

Mortality and Time to Death in Very Low Birth Weight Infants: California, 1987 and 1993

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ABSTRACT. *Background.* Recent advances in perinatal technology have dramatically increased the survival of very low birth weight (VLBW) infants (<1500 g). The possibility that these advances may also prolong the time to death and increase pain and suffering has been of concern, but there have been no population-based evaluations of this issue.

Methods. Infant, neonatal, and postneonatal mortality rates and time to death for infants 500 to 749 g, 750 to 999 g, 1000 to 1499 g, and all VLBW infants born during 1987 were compared with those outcomes for infants born in 1993 using statewide California linked birth/death cohort files. To assess the effects of improved survival and changes in time until death, we calculated the total days of life preceding an infant death per 1000 live born infants (TDD).

Results. VLBW infants comprised .96% of California's live births in 1987 and .92% of those in 1993. Between 1987 and 1993, VLBW infant mortality rate decreased 28.4% (from 290.7 to 208.3 per 1000 live born VLBW infants), VLBW neonatal mortality rate decreased 30.3% (from 244.5 to 170.4), and VLBW postneonatal mortality rate decreased 25.3% (from 61.2 to 45.7 per 1000 VLBW alive at 28 days; $P < .05$ for each rate). Infant mortality rates decreased by 18.8% (718.1 to 583.0 per 1000) for infants 500 to 749 g, 43.3% (375.1 to 202.6) for infants 750 to 999 g, and 40.1% (127.9 to 76.7) for infants 1000 to 1449 g ($P < .05$ for each group). Neonatal mortality and postneonatal mortality rates also decreased in all 3 VLBW subgroups. These reductions in mortality rates were not accompanied by a significant difference in the distribution of times to death or a significant increase in the average time to death for all VLBW infants (22.0 vs 23.6 days) or for those with birth weights of 500 to 749 g (12.7 vs 71.5 days). Reduced mortality in larger infants was accompanied by an increase in the average time to death, from 24.3 to 32.5 days in infants 750 to 999 g and from 32.3 to 47.0 days in infants 1000 to 1449 g. TDD decreased from 6410 to 4908 days for all VLBW infants. TDD was also reduced 26.4% (2401 days), 24.3% (2115 days), and 22.5% (1043 days) for the 3 VLBW birth weight groups.

Conclusions. Both mortality rate and timing of death are important when assessing the impact of advances in perinatal technology. Although the average time to death was significantly increased in VLBW infants weighing >750 g, between 1987 and 1993, advances in perinatal

technology dramatically decreased VLBW mortality. In the State of California in 1993, this resulted in 452 fewer VLBW deaths and 8233 fewer days preceding a VLBW death than expected. *Pediatrics* 2000;105(3). URL: <http://www.pediatrics.org/cgi/content/full/105/3/e37>; *very low birth weight, mortality, neonatal mortality, postneonatal mortality, infant mortality, time until death.*

ABBREVIATIONS. VLBW, very low birth weight; IMR, infant mortality rate; NMR, neonatal mortality rate; PNMR, postneonatal mortality rate; TDD, total days of life preceding an infant death per 1000 live born infants.

Over the last decade, advances in perinatal care, such as antenatal steroids and surfactant therapy, have resulted in a dramatic decrease in the mortality rate for very low birth weight (VLBW) infants.¹⁻⁷ Although the decrease in mortality rate is a clear benefit, there has been concern that these interventions could also "prolong dying, extend suffering, or use resources for infants who will eventually die."^{6,8} Several recent studies have examined the issue of time to death in the context of improved survival related to exogenous surfactant therapy. Although many hospitals experienced that most deaths occurred in the first days after birth with little prolongation of time until death,⁸⁻¹¹ at least 1 documented prolongation of time to death by 15 days in treated versus untreated infants.¹² To investigate the issue of modern technology and prolonged dying, Meadow et al⁸ reviewed their experience with the pattern of death in 429 infants weighing 400 to 1000 g who were admitted to the University of Chicago Medical Center Newborn Intensive Care Unit during 1989-1991. They conclude that the majority of these infants die quite early so that, at their institution, differences in birth weight-specific mortality vanish by day 4 of life. An important limitation of these studies is that they report the experience of specific institutions. As such, it is difficult to sort out the extent to which their findings reflect general effects of advances in perinatal technology in contrast to specific effects of perinatal technology within the context of the patient mix and treatment styles of these various institutions. The purpose of this study was to gain an understanding of the effects of advances in perinatal care on an entire population by investigating the mortality and time to death for all VLBW infants born in California during 1987 and 1993.

