# Causes of death in neonatal intensive care units

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## Introduction

Of the approximately 130 million babies born each year, an estimated four million babies die in the neonatal period. Globally, the main causes of death are estimated to be preterm birth (28%), severe infections (26%) and asphyxia (23%). [1] New South Wales (NSW) is the most populous state in Australia with approximately 86,000 births per year. In 2006, 6,044 babies in NSW were registered to neonatal intensive care units (NICUs), representing 2.3% of total live births in that year. [2] Gestational age is highly correlated with birth outcomes including mortality. Each extra week of time spent in utero increases an infant's chances of survival significantly, and by 27 weeks of pregnancy, over 90% of infants will survive.

There are significant differences between common causes of death in the pre-term population (less than 37 weeks gestation) and the term population (37+ weeks gestation). The most notable difference is an approximate five-fold increase in deaths caused by congenital neurological malformations in the term population compared with the pre-term population [3]. Premature infants have a considerably higher chance of dying than full-term infants. However, improved neonatal care, particularly the widespread use of surfactant replacement and antenatal steroids, has almost halved neonatal mortality in many parts of the world. [1] Between 1985 and 1991 in the United States, the overall neonatal mortality rate declined from 5.4 to 4.0 per 1,000 live births. An understanding of causes of neonatal death and changes in mortality rates is critical for prenatal counselling, decision making, quality control and further improvement in management.

In NSW, newborn infants are admitted to NICUs under the following criteria: gestational age less than 32 weeks, birth weight less than 1,500 grams, need for mechanical ventilation for four hours or more, continuous positive airways pressure for four hours or more and/or major surgery, defined as opening of the body cavity.

Newborns admitted to NICUs are cared for by a highly specialised team of medical, nursing and allied health staff. Despite the level of sickness and intensity of morbidities of NICU patients, mortality rates are relatively low. Neonatal mortality rate is defined as the number of neonatal deaths per 1,000 live births and includes all deaths of infants within 28 days after birth.

Each neonate who dies in the NICU represents not only a financial cost to the community but more importantly, a significant emotional stress and grief for the involved parents and staff. Systematic audits are the first step in the descriptive epidemiology of neonatal mortality and a necessary means for identifying the cause(s) of death. [3] Accurate documentation of causes of neonatal death enables analysis of change in neonatal death rates and causes over time, and allows for assessment of their preventability through improved management. As such, it has been found that there have been substantial changes in the causes leading to death in the NICU. These changes may reflect the combined effects of prenatal diagnosis and changing community and medical attitudes. [4] Therefore, a NSW and Australian Capital Territory (ACT) state-wide audit is indicated to determine the common causes of death in NICUs, which will form the basis for continuing quality improvement and outcome evaluation.

## Epidemiology and common causes of death in the neonatal population

The proportion of deaths that occur in the neonatal period is increasing, reaching 38% in 2,000. [1] Three-quarters of neonatal deaths occur in the first week of life. The highest risk of death is on day one, with 25-45% of neonatal deaths occurring within the first 24 hours of life. An Irish study found that 89% of term infants in their 2004 cohort died within the first week of life, and the rest died between the seventh and 28th day of life. [5] In a cross sectional survey covering a population of 1,316,681, information was collected retrospectively for a one-year reference period on 30,473 births and 1,521 neonatal deaths from five rural sites in India. Of all neonatal deaths, 39.3% occurred on first day of life, and 56.8 % during the first three days, which highlights the importance of the first three days as the most hazardous phase of life. [6]

