Preterm Birth: A Cost Benefit Analysis

Susan Rushing, SB, and Laura R. Ment, MD

Advances in prenatal and perinatal treatment of preterm and VLBW infants have dramatically increased the survival rate of these infants. Some interventions decrease long term sequelae associated with preterm birth, making them more cost-effective than other treatments. This paper reviews the cost-effectiveness of therapies targeted to protect the preterm brain. Birth in a center with a NICU improves survival and decreases the rate of severe neurologic disability. Administration of antenatal steroids increases survival and decreases rates of periventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress syndrome, and severe disability. Administration of antenatal steroids decreases costs per additional survivor. Addition of surfactant to the treatment of PT infants has also decreased treatment costs. Administration of surfactant is beneficial for symptomatic RDS but recognizes a greater benefit when given to infants younger than 30 weeks gestation prophylactically. Treatment with prophylactic indomethacin decreases the rate of intraventricular hemorrhage and results in cost savings in survivors. Postnatal administration of dexamethasone can lead to severe disability when administered before 7 to 10 days of life. Postnatal dexamethasone does not increase survival or decrease rates of chronic lung disease.

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Despite the development of sophisticated care techniques, the incidence of neurodevelopmental disability among the survivors of newborn intensive care remains high. As newborn special care enters its fifth decade, survival rates for very low birth weight (VLBW) infants have steadily increased, but the incidence of cerebral palsy (CP) has not changed over the past 10 years and, at age 8 years, over 50% of VLBW preterm children require special educational services and 15% have repeated at least one grade in school. These data suggest that the neurodevelopmental sequelae of preterm birth now represent a major pediatric public health problem. A recent analysis by the Center for Disease Control suggests that the average lifetime costs per person with mental retardation are $1,014,000; the average lifetime costs for each individual with CP are $921,000. These 2003 dollar figures reflect only the medical, educational and other support services used by persons with mental retardation or CP; they do not address the hidden costs of care for children with developmental issues, such as those associated with treating the psychosocial and family problems that may result.

As the gestational age at which perinatologists and neonatologists resuscitate VLBW and preterm infants decreases, the concern for prevention of injury to the developing brain increases. Periventricular brain injury, severe respiratory failure, the absence of antenatal corticosteroid exposure and delay in regaining birth weight are all strong predictors of significant disability in survivors. A number of advances have been made in the treatment of preterm infants that show promising survival and outcome benefits. The long term health sequelae of these therapies along with their significant cost have made their use the object of considerable scrutiny, however. We review the cost of treatments aimed at preventing severe disability in the VLBW preterm infant.

Neurodevelopmental Outcome of Preterm Birth

The sequelae of preterm birth have been well described. At age 8 years, more than 50% VLBW, preterm children require special assistance in the classroom, 20% are in special education, and 15% have repeated at least one grade in school. The incidence of those with CP ranges from 8 to 24%, depending on birth weight and birth year. Addition-
ally, 10 to 20% of infants with CP are reported to suffer significant cognitive handicaps. Several investigators have reported that prematurely born infants experience structural delay in postnatal brain development when compared with term neonates. Regions serving math and verbal skills appear especially vulnerable in the developing preterm brain.

## Assessment of Risk for Injury to Developing Brain

Critical to the implementation of prevention strategies is the identification of risk factors for injury to the developing brain. Thus, although several early studies reported that cognitive outcome was directly related to gestational age at birth, recent data suggest that medical risk factors may be equally important predictors of neurologic outcome. Chief among the medical risk factors are grades 3 to 4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and posthemorrhagic hydrocephalus. The incidence of IVH is inversely related to gestational age (GA), and parenchymal involvement of IVH is more common among infants with the lowest GAs. Current data suggest that 25% of infants born weighing 501 to 750 g and 11% born between 741 and 1000 g still develop grade 4 IVH. In the newborn period, infants with IVH are at risk for seizures and posthemorrhagic hydrocephalus; 5 to 10% of preterm infants with IVH suffer seizures and as many as 25 to 50% of infants with Grade 4 IVH experience posthemorrhagc hydrocephalus. Finally, mortality is higher in those infants with IVH compared with GA-matched subjects without IVH.

Infants with parenchymal involvement of hemorrhage suffer high rates (45 to 86%) of mental retardation and cerebral palsy. In Pinto-Martin’s study, grade 4 IVH was associated with CP [odds ratio (OR), 15.4; 95% CI 7.6 to 31.1]. Perhaps more importantly, recent data demonstrate that Grade 4 IVH is strongly associated with mental retardation at 2 to 9 years (OR ranging from 9.97 to 19.0). Further, even children with low grade hemorrhages are at cognitive disability when compared with their non-IVH GA-matched peers. In Pinto-Martin’s study, any grade IVH alone was associated with CP (OR 3.14; 95% CI, 1.5 to 6.5). These difficulties may be attributable in part to the long-lasting alterations in cerebral blood flow following IVH and the secondary impact on corticogenesis and connectivity in developing brain.