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Received for publication May 21, 1999; accepted Oct 21, 1999.

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METHODS

A linked birth/death cohort database, which includes all live born infants born in California, was used to compare outcomes of infants with birth weights of 500 to 1499 g born during 1987 or 1993, the earliest and most recent years for which these data were available. Development of this database to assess risk-adjusted perinatal outcomes in California hospitals has been previously described.^{13,14} On the linked birth/death certificate file, the time of death is given in hours for the first day after birth and in days thereafter. Infants who died during the first day after birth were given a time to death in hours. Those who died during the second day after birth were given a time to death of 48 hours, and those who died during the third day after birth were given 1 of 72 hours. The California linked birth/death file does not indicate if death occurred during the first hospitalization or a subsequent hospitalization.

All analyses were performed on the entire VLBW cohort (500–1499 g) and for each of 3 subgroups consisting of infants with birth weights of 500 to 749 g, 750 to 999 g, or 1000 to 1499 g. These weight groupings were chosen following preliminary analysis at 100-g intervals. We calculated birth weight-specific infant mortality rate (IMR = the number of deaths in the first 365 days per 1000 live births within the weight group), the neonatal mortality rate (NMR = the number of deaths in the weight group during the first completed 27 days after birth per 1000 live births within the weight group), and the postneonatal mortality rate (PNMR = the

number of deaths between 28 and 365 days after birth per 1000 survivors to 28 days within the weight group).

Average and median times to death and the cumulative percent of deaths at the end of the first 24 hours, at the end of the first week and at the end of the first month after birth were calculated. To estimate the overall effect of improved survival in the face of increased average time until death, we computed the total days preceding death per 1000 live births (TDD).

Considering 1987 and 1993 as 2 points in a large time period, we used the Kolmogorov-Smirnov goodness-of-fit test¹⁵ to compare the relationship between the cumulative percent of death curves and the standard National Center for Health Statistics method¹⁶ to test for significant differences in mortality. The use of the term significant indicates $P < .05$.

RESULTS

Between 1987 and 1993, the number of live births for the State of California increased from 508 740 to 589 630. This increase in births was nearly proportionate to the change in population, resulting in a slight increase in birth rate (18.4 to 18.7 live births per 1000). VLBW infants made up .96% of live births in 1987 and .92% in 1993.

Mortality statistics for VLBW infants in California

TABLE 1. Comparison of VLBW Mortality: California, 1987 and 1993

Birth Weight	All VLBW	500 to 749 g	750 to 999 g	1000 to 1499 g
*Live births				
1987	4888	908	1134	2846
1993	5482	1115	1249	3118
Deaths				
1987	1421	652	405	364
1993	1142	650	253	239
Percent of VLBW deaths				
1987	100.0	45.9	28.5	25.6
1993	100.0	56.9†	22.2†	20.9†
Infant mortality				
1987	290.7	718.1	357.1	127.9
1993	208.3†	583.0†	202.6†	76.7†
Neonatal mortality				
1987	244.5	654.2	296.3	93.1
1993	170.4†	531.8†	146.5†	50.7†
Postneonatal mortality				
1987	61.2	184.7	86.5	38.4
1993	45.7†	109.2†	65.7	27.4†
Average time to death (d)				
1987	22.0	12.7	24.3	36.3
1993	23.6	11.5	32.5†	47.0†
Median time to death (d)				
1987	1	.3	2	7
1993	1	.3	8	7
Total days preceding death (per 1000 births)				
1987	6410	9085	8693	4647
1993	4908†	6684†	6578†	3604†
Percent of deaths in 1st d (for weight group)				
1987	45.4	63.5	33.8	25.8
1993	48.7	62.2	31.2	30.6
Percent of deaths in 1st wk (for weight group)				
1987	66.8	80.7	60.3	49.2
1993	65.5	79.1	47.4†	47.7
Percent of deaths in 1st mo (for weight group)				
1987	84.1	91.1	83.0	72.8
1993	81.8	91.2	72.3†	66.1

* During 1987 and 1993, there were 508 740 and 589 630 live born births in California. Cohort includes all live born births weight 500 to 1499 g. Within each weight group, infant mortality is the number of deaths per 1000 live born births during the first 365 days of life; neonatal mortality is the number of deaths per 1000 live born births during the first completed 27 days of life; postneonatal mortality is the number of deaths from day 28 to day 365 per 1000 infants surviving the first 27 days of life.