Globally, the main causes of death are estimated to be preterm birth (28%), severe infections (26%) and asphyxia (23%). [1] Of the remaining deaths, congenital anomalies account for 7%. The leading cause of infant death in the United States in 2004 was congenital malformations, deformations and chromosomal abnormalities (congenital malformations), accounting for 20% of all infant deaths. Disorders relating to short gestation and low birth-weight, not elsewhere classified, were second, accounting for 17% of all infant deaths. This was followed by Sudden Infant Death Syndrome (SIDS), accounting for 8% of infant deaths. The fourth and fifth leading causes - newborns affected by maternal complications of pregnancy (maternal complications) and accidents (unintentional injuries) - accounted for 6% and 4% respectively of all infant deaths in 2004. Together the five leading causes accounted for 55% of all infant deaths in the United States of America (USA) in 2004, [7] as illustrated in Figure 1. On the other hand, an Irish neonatal mortality survey found prematurity to be the leading cause of death in 2004, accounting for 45% of total deaths. In 2002, 1999 and 1987 prematurity accounted for 36%, 37% and 40% respectively. In all previous years congenital malformations were the leading cause of death. Congenital malformations accounted for 32% of the total cause of death in 2004. Seventy-eight percent of these died within the first week of life. [5]

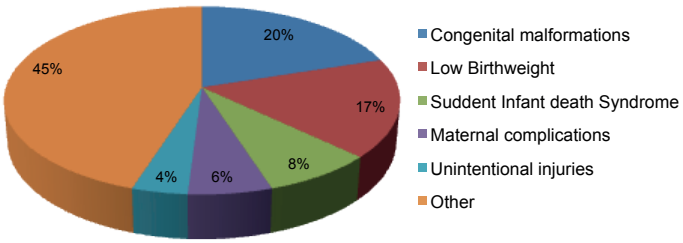


***Figure 1.*** *Profile of leading causes of death in USA in 2004. [7]*

## Comparison of preterm and term population-mortality rates and causes of death

Gestational age is highly correlated with birth outcomes including mortality. Each extra week of time spent in utero increases an infant's chances of survival significantly and by 27 weeks of pregnancy, over 90% of infants will survive. Figure 2 details the percent survival at each gestational age. There are significant differences between common causes of death in the pre-term population and term population. The most notable difference is an approximate five-fold increase in deaths caused by congenital neurological anomalies in the term population compared with the pre-term population. [3] Other differences include an increased proportion of congenital malformation deaths and deaths in the 'other' category amongst term infants, compared with an increased proportion of cardio-respiratory deaths and deaths due to infection or gastrointestinal problems in the pre-term population. [8]

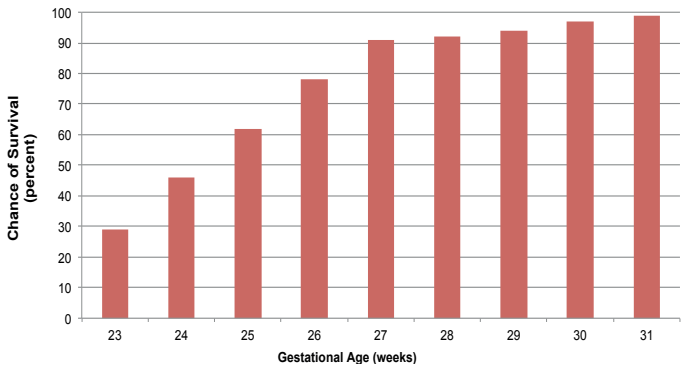


***Figure 2.*** *Percent survival at each gestational age. [9]*

An Irish study which examined a cohort of term infants in 2004 found that congenital malformations were the leading cause of death and accounted for 48% of total deaths. Chromosomal abnormalities and cardiac malformations were found to be the two leading groups of specific congenital malformations. Asphyxia was the second most common cause of death, occurring in 9% of the total deaths, which compares to 7.5% of deaths in 2002 and 8% of deaths in 1987. Other causes of death in term infants included infection, SIDS and splenic rupture (<1%). [5]

