ARTICLE

How Infants Die in the Neonatal Intensive Care Unit

Trends From 1999 Through 2008

Julie Weiner, DO; Jotishna Sharma, MD; John Lantos, MD; Howard Kilbride, MD

Objective: To determine whether trends toward decreasing use of cardiopulmonary resuscitation at the time of death and increasing frequency of forgoing life-sustaining treatment had continued, as few studies quantifying mode of death for hospitalized infants have been conducted in the last 10 years.

Design: Retrospective descriptive study.

Setting: Regional referral neonatal intensive care unit.

Participants: Infants who died from January 1, 1999, to December 31, 2008. Infants were categorized into following categories: (1) very preterm (≤32 weeks' gestation); (2) congenital anomaly; and (3) other.

Main Outcome Measures: The primary outcome was level of clinical service provided at the end of life (care withheld, care withdrawn, or full resuscitation).

Results: For 10 years, 414 neonatal patients died. Of these, 61.6% had care withdrawn, 20.8% had care withheld, and 17.6% received cardiopulmonary resuscitation. The percentage of deaths that followed withholding of treatment rose by 1% per year ($P=.01$). Most of this change was accounted for by withholding of therapy in the very premature group.

Conclusion: During the 10-year period, the primary mode of death in this regional referral neonatal intensive care unit was withdrawal of life-sustaining support. When death is imminent or medical care is considered futile, the approach is thought to provide a peaceful, controlled setting. Significant increase in withholding of care suggests improved recognition of medical futility and desire to provide a peaceful death.

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Duff and Campbell[1] first described withdrawal of care in their 1973 groundbreaking study of neonatal deaths. Approaches to end-of-life decisions have changed over time and vary among neonatal intensive care units (NICUs). Currently, most childhood deaths in the United States occur during the neonatal period and most neonatal deaths follow a decision to withhold or withdraw life-sustaining treatment.[2,3] In 12 recent studies of modes of death in NICUs, the proportion of deaths that followed decisions to forgo treatment ranged from 25% to 93%.[3-14]

A few studies have looked at trends in end-of-life NICU decisions. Hagen et al,[3] comparing a 2-year cohort from 1987-1988 and 1997-1998, alluded to changes over time in deaths at a referral tertiary NICU. They found that more deaths followed decisions to forgo life-sustaining treatment in the later period compared with the former (23% vs 64%; $P<.001$). Singh et al[5] found similar trends—the percentage of infants who had "do not resuscitate" orders increased between 1988 and 1998 from 39% to 56%. The percentage of infants who had mechanical ventilation withdrawn increased from 10% to 42% during these years.

There have been few such studies recently. We questioned whether the trends in the 1990s toward decreasing use of cardiopulmonary resuscitation (CPR) at the time of neonatal death had continued. We hypothesized that withdrawal and withholding treatment had continued to increase over the last 10 years.

METHODS

This study is a retrospective descriptive study involving infants who died in the NICU at Children's Mercy Hospital, a regional referral center without an on-site delivery service, from January 1, 1999, to December 31, 2008. The referral base comprised urban, rural, and subur-

Author Affiliations:
Departments of Neonatology, Children's Mercy Hospital (Drs Weiner, Sharma and Kilbride) and Pediatrics, Children's Mercy Bioethics Center (Dr Lantos), University of Missouri, Kansas City.

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ban populations, with no change in referral pattern during the 10-year study period. There were 417 infant deaths in the NICU during this time period. The medical records of all infants were reviewed. The study was determined to be exempt by the Pediatric Institutional Review Board of Children's Mercy Hospital.

Independent variables collected were: maternal age, gestational age, birth weight, diagnosis, sex, and age at death. We categorized the admission diagnosis broadly so that subjects all fit into 1 of the following 3 categories: (1) very preterm (≤32 weeks' gestation); (2) congenital anomaly (included preterm and term infants); and (3) other (this category included infants born at >32 weeks without congenital anomalies). Diagnosis was determined by documentation in the medical record at the time of death. The very preterm group and the other group were then separated into specific diagnoses: sepsis, hypoxic-ischemic encephalopathy, necrotizing enterocolitis, respiratory insufficiency, intracranial bleeding, extreme prematurity, or other.

