucocorticoids. The most common reason provided was the urgent need for delivery or no prenatal care (n = 97 out of 501, 20%); however, in 40 out of 501 (8.0%) preterm infants there were no contraindications to maternal antenatal steroids, yet they were not given.

Hospital-acquired infections were reported in 31 (4.8%) infants. There were 22 (3.4%) infants with a report of an adverse event, and although most were not the immediate cause of death, the associated complication may have contributed to the death. In 5 infants, the diagnosis and treatment of sepsis was delayed: 3 died within 7 days after birth (2 had Escherichia coli, and 1 had Haemophilus parainfluenzae), and 2 died after 7 days (1 had congenital herpes, and 1 had methicillin-resistant Staphylococcus aureus). Intubation was difficult and delayed in 5 infants. Three preterm infants had profound hypothermia (<34°C); in 2, hypothermia developed before transport to level 1 hospitals, and in 1 the infant was hypothermic after returning from the operating room. In 3 infants, NICU-specific feeding protocols were not followed and were considered to have contributed to NEC. In 2 infants, the diagnosis of pericardial effusion associated with indwelling central lines was delayed; in 1 case (infant with gastrochisis), the associated tamponade was thought to be the cause of death. In the other case, the pericardial effusion was treated successfully with pericardiocentesis, and the death was attributed to hypoplastic left heart syndrome. One infant died of surgical complications for Hirschsprung disease, and 1 infant died after placement of a gastrostomy tube from complications of peritonitis. An infant with hypoplastic left heart died during cardiac catheterization. There was a delay in providing blood for 1 infant with profound anemia due to fetomaternal hemorrhage.

**DISCUSSION**

The factors associated with death in infants admitted for NICU care are multifactorial and diverse, and they change with EGA. At lower gestational ages, mortality is most commonly caused by extreme prematurity and its complications, namely RDS, IVH, NEC, and sepsis. With increasing EGA, the etiology of mortality shifts to HIE and genetic and structural anomalies. Efforts to decrease NICU mortality in premature infants should therefore focus on preventing or delaying preterm birth and optimizing therapies that may decrease IVH, NEC, RDS, and sepsis. In more mature infants, targets should include preventing and managing HIE and defining optimal management strategies for infants with nonlethal anomalies.

Eighty-six percent of infants who died were <37 weeks’ EGA at birth, and 36% were <25 weeks. The most common modifiable factor associated with mortality was the delivery of an infant at a center without appropriate support (10%). For prematurely born infants, administration of antenatal steroids and management by maternal-fetal specialists increase survival.5,6 A substantial percentage of extremely premature infants were offered care but died despite intensive care. Recent studies demonstrate variability in the prenatal care offered to such infants7,8 and suggest that improvements can be made.

Respiratory failure, sepsis, IVH, and NEC are often the cause of death and are modifiable events (eg, through use of antenatal steroids). Addressing public health, organizational, and medical care issues in the perinatal period, ensuring good access to prenatal care, promoting delivery of at-risk infants at centers with appropriate neonatal care, and consulting with high-risk maternal-fetal specialists could reduce mortality in prematurely born infants. Our findings emphasize the importance of close collaboration between obstetrics and neonatology to decrease NICU mortality from prematurity.

The primary cause of death on the death certificate was commonly misleading. Although the most common causes of death were related to complications of prematurity, its classification as a cause of death has limited our ability to modify preventable causes of death. It is often difficult to assign a single event as the cause of death, and many infants have confounding factors associated with their death. Also, the accuracy of death certificates is hampered by the requirement that they be completed shortly after death. There is no mechanism to improve the accuracy of the death certificate through revision after return of additional pertinent information or autopsy results. Having accurate information on causes of death is essential for evaluating potential solutions.9

Our study has limitations. A root cause analysis may not identify all the factors associated with an infant’s death. Only 74 infants had an autopsy performed, and in 53 out of 74 (72%) an important finding was noted. It is likely we missed some important factors, such as the expertise of the health care providers providing care, underlying family beliefs and health care decisions about comfort care, and missed diagnoses.

The findings in this study have implications for how NICUs should
conduct quality improvement efforts related to mortality. The development of a mortality database for NICUs that focuses on the issue of preventability and modifiable factors (public health, organizational, and medical) affecting mortality may advance our understanding of causes of death in the NICU.

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