## The Cost of Care

Medical decisions made during pregnancy and at the time of delivery can have great impact on the development of the preterm infant’s brain. Treatments and accommodations offered to the mother and fetus are often costly. This section reviews some of the key studies that have estimated both the financial cost of care and the indirect social costs associated with preterm birth.

Comparing costs requires familiarity with the methods used to make such estimates. Many studies look at hospital costs alone. However, a more rigorous analysis of cost will include both direct costs (hospital fees, drug therapy, doctor’s visits, etc.) as well as indirect costs (lost earning potential of the patient, costs of care for the infants, parent’s lost earning potential, travel for parents, child care for siblings, etc.). While it is possible to assign a numerical value to the cost of a given treatment, preferences for outcomes also depend on prevailing ethical and moral standards about life, death and disability.

## Predictors of Disability and Cost of Care

Gestational age at birth is the strongest predictor of medical service costs during the first 5 years of an infant’s life. The adjusted mean cost of hospital services in the first 5 years of life for infants born between 1970 and 1993 and treated in the British National Health Services were $22,798 for infants born at less than 28 weeks and $18,654 for those born between 28 to 31 weeks measured in 1998 US dollars (as derived from data based on British sterling).

Birth weight is also a strong predictor of hospital service costs during the neonatal period. In Petrou’s review of studies published since the 1970s, hospital service costs alone for infants born weighing less than 1000 g were 75% higher, on average, than those incurred by infants born weighing 1000 to 1499 g, and more than four times higher, on average, than those incurred by infants born weighing at least 1500 g. In addition, year of birth, sex, survival period, multiplicity, maternal age, and the number of days the mother was hospitalized before birth were also significant predictors of postnatal in-hospital medical costs.

## Birth in a Facility with a NICU Increases Survival and Enhances Neurodevelopment

Infants born at a center with a perinatal unit are more likely to survive and fair better neurodevelopmentally than infants born elsewhere (Table 1). Yu studied the developmental outcome of extremely low birth weight (ELBW) infants born between 1979 and 1980 (before the use of surfactant therapy). The group was assessed at ages 2, 5, and 8 years (corrected age). Yu found a direct correlation between increased survival and delivery in a hospital with a NICU. Eighteen percent of all 1979 cohort survivors had a severe disability (nonambulatory cerebral palsy, IQ score <2 SD below the mean, or bilateral blindness). However, infants that were born in a center with a NICU had a significantly lower severe disability rate than those born in centers without a NICU: 15 versus 50% at 2 years, 15 versus 38% at 5 years, and 13 versus 39% at 8 years.

Cost of treatment in the NICU has primarily been assessed according to birth weight (Table 2). Petrou compared the studies in this area and concluded that for babies born at less than 1000 g, there was a cost per additional survivor of between £84,490 and £174,040 (1998 £ sterling). When mea-
sured in terms of additional life year gained the cost effectiveness ratio fell to between £4440 and £15,790. When the outcome was measured in terms of an additional quality adjusted life year (QALY) gained, the cost-effectiveness ratio fell to between £4190 and £38,030. Higher birth weight infants are on average less costly to treat in the NICU and incur less cost per additional life year gained and less cost per additional QALY.55,56

Antenatal Steroids: Better Outcome, Low Cost

Many studies have examined antenatal treatment with steroids and it is well accepted that antenatal steroids improve mortality and morbidity for VLBW preterm infants (Tables 1 and 2). When two injections of corticosteroids are given to the mother before a preterm delivery, instances of respiratory distress syndrome, neonatal mortality, and intraventricular hemorrhage are reduced.57 However, in some pregnancies it is common for women to receive multiple doses of antenatal steroids; currently, there are no human study data suggesting neurodevelopmental harm associated with such treatment.58,59

In a meta-analysis of corticosteroid trials from 1972 to 1994, in utero exposure to corticosteroids has resulted in a 50% reduction in neonatal respiratory distress syndrome (RDS).60 Crowley found that eight clinical trials show a clear benefit of antenatal steroids to even the highest risk preterm infants born at less than 31 weeks (OR 0.41, 95% CI).60 More recent data suggests that only betamethasone and not dexamethasone is associated with reduced neonatal mortality and reduced periventricular leukomalacia (PVL).61,62