We used 3 categories to describe the mode of death: (1) full resuscitation; (2) treatment withheld; or (3) treatment withdrawn. Full resuscitation included patients who received CPR at the time of death. Withholding of treatment was defined as withholding potentially life-sustaining treatment, which included not only withholding CPR but also not providing additional interventions (ventilator changes despite hypoxemia, no additional therapies despite hypotension, withholding artificial feedings). Withdrawal of intervention was defined as infants being removed from ventilator, continuous positive airway pressure, or supplemental oxygen. The treatment withdrawn category was further subdivided into stable and unstable, using criteria described by Verhagen et al.[4] Unstable was defined as having any 2 of the following criteria: persistent desaturation despite 100% oxygen on mechanical ventilation, hypotension despite volume infusion and inotropes, protracted bradycardia, or anuria for more than 24 hours.

Parental involvement in end-of-life decision making was determined by review of medical record documentation of discussions with parents regarding a plan for the infant's death. Mode of death and diagnosis at time of death were obtained for all infants. All documentation concerning end of life was reviewed including documentation by physicians, social workers, chaplains, and nursing staff. Some variables were more difficult to obtain owing to insufficient documentation. Extent of parental involvement, use of family-care conferences, and involvement of a multidisciplinary team were not well documented in some medical records. If a discussion with the family regarding the end of life occurred, either in a family care conference, in person or via phone, or if parents were documented as present at time of death, they were counted as being involved in the end-of-life decision. The primary outcome was mode of death: care withheld, care withdrawn, or full resuscitation.

Continuous variables were analyzed using analysis of variance with Tukey post hoc comparisons or Wilcoxon rank sum tests, where appropriate. Categorical variables were analyzed with χ^2 or Fisher exact tests. Linear regression and R^2 were used to evaluate trends. A significance level of $P \leq .05$ was used. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

There were 7240 NICU admissions from 1999-2008. Thirty-seven percent of admissions were very preterm; 23% of these infants also had major congenital anomalies. Overall, 36% of admitted infants had a congenital anomaly (**Table 1**).

Table 1. Neonatal Intensive Care Unit Admissions and Deaths, 1999-2008

Category	No. (%) All Admissions (n=7240)	No. (%) Deaths (n=414[a])
Diagnostic categories		
Very preterm (≤32 wk)	2063 (28)	146 (35)
Congenital anomaly	2570 (36)	185 (45)
Very preterm	616	32
Other[b]	2607 (36)	83 (20)

[a] Excludes 3 deaths (see text).
[b] "Other" refers to those of greater than 32 weeks' gestation without congenital anomalies

Four hundred seventeen infants died in the NICU during the 10-year time period. Three were excluded because they were atypical NICU admissions. Two of these were admitted to the NICU postcardiac surgery unit for extracorporeal membrane oxygenation at 8 months and 2 years of age because, at that time, extracorporeal membrane oxygenation at our institution was only done in the NICU. The other infant was admitted at 2 months of age with group B streptococcal sepsis and died within 24 hours of admission. The remaining 414 infant deaths were included in this study. Forty-five percent of the deaths were due to major congenital anomalies; 17% of these infants were also very preterm. Thirty-five percent of the deaths were of very preterm infants without congenital birth defects.

Of the infants who died with a birth defect, the leading diagnoses were congenital heart disease (38.4%), congenital diaphragmatic hernia (21.1%), and trisomies 13/18 (11.4%). Cause of death in the very premature infant category included extreme prematurity (35.6%), necrotizing enterocolitis (26.0%), intraventricular hemorrhage (8.2%), respiratory insufficiency (12.3%), and sepsis (9.6%). These proportions remained stable throughout the study period. Demographics of the infants who died are noted in **Table 2**.