On the other hand, a Wellington study showed that just under half the total of deaths due to infection occurred in infants of less than 37 weeks gestation, even though such groups only make up 25% of all neonatal deaths. Four of six deaths due to bacterial infection were congenital. [10] A large proportion of cardio-respiratory deaths in the pre-term population may be indicative of the level of approach in different NICUs. The more aggressive the approach to resuscitation, the more likely deaths are caused by cardio-respiratory factors; in NICUs with a less aggressive approach, those same infants may die due to extreme prematurity without any viable chance of further survival. [4] Finally, extreme prematurity makes up the majority of deaths in the pre-term population while congenital malformation makes up the majority of deaths in the term infant population. [11]

Premature infants have a considerably higher chance of dying than full-term infants and at an earlier postnatal age. Tomashek *et al.*'s study [12] found that 38% of all neonatal deaths among late-preterm infants occurred during the early neonatal period (within seven days after birth), compared with 22% for term infants. Furthermore, late-preterm infants were nearly six times more likely than term infants to die during their first week of life (2.8 versus 0.5 deaths per 1,000 live births). Khashu *et al.*'s [13] population study compared the mortality of late preterm infants to those born at term. An analysis was performed of all singleton births between 33 and 40 weeks gestation (divided into two groups: late preterm (33-36 weeks) and term (37-40 weeks)) from April 1999 to March 2002 in the province of British Columbia, Canada. It was found that neonatal mortality rates were significantly higher in the late preterm group. In the Netherlands in 2006, [14] 1.3 million deaths were analysed and it was found that perinatal mortality was 9.8 per 1,000 total births (fetal mortality 6.8 per 1,000 births and early neonatal mortality 3.1 per 1,000 live births). The very preterm births (22.0-25+6 weeks of gestation) accounted for 29% of all perinatal mortality with a mortality risk of 935 per 1,000 births. Full-term births (≥ 37.0 weeks) accounted for 26% of all perinatal mortality with a mortality risk of 2.8 per 1,000 births. More than half (55%) of all infant deaths in the United States in 2004 occurred in infants born at less than 32 weeks gestation, when they only account for 2% of all live births. In addition, mortality rates for the late preterm population (34-36 weeks) were three times more than those of the term population. [15]

## Mortality rates for varying gestational age groups in the very preterm population

The pattern of survival differs for varying gestational groups, with survival rates increasing with gestational age. Serenius *et al.* [16] stated that survival rates are 43%, 63%, and 77% at 23, 24, and 25 weeks gestation respectively amongst infants delivered in two Swedish tertiary centres in 1992-1998. Table 1 summarises the findings of a prospective observational study of all infants with a gestational age of 22 to 27 weeks who were born in Norway in 1999 and 2000 which revealed similar results. [17] The survival rates were found to be increasing with gestational age from 0% for <23 weeks in both cohorts to 82% and 93% for 27 weeks in the 1999 and 2000 cohorts respectively.

***Table 1.*** *Survival rates for varying gestational groups in two cohorts, 1999 versus 2000. [17]*

| Gestation (weeks) | 1999 cohort | 2000 cohort |
|---|---|---|
| <23 | 0% | 0% |
| 23 | 16% | 39% |
| 24 | 44% | 60% |
| 25 | 66% | 80% |
| 26 | 72% | 84% |
| 27 | 82% | 93% |

Inversely, the mortality rate decreases with increasing gestational age as indicated in Synne *et al.*'s study [18] where the mortality rate was 84% at 23 weeks, 57% at 24 weeks, 45% at 25 weeks, 37% at 26 weeks, 23% at 27 weeks, and 13% at 28 weeks gestational age, amongst infants <30 weeks at British Columbia's tertiary centre from 1983 to 1989. Furthermore, for each gestational age, mortality rate versus birth weight plots showed a decreasing mortality rate with increasing birth weight, except for infants who were large for gestational age. [18] A prospective cohort study of preterm infants born at Royal Women's Hospital, Melbourne from January 1994 to December 1996 describes the mortality rate for preterm infants (23-36 weeks gestation). The total mortality rate was found to be 4.8%, which diminished rapidly between 23 and 28 weeks gestational age (from 64.5% at 23 weeks to 4.0% at 28 weeks), then more slowly, to reach 0.4% at 36 weeks. [19]