### Table 1 Risk Factors Associated with Adverse Outcomes

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mortality</th>
<th>Risk of IVH</th>
<th>Risk of RDS and/or CLD</th>
<th>Risk of NEC</th>
<th>Severe Disability Rate</th>
<th>PVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth in NICU</td>
<td>Improved</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Improved</td>
</tr>
<tr>
<td>Antenatal Steroids</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Reduced</td>
<td>Data not available</td>
<td>Reduced</td>
<td>Data not available</td>
<td>Unchanged</td>
<td>Data not available</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Unchanged</td>
<td>Reduced</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Postnatal Dexamethasone</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged rate of CLD except in high dose early administration</td>
<td>Increased GI perforation</td>
<td>Increased if given with 96 hours of birth</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

Note: Data derived from Mugford,65 Yu,54 Fowlie,82-84, Moya,73, Halliday,79,84, Ment,85, and Hohlagschwandtner.86

### Table 2 Cost of Specific Treatments

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Cost per Additional Survivor</th>
<th>Additional Cost per Additional Life Year Gained</th>
<th>Additional Cost per Additional QALY Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth in NICU</td>
<td>£84,490-£174,040 (1998 £ sterling)</td>
<td>£4,440-£15,790</td>
<td>£4,190 and £38,030</td>
</tr>
<tr>
<td>Ante-Natal Steroids</td>
<td>£56,080-£89,680 14% reduction</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Surfactant</td>
<td>$66,800 (1992 US dollar) 9% reduction</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Prophylactic Indomethacin compared to standard NICU treatment</td>
<td>NA</td>
<td>$585 savings</td>
</tr>
<tr>
<td>Post-Natal Dexamethasone</td>
<td>After 7-10 day of birth Negative cost-benefit b/c of increase rate of severe disability Positive cost benefit</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note. Derived from Petrou,52 Mugford,65 Yu,54, and Halliday.87
Use of antenatal corticosteroids can lead to a net savings in cost per life saved for infants younger than 31 weeks and for infants under 2000 g. In 1991, Mugford estimated the cost savings of antenatal corticosteroids in eligible patients based on the cost of caring for infants with and without respiratory distress. Mugford estimated administering antenatal corticosteroids to expectant mothers of less than 35 weeks gestation would reduce the average cost per baby by 10%, with a 14% reduction in the average cost per survivor. However, if antenatal steroids were only administered to expectant mothers of less than 31 weeks gestation, prenatal administration of corticosteroids would increase total costs by 7% and reduce the cost per survivor by 9%.

The use of antenatal corticosteroids appears to reduce overall health care costs. In Crowley’s review, the odds of both periventricular hemorrhage and necrotizing enterocolitis were reduced in infants exposed to antenatal steroids. Additionally, studies have not found long term developmental sequelae in infants exposed to corticosteroids. The reduction in neonatal care cost for surviving infants outweighs the relatively low cost of the medication, its administration, and monitoring of the mother, making antenatal corticosteroid use very cost-effective.

**Surfactant: High Cost but High Benefit**

Surfactant is used to treat Respiratory Distress Syndrome (RDS). The phospholipid reduces the surface tension in the lungs and prevents the alveoli from collapsing. Until the infant is able to breathe on its own, a mechanical ventilator is needed. Although surfactant and mechanical ventilation are expensive therapies, they are cost effective.

Traditionally, surfactant was administered once signs of RDS were clinically observed. Surfactant treatment for symptomatic RDS did not increase cost per survivor. For heavier babies with symptomatic RDS, surfactant treatment actually led to decreased costs. Heavier babies are more likely to survive. In these infants, the decrease in cost resulted from prevention of severe, chronic disease.

Early use of surfactant increases survival. Use of surfactant before signs of RDS emerge is cost effective in infants born at less than 30 weeks gestation. Egbert found that for infants weighing 800 to 1000 g prophylactic surfactant treatment resulted in a net additional cost per additional survivor. When prenatal steroids and prophylactic surfactant were given to all preterm infants less than 30 weeks gestation more infants survived and the number of necessary hospital days decreased, making combination therapy more cost effective than either alone.

In infants born as early as 24 to 26 weeks gestation, surfactant has helped to double the survival rate in the surviving population, without increasing the rate of severe disability, which remained below 10%. These data are shown in Table 3.

Surfactant coupled with ventilation therapy leads to a decrease in cost per additional quality-adjusted life-year gained for infants born at gestational age 24 to 26 weeks. Expressed in terms of 1992 U.S. dollars, the cost per ELBW survivor was $61,900 in 1979 to 1980, $72,800 in 1985 to 1987, and $66,800 in 1991 to 1992. Comparing 1985 to 1987 with 1979 to 1980, the cost per additional quality-adjusted ELBW survivor was $90,700, and the cost per additional quality-adjusted life-year gained was $4700. Comparing 1991 to 1992 with 1985 to 1987, the equivalent costs were $72,500 and $3800, respectively, showing that the incremental cost during primary hospitalization had actually fallen in the postsurfactant era.