The primary mode of death in the NICU was withdrawal of therapy. During this 10-year period, 61.6% of infant deaths followed withdrawal of therapy, 20.8% followed withholding of therapy, and 17.6% died despite attempted CPR (Table 2). Within the treatment-withdrawal group, approximately equal numbers of infants were considered unstable vs stable at the time of death (52.2% vs 47.8%) based on Verhagen et al[4] criteria and there was no significant change in the stable and unstable categorization during the 10-year time period. Patients who received CPR at the time of death had a lower gestational age than those who did not (30.4 vs 33 weeks; $P=.001$). There were no significant statistical relationships between maternal age, infant sex, or age at time of death and mode of death (**Table 3**). During the 10-year period, the percentage of deaths that followed withholding of life-sustaining treatment increased. **Figure 1** displays the percentage of each mode of death for all infants. Infant deaths due to withholding of treatment increased on average by 1.03 death per year ($P=.01$). This change was primarily accounted for by increased with-

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Table 2. Demographics of Neonatal Intensive Care Unit Deaths, 1999-2008

Characteristic	Very Preterm (n=146)	Congenital Anomaly (n=185)	Other (n=83)	Total (N=414)
Gestational age, mean (SD), wk	25.6 (2.4)	35.9 (3.6)	37.6 (2.2)	32.6 (6)
Range	22-32	24-42	32-41	22-42
Birthweight, mean (SD), g	833 (384)	2554 (901)	3092 (804)	2055 (1182)
Range	344-2800	380-6700	1600-6450	344-6200
Age at death, mean (SD), d	37 (59)	20 (32)	23 (32)	26 (44)
Range	1-279	1-233	1-172	1-279
Sex, %				
Male	56	61	60	59
Female	44	39	40	41
Maternal age, mean (SD), y	25.7 (6.4)	27 (6.8)	26.9 (6.1)	26.5 (6.4)
Range	15-43	18-44	18-42	15-44
Mode of death, No. (%)				
Care withdrawn	77 (52.7)	118 (63.8)	60 (72.3)	255 (61.6)
Care withheld	31 (21.3)	43 (23.2)	12 (14.5)	86 (20.8)
Cardiopulmonary resuscitation	38 (26)	24 (13)	11 (13.2)	73 (17.6)

Table 3. Mode of Death for Neonatal Intensive Care Unit Patients, 1999-2008

Characteristic	Care Withdrawn (n=255)	Care Withheld (n=86)	CPR (n=73)	*P* Value
Gestational age, mean (SD), wk	33.4 (5.8)	32.4 (5.8)	30.4 (6.4)	<.001[a]
Birth weight, mean (SD), g	2213 (1175)	1969 (1180)	1633 (1087)	.30
Range	344-6450	355-6700	435-4920	
Age at death, mean (SD), d	23 (37.8)	35.2 (51.3)	30.1 (54.3)	.07
Range	1-240	1-269	1-279	
Maternal age, mean (SD), y	27.0 (6.7)	25.8 (6.1)	25.8 (5.8)	.24
Range	15-44	15-41	16-40	
Parent-directed end-of-life care, %	95.7	93.0	46.6	<.001[b]

[a] *P* value significant for mode of death and gestational age for care withdrawn and cardiopulmonary resuscitation (CPR).
[b] *P* value significant for mode of death and parent-directed end-of-life care.

holding of therapy for deaths in the very preterm group. **Figure 2** displays the percentage of very preterm–infant death for each mode of death. For very preterm infants, deaths following withheld treatment increased by 0.7 per year ($P=.04$). During the 10-year period, withholding care significantly increased from less than 10% to more than 30% ($P<.001$). During the same time period, use of CPR at death tended to decrease ($P=.07$). For infants who died with congenital anomalies and the other category, there were no significant changes in mode of death over time.