Changes in mortality rates overtime and the relationship between causes of death and postnatal age of death

Between 1985 and 1988 in the USA, the overall neonatal mortality rate declined by approximately 12%, from 5.4 to 4.7 per 1000 live births. Between 1988 and 1991, the overall neonatal mortality rate further declined by approximately 15% from 4.7 to 4.0 per 1,000 live births. The greater decline in the neonatal mortality rate in the later period resulted primarily from the reduction in the rate of mortality caused by respiratory diseases. [20]

Premature infants have a considerably higher chance of dying than full-term infants. However, improved neonatal care, particularly the widespread use of surfactant replacement and antenatal steroids has almost halved neonatal mortality in many parts of the world. [1] Stoelhorst *et al.* [21] found that the neonatal mortality rate in the USA declined from 4.63 per 1,000 live births in 2003 to 4.52 in 2004, while Gonzales *et al.* [22] found that the neonatal mortality rate in Chile between 1990 and 2000 decreased from 8.3 to 5.7 per 1,000 live births during that period. Furthermore, an Irish study found that the mortality rate decreased from 5.3 per 1,000 live births in 1987, to 3.1 per 1,000 live births in 2002, to 2.9 per 1,000 live births in 2004. [5] Kramer *et al.* [23] presented infant mortality rates for all live births in Canada and the United States for 1985 and 1995, and 1985-1987 and 1992-1994. Mortality rates were lower in Canada for both time periods. Table 2 illustrates the decreases in infant mortality over the two time periods.

***Table 2.*** *Infant mortality per 1,000 births amongst all live births, United States 1985 and 1995, and Canada 1985-1987 and 1992-1994. [23]*

| Age Group | United States | | Canada | |
|---|---|---|---|---|
| | 1985 | 1995 | 1985-1987 | 1992-1994 |
| Early Neonatal (age 0-6d) | 5.7 | 4.0 | 4.1 | 3.3 |
| Late Neonatal (age 7-27d) | 1.1 | 1.0 | 0.9 | 0.7 |
| Postneonatal (age 28-364d) | 3.6 | 2.6 | 2.9 | 2.2 |
| Total | 10.4 | 7.5 | 7.8 | 6.2 |

The reduction in mortality is primarily due to increased survival of infants born below 1,500g birth-weight and 32 weeks' gestational age in the periods before and after institution of surfactant therapy. [23] This is further explored in Wong *et al.*'s study [10] which suggests that mortality rates for term and preterm infants <37 weeks gestation were stable with a significant decrease in the mortality rate for infants <24 weeks gestation observed. For all infants, there was also a decrease in death due to congenital anomaly and prematurity but an increase in death due to infection and neurological causes.

Luke and Brown [24] conducted a study which also demonstrated the significant reduction in infant mortality achieved during the 1990s by comparing two cohorts, 1989-1991 and 1999-2001. The reductions were greater for early preterm (<33 weeks) compared with moderate preterm (33-36 weeks) and term (37-43 weeks) birth, [24] which is in line with the results of Kramer *et al.*'s study. [23,24] In the 25 to 28 week gestational age group, the percentage of neonatal deaths decreased from 13.1% to 12.1%, in the 29 to 32 week gestational age group it decreased from 7.0% to 6.3%, in the 33 to 36 week gestational age group it decreased from 12.3% to 12.2%, in the 37 to 40 week gestational group it decreased from 33.0% to 31.8%, and in the 41-43 week gestational age group, it decreased from 10.8% to 6.7%. [24]

As aforementioned, the widespread use of surfactant replacement and antenatal steroids in the early 1990s greatly contributed to reductions in neonatal mortality rates. Stoelhorst *et al.*'s [21] comparison of two cohorts from 1983 and 1996-1997 of very preterm infants highlights significant changes which occurred over that period of time and the consequent reductions in mortality. The overall mortality rate decreased from 30% in the 1983 cohort to 11% in the 1996-1997 cohort, and the rate of mortality was lower across all gestational age categories for the 1996-1997 cohort, as illustrated in Figure 3.