Kilpatrick found that the survival rates of infants treated with prenatal corticosteroids and postnatal surfactant born at 24 weeks gestation was 53% compared with 80% in infants born at 25 or 26 weeks. The cost to produce a survivor was 63% higher for infants born at 24 weeks gestation, and only 35% of these infants were free from severe disability. Though therapies like antenatal corticosteroids and surfactant can be used to rescue even very young infants, physicians and parents should recognize the higher risk of severe disability and increased cost associated with saving infants of 24 weeks gestation and younger. If possible, a delay in delivery by even 1 week (from 24 to 25 weeks gestation) may lead to cost savings and increase a neonate’s chance of survival and life without severe disability.

**Indomethacin**

Indomethacin is a prostaglandin inhibitor, which has traditionally been used to close a patent ductus arteriosus (PDA) in preterm infants. Recent trials have used Indomethacin in an attempt to prevent intraventricular hemorrhage (IVH), a brain injury highly correlated to poor neurodevelopmental outcome.

Indomethacin is given after birth in three doses. The cost of this therapy is approximately $70, whereas the cost to surgically repair a PDA is more than $11,000. Indomethacin used prophylactically in VLBW infants is a cost-effective way to decrease rates of both PDA and IVH. In a study comparing indomethacin to standard NICU treatment, Moya found no difference in the expected survival rate of the indomethacin group. However, there was a significant difference in quality-adjusted life years, resulting in 11 and 10 years for the indomethacin and control groups, respectively. The inhospital cost of the indomethacin treated cohort was lower than the control group with rates of $95,157 and $99,955.

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**Table 3 Survival Pre-and Post-Surfactant**

<table>
<thead>
<tr>
<th>GA of Infant at Time of Birth</th>
<th>Survival Rate Pre-Surfactant</th>
<th>Survival Rate Post-Surfactant</th>
<th>Severe Disability Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 weeks</td>
<td>7%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>24 weeks</td>
<td>30%</td>
<td>33%</td>
<td>14%</td>
</tr>
<tr>
<td>25 weeks</td>
<td>31%</td>
<td>58%</td>
<td>6%</td>
</tr>
<tr>
<td>26 weeks</td>
<td>55%</td>
<td>72%</td>
<td>9%</td>
</tr>
<tr>
<td>27 weeks</td>
<td>67%</td>
<td>77%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Note. Derived from Yu et al.88,89
respectively. The cost per quality added life year was lower in the indomethacin group than in the control group with costs of $8443 and $9168, respectively.

Prophylactic indomethacin has been shown to effectively reduce the rate of intraventricular hemorrhage (Table 1). However, a meta-analysis by Fowlie suggests that the reduction in IVH does not translate into decreased rates of cerebral palsy, low IQ, blindness, or sensorineural deafness. Indomethacin was not found to increase rates of necrotizing enterocolitis or bronchopulmonary dysplasia (BPD).

### Postnatal Dexamethasone: Low Cost but Increased Handicap

Treatment with dexamethasone, a powerful long-acting glucocorticoid, in the postnatal period is controversial. Dexamethasone is used to help wean infants from the ventilator and thought to reduce primary respiratory morbidity. Despite short-term improvements in bronchopulmonary dysplasia, dexamethasone has not been shown to improve survival or rates of chronic lung disease (CDL). Furthermore, treatment with postnatal dexamethasone has been associated with a number of deleterious effects including: increased rates of growth retardation, hyperglycemia, hypertension, infection, hypertrophic cardiomyopathy, gastrointestinal perforation, cerebral palsy, and developmental delay (Table 1).

Although the cost of even a long course of dexamethasone is relatively inexpensive, a cost-benefit analysis requires one to factor in the numerous complications now known to be associated with treatment (Table 2). The benefits of dexamethasone vary based on the age of the infant at the time of administration. Halliday estimates that the cost-benefit ratio would be negative (ie, the adverse outcomes outweigh the potential reduction in CLD) for early administration within 96 hours of birth. However, the cost-benefit ratio would be positive after 7 to 10 days of life.

### Conclusion

Advances in prenatal and perinatal treatment of preterm and VLBW infants have dramatically increased the survival rate of these infants. Birth in a center with a NICU improves survival and decreases the rate of severe disability. Administration of antenatal steroids increases survival and decreases rates of periventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress syndrome, and severe disability. Administration of antenatal steroids decreases the cost per additional survivor. Addition of surfactant to the treatment of PT infants has also decreased treatment costs. Administration of surfactant is beneficial for symptomatic RDS but recognizes a greater benefit when given to infants younger than 30 weeks gestation prophylactically. Treatment with prophylactic indomethacin decreases the rate of intraventricular hemorrhage and results in cost savings in survivors. Postnatal administration of dexamethasone can lead to severe disability when administered before 7 to 10 days of life. Postnatal dexamethasone does not increase survival or decrease rates of chronic lung disease.

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### Acknowledgment

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