As documented in the medical records, parents were involved in the decision concerning mode of death 86.5% of the time. The goal for end-of-life decision making in the study NICU included use of a multidisciplinary team approach, with parent involvement a high priority. Family care conferences involving physicians, neonatal nurse practitioners, nurses, social workers, chaplains, and family members were held when needed for all critically ill infants as parents were available. Conferences allowed for discussion of medical information and options regarding care strategies for families to consider. Decisions concerning the end-of-life process were made jointly with the parents and medical team in accordance with the Committee on Fetus and Newborn statement concerning withdrawal of support in newborns.[15] During the 10-year study period, the very preterm group had the lowest parent-directed end-of-life care (79%), while the other group was more likely to have parents active in the decision at time of death (96%; $P<.001$). Parents were least likely to participate in end-of-life planning when the mode of death was full resuscitation (47%; $P<.001$). For infants with withdrawn or withheld treatment, parents directed the end-of-life decision 96% and 93% of the time, respectively. Parental involvement in guiding mode of death for preterm infants increased from 41% in 1999 to 94% in 2008 ($P=.04$).

COMMENT

During the 10 years, the primary mode of death in this regional referral NICU was withdrawal of life-sustaining support, representing nearly two-thirds of NICU deaths. This finding was unchanged through the 10-year study period. Withdrawal of support remained the leading mode of death for all infant deaths in the NICU as well as for each diagnosis category. This finding is similar to other recent studies indicating that removal of life-sustaining support is the primary neonatal mode of death, ranging from 58% to 75%.[3,7,9] This approach represents a change from Duff and Campbell's[1] original descrip-

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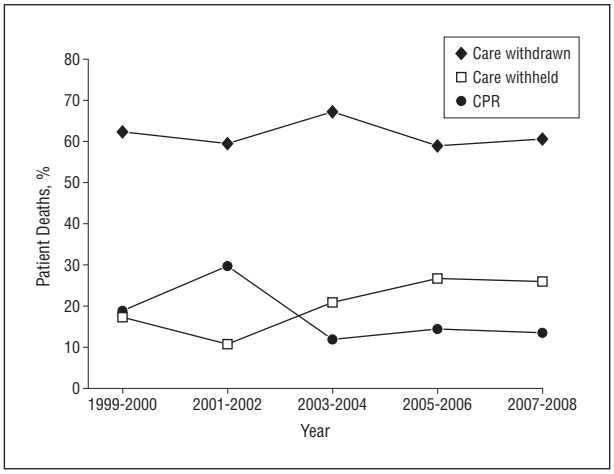

Figure 1. Mode of death for all neonatal intensive care unit deaths over 10 years.

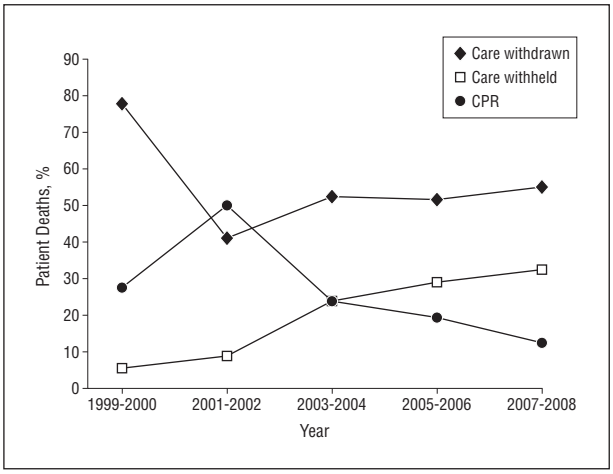

Figure 2. Mode of death for very preterm infants over 10 years.

tion of neonatal death, with 86% following full resuscitation. Studies from 1988 also indicate withdrawal of treatment was the mode of less than 20% of neonatal deaths; however, by 1998 this mode was approximately 40% of all NICU deaths.[3,5] Withdrawal of life-sustaining treatment remains the primary mode of death for infants in the NICU setting, with no apparent change during the last decade at our institution.