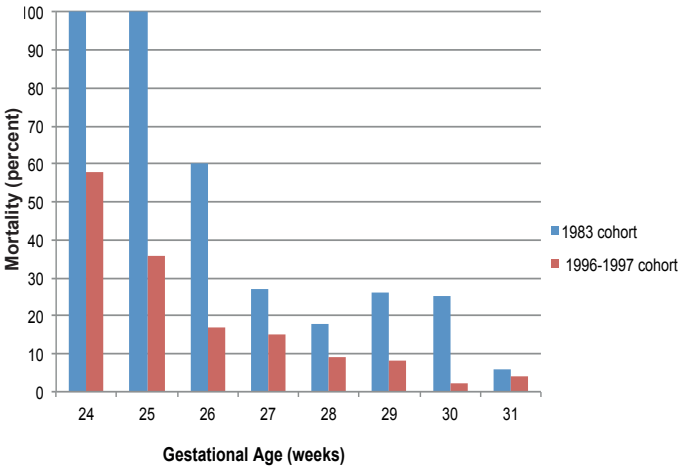


***Figure 3.*** *Mortality according to gestational age in two separate cohorts. [21]*

In addition to the reduction in neonatal mortality rates, the comparison of the two cohorts also highlighted an increase in postnatal age of death overtime, and a lesser percentage of early neonatal death. In the 1996/1997 cohort, the non-surviving infants died after an average of 12.7 days, compared with 5.9 days for the 1983 cohort. Early neonatal death was 55% in the 1996/1997 cohort, with 34% of deaths occurring within the first 24 hours of life. This compares with 93% of early neonatal deaths in the 1983 cohort, and 71% within the first 24 hours of life. Late neonatal death (between seven and 28 days after birth) was 38% in the 1996/1997 group and 0% in the 1983 group. The most important cause of death in both groups was respiratory distress syndrome.

There is a distinct relationship between postnatal age of death and causes of death. Tomashek *et al.*'s study [12] from 1995 to 2002 found that between those years, rates of overall early neonatal mortality declined significantly in both late-preterm infants (by 22.2%) and term infants (by 28.6%). During the early neonatal period, congenital malformations, and intrauterine hypoxia and birth asphyxia were the two leading causes of death for both late-preterm and term infants. [25] Late-preterm neonates were nearly 19 times more likely than term infants to die of atelectasis, ten times more likely to die of maternal pregnancy complications and six times more likely to die of congenital malformations in the early neonatal period. Hydrops fetalis, disorders related to short gestation and low birth weight, and respiratory distress of the newborn were other important causes of early neonatal death. The overall late neonatal mortality rate did not change significantly between 1995 and 2002; however such rates were three times higher in late-preterm infants than in term infants throughout the study period. Congenital malformations and SIDS were the two leading causes of death in the late neonatal period. Other important causes of late neonatal death include necrotising enterocolitis and bacterial sepsis of the newborn. [12]

## Conclusion

Neonatal mortality continues to cause emotional grief and place a financial burden on the health system and the community. An understanding of causes of neonatal death and changes in mortality rates is critical for prenatal counselling, decision making, quality control and further improvement in management. Literature surrounding mortality rates and causes of death in the neonatal population does exist and suggests a decrease in mortality rates over the last decade, and highlights differences in causes of death for varying gestational age groups. Despite this, gaps in research have been identified and as such, it is indicated that a NSW state-wide audit be conducted to classify detailed, accurate and specific causes of death amongst the neonatal population. This will allow for the identification of trends, and to elicit

targets for intervention and aid in the improvement of neonatal care and resource allocation, specifically in NSW.

## Conflicts of Interest

None declared.

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