† Significant difference between 1987 and 1993 ($P < 0.05$).

in 1987 and 1993 are compared in Table 1. The IMR and NMR decreased for all VLBW infants and for those in each weight stratum. PNMR for infants who survived the first 28 days were significantly lower in the 500- to 749-g and 1000- to 1499-g birth weight groups and for all VLBW infants. Because improvement in IMR was greatest among the larger infants, infants with birth weights of 500 to 749 g accounted for a significantly larger proportion of deaths among VLBW infants in 1993, and larger infants accounted for correspondingly smaller proportions of the VLBW infants who died. Unlike the experience reported by Meadow et al,⁸ we found that substantial differences in birth weight-specific mortality persisted through the first year after birth.

The average time preceding death during the first year after birth increased slightly for all VLBW, but this was not statistically significant and the median time until death did not change (Table 1). For VLBW infants as a group, the percentages of deaths that occurred in the first day, week, or month did not change. For infants 500 to 749 g, there was no change in the pattern of infant mortality between the 2 time periods, as reflected by virtually identical curves for cumulative percent of deaths over the first year of life (Fig 1A), despite a substantial reduction in mortality rates. For infants born at 750 to 999 g, there was a significant increase in both average and median times until death time. There was no difference between 1987 and 1993 in the percentage of the infant deaths that occurred in the first day, but deaths were substantially delayed among infants who survived that period (Fig 1B). Among infants with birth weights of 1000 to 1499 g, median time to death was unchanged but the average time until death increased by nearly 50%. For this weight group, a slightly greater proportion of deaths occurred during the first 24 hours in 1993. The increase in time to death occurred in infants who survived the first week and was most notable for those who survived the first month after birth (Fig 1C).

To estimate the effect on the entire population of increased average time until death in the face of improved survival, we computed the total days preceding death per 1000 live births. For all VLBW infants, TDD per 1000 decreased 23.4% from 6410 to 4908. Reductions of a similar magnitude (26.4%–22.5%) were seen in each weight group (Table 1).

DISCUSSION

With the recent dramatic advances in perinatal technology and VLBW survival, attention has turned not only to improvement in survival but also the pattern of death in those infants who were supported with advanced technologies but did not survive. Of major concern is the possibility that these technologies might prolong their time to death, thereby increasing pain and suffering. This possibility has both an intuitive and historic basis. The intuitive notion is that a technology that is capable of dramatically improving survival in infants who would have previously been expected to die may only be partially successful in some marginal infants. For these infants, the technology's partial success would be evi-