Although there was no change in frequency of withdrawal of treatment in our study during the last decade, there was a significant increase in withholding of treatment for very preterm infants. At the beginning of the decade, about 10% of preterm infants who died had treatment withheld. By the end of the period, withholding treatment was about as frequent for very preterm infants as for those with congenital anomalies (>25% of cases). During the same period, in our NICU, there was a concomitant declining trend for full resuscitation prior to death. There are few published data to compare with these findings. Most studies of neonatal deaths do not clearly distinguish withholding from withdrawing care, so comparable analyses are not available. One study by Singh et al[5] suggested that withholding of CPR in the NICU decreased over time (15% of CPR withheld in 1998 compared with 4% responsible for NICU deaths in 1988). In that study, the authors combined categories of withholding and withdrawing of treatment and showed an increase in these modes.

Why might physicians be more likely to withhold treatment? Although this change in end-of-life care could reflect patient or parent differences over time, those explanations would seem unlikely because the referral pattern, maternal age, admitting diagnoses, and condition at time of death did not change over the study period. The change seen in management of death would seem more likely to account for a change in physicians' practice. In 2000 and 2003, statements from the American Academy of Pediatrics and the Institute of Medicine called for improvement in care for the dying neonate, creating greater awareness among caregivers regarding the end-of-life process.[16,17] More recently, the American Academy of Pediatrics' Committee on Fetus and Newborn[15] indicated that there is no ethical difference between withdrawal and withholding of an intervention. When death is imminent or medical care is considered futile, the goal is to provide a peaceful, controlled setting for the infant and family. The increased use of withholding care (not only withholding CPR but also avoidance of additional life-prolonging interventions) may suggest improvement in earlier recognition of medical futility and a desire to provide a peaceful death for the dying infant.

In this study, parental input at the time of the infant's death varied based on mode of death and diagnosis. Variation in parental involvement occurred in spite of routinely making available family conferences for seriously ill infants, offering parents the opportunity to review medical management and discuss options for end-of-life care. Less than half of the parents of infants who died with full resuscitation provided input regarding their wishes for their infant's mode of death. In some cases, acute deterioration prior to death may account for the lack of parental direction at the time of death. However, during the 10-year study period, an increase in withholding of treatment for very preterm infants was accompanied by increase in parental direction at time of death. It is unclear from our data whether the greater parent involvement may have resulted in change of mode of death or whether greater use of redirection of care resulted in more parental involvement for these infants.

Study limitations include the retrospective study design, which meant reliance on review of medical records for details of care. Information regarding communication between the physicians and families may not be fully documented, cofounding interpretation of that variable. In some cases, details of the death circumstances, including determining terminal and nonterminal redirection of care, were difficult to assess. However, these limitations of medical record review would apply equally for the entire 10-year period, thus not affecting the interpretation of changes over time. This study is of a single referral NICU, making generalizability difficult. However, our study was able to obtain its goal of illustrating end-of-life practices in a large cohort of patients over a 10-year period and generate further discussions on this important topic.

In conclusion, we were able to describe circumstances surrounding the dying neonate at one regional

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referral level IIIc NICU. We found the primary mode of death in our NICU was withdrawal of life-sustaining support. Over time there has been an increase in withholding of care, accompanied by a decrease in resuscitation at the time of death for very preterm infants. Our study alludes to possible differences in mode of death for infants with congenital anomalies and very preterm infants. Further investigation of this relationship is warranted. Also, parental involvement should be a high priority in end-of-life decision-making. Further studies on the most effective ways to incorporate parents into this process for newborns are needed.

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Correspondence: Julie Weiner, DO, Children's Mercy Hospitals and Clinics, 2401 Gillham Rd, Kansas City, MO 64119 (jweiner@cmh.edu).
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The fact is the sweetest dream that labor knows.
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