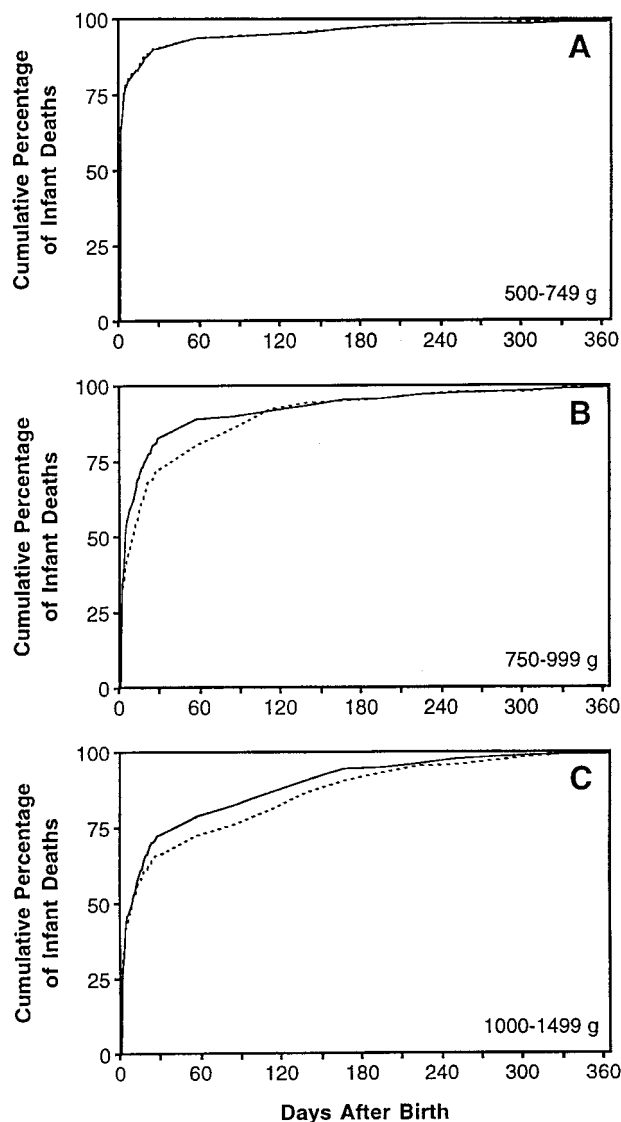


Fig 1. Cumulative percentage of infant deaths in 1987 (solid lines) and 1993 (broken lines) for infants born in California at birth weights of 500 to 749 g (A), 750 to 999 g (B), and 1000 to 1499 g (C). Cohorts include all live births in California during 1987 and 1993. An infant death is the death of a live born infant in the first 365 days after birth. The distributions of deaths within the first year after birth are significantly different between the 2 time periods for the groups with birth weights of 750 to 999 g and 1000 to 1499 g (Kolmogorov-Smirnov test; $P < .05$).

dent as an increase in the time and suffering preceding death. From a national historic perspective, there is evidence that advances in perinatal technology and regionalization of care have both decreased infant mortality and prolonged time until death.^{17–21} From 1950 to 1970, the period before the development of perinatal intensive care and regionalization, the IMR in the United States fell from 29.2 to 20.0 deaths per 1000 live births. The NMR decreased 26% (20.5 to 15.1), whereas the mortality rate per 1000 live births in the postneonatal period (PNMR = IMR – NMR) dropped 43.7% (8.7 to 4.9). During this period, the percentage of IMR accounted for by NMR rose from 70.2% to 75.5%, and the percentage of NMR accounted for by deaths during the first 7 days after birth rose from 86.8% to 90.1%, suggesting a reduc-

tion in average time to death.²² Wide dissemination and additional refinement of perinatal technology and regionalization of care between 1970 and 1987 was accompanied by a reversal of this trend. During this period, NMR fell by 57% (to 6.5 per 1000), whereas PNMR only decreased by 27% (to 3.6 per 1000). The larger decrease in NMR was accompanied by a decrease in the percent of IMR accounted for by NMR (75.5% to 64.4%) and by a decrease in the percentage of NMR accounted for by death during the first week after birth (90.1% to 83.1%). Although these changes could be accounted for by a more rapid advancement in the effectiveness of interventions aimed at the causes of neonatal mortality, there was also evidence that some deaths that would have been expected to occur during the neonatal period had been postponed into the postneonatal period.¹⁷⁻¹⁹

Beginning in 1987, rapid diffusion of new perinatal technologies dramatically improved survival of premature infants. A major concern was that this improved survival might also be accompanied by prolongation of time until death among nonsurvivors. Several analyses based on outcomes of VLBW infants at single or multiple institutions suggested that the time to death did not increase with the introduction of exogenous surfactant therapy.⁹⁻¹¹ However, these findings could be institution-specific, and 1 institution reported prolongation of time to death by 15 days in infants who received surfactant therapy.¹² To minimize the potential for institutional selection or practice biases, we performed a population-based comparison of mortality and time until death for all VLBW infants born in California during 1987 and 1993. Although these 2 years were chosen for convenience, they represent a time span in which major advances in perinatal care have been described.¹⁻⁴ The birth rate, proportion of VLBW births, and distribution of birth weights within the VLBW group did not change between these sample periods. There were significant decreases in NMR, PNMR, and IMR. During the study period, a 28.4% decrease in VLBW infant mortality resulted in statewide survival of 452 infants who would have died in 1987. There were no changes in average or median time until death or in the percentages of deaths occurring in the first day, week, or month. These results suggest that reduced mortality for VLBW infants was not associated with postponement of neonatal deaths into the postneonatal period in 1993.

When mortality is analyzed for different weight strata within the VLBW category, a more complex picture emerges. For the smallest infants (500-749 g), there was no increase in the average time to death (Table 1) or displacement in the cumulative mortality curve (Fig 1A), despite a 18.8% reduction in the mortality rate. For infants 750 to 999 g, a 43% reduction in the infant mortality rate was associated with an 8.2-day increase in the average time to death. Prolongation of time to death in these infants was apparent by the second day after birth (Table 1 and Fig 1B). In infants 1000 to 1499 g, a 40% reduction in the infant mortality rate was associated with a 10.7-day increase in the average time to death, although the median time to death was unchanged. This in-

crease in time to death was restricted to those infants who survived the first week after birth (Fig 1C).

These different patterns of changes in mortality for the 3 weight strata suggest that the new technologies responsible for reduction of infant mortality rates have different effects on mortality across weight strata. For the smallest infants, there was no increase in the average time to death. In this group, contrary to intuition, the ability of the newer technologies to increase survival seems to be an all or none phenomenon. However, as pointed out by Tyson and colleagues,²² the clinical approach to these small infants represents a complex decision based on a variety of factors, such as the probability of survival, the perceived pain and suffering associated with intensive care, and the quality of life for survivors. From this perspective, the modest increase in survival for infants 500 to 749 g (18.8%) and the stability of time preceding death could also be interpreted as resulting from a less aggressive application of new technologies to the care of these extremely immature infants. It is also important to determine whether the increased average time to death in the larger VLBW infants reflects prolongation of the time until death for individual infants as observed in the 1970s¹⁷⁻¹⁹ or is the result of preferential reductions in early rather than late mortality. Understanding the factors responsible for these different patterns will require an analysis of mortality stratified by postnatal age, birth weight, and clinical differences between infants who die early and those who die late. As a first step, we are in the process of examining differences in the demographics and causes of death in VLBW infants using the California linked birth/death data. However, this population-based dataset does not contain the detailed clinical information (maternal-fetal risk factors, condition at birth, initial response to therapy, etc) that may be essential for this analysis.

When assessing societal impacts of a new technology, it is crucial to account for its costs and adverse or undesired effects as well as its beneficial effects. Potential adverse social effects of advances in care of VLBW infants include increased pain and suffering during the initial hospital course, stress placed on family members, and long-term physical and functional impairments in survivors. Economic effects may include longer hospital stays or increased resource utilization. This information is not available on the California linked birth/death certificate, precluding examination in this study. However, the concern that these advances may increase fruitless suffering among VLBW infants can be addressed, at least in part, using this data. Although pain or suffering experienced during a course of neonatal intensive care may be acceptable when it results in survival of a healthy infant, an increase in suffering among infants who do not survive, suggested by the increase in the average time to death noted for VLBW infants with birth weights of 750 to 1499 g, is not so easily rationalized. In an attempt to give some context to an increased average time till death in the face of decreased mortality, we directly examined the TDD of a specific weight group. In California, advances in perinatal technology and neonatal care

between 1987 and 1993 resulted in a decrease in TDD of 2401, 2115, and 1043 days per 1000 live births weighing 500 to 749 g, 750 to 999 g, and 1000 to 1499 g, respectively. For all VLBW infants, TDD decreased from 6410 to 4908 days per 1000 live born VLBW infants. However, if time till death in 1993 had remained at 1987 levels, TDD per 1000 VLBW births would have decreased an additional 10.9% to 4210 days. This estimate (obtained by summing the products of each weight group's fraction of 1993 VLBW births, 1993 mortality, and 1987 average time to death) points out that the reduction of TDD between 1987 and 1993 was exclusively attributable to decreased VLBW mortality. It also gives a sense of the extent to which the potential reduction in TDD resulting from decreased mortality alone was compromised by increased time until death. It is important to note that TDD must not be used in isolation or serve as a primary objective of health policy because it is dependent on both mortality and times to death. Reduction in TDD could also be achieved by denying medical support to VLBW infants, permitting or promoting early deaths.

Although the increased time to death in the larger infants resulted in only 16% more days before death than would be expected without this change (4908 rather than 4210 days per 1000) the infants whose deaths are delayed, in effect, bear this cost of improved outcomes for those who do survive. Unfortunately, it is not easy to identify these infants prospectively. Those responsible for the care of VLBW infants must attempt to identify infants who will not benefit from aggressive intensive care as early as possible, to ensure their comfort, minimize the application of ineffective interventions, and avoid unnecessary prolongation of suffering for these infants as much as possible.

ACKNOWLEDGMENTS

We thank the Maternal and Child Health Branch, California Department of Health Services for their support of the Perinatal Profiles Database (Contract 97-11045).

We thank Malika Stoll, Amy Marks, and Connie Gee for their help in preparing this manuscript.

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Pediatrics 2000;105:e37

DOI: 10.1542/peds.105.3.e37

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