Use of the laboratory in prediction of outcome in the high-risk newborn

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This paper reviews our ability to predict survival and neurodevelopmental outcome in the newborn period. Traditionally, prognosis is based on individual risk factors or disease states. The laboratory plays an important role in diagnosing some of these. For example, prenatal and newborn screening are important in the diagnosis of chromosomal abnormalities and inborn errors of metabolism. Abnormal bilirubin, glucose, and pH values in the newborn period are risk factors for death and abnormal neurodevelopment, and the degree of abnormality imparts additional information. Many newborns have multisystem disorders, and it is only when multiple variables are considered that outcome can be predicted. Three neonatal scores that incorporate multiple variables are discussed. Methodologic difficulties in determining outcome are reviewed and illustrated with survival and morbidity rates of very premature babies. The laboratory is one of many prognostic variables. The evaluation of how laboratory services are provided is difficult but important.

INDEXING TERMS: neurodevelopment • mortality • severity of illness scores • low birth weight

The concept that the laboratory plays a role in outcome assessment of the high-risk newborn is a new one. This paper reviews the prediction of survival and neurodevelopmental status in the newborn period.

Development is defined as the process of growth and differentiation [1]. Neurodevelopment refers more specifically to the nervous system, and in this paper refers to the acquisition of developmental milestones (e.g., walking, talking, reading, writing). Neurodevelopmental status reflects not only the functional adequacy of the maturing brain, but also other factors such as the senses, the motor system, and the environment (e.g., stimulation provided by parents). The term “outcome” indicates the neurodevelopmental or functional state of a child as a result of a neonatal condition.

Traditionally, prognosis is based on individual risk factors or disease states, and the laboratory plays an important role in diagnosing some of these disease states and risk factors. For example, prenatal screening and newborn screening are important in the diagnosis of chromosomal abnormalities and inborn errors of metabolism. Abnormal bilirubin, glucose, and pH values in the newborn period are risk factors for death and abnormal neurodevelopment, and the degree of abnormality imparts additional information.

However, many newborns have multisystem disorders, and it is only when multiple variables are considered that survival and developmental status can be predicted. Recent scores incorporate multiple variables that have been developed for the newborn. Three of these scores will be discussed here.

Some of the methodologic difficulties encountered in determining prognostic outcome are reviewed, and the outcome of the premature baby is then used to illustrate several of these points.

The role of the laboratory in monitoring at-risk newborns for determining prognosis and future directions in this field are also discussed.

Causes of Abnormal Neurodevelopment [2–4]

Factors that have a negative impact on the outcome of a baby can be categorized as follows: factors intrinsic to the fetus, insults to the fetus during pregnancy, and insults in the perinatal and neonatal periods. In addition, environmental and medical problems in infancy and childhood may affect an individual’s future. Examples of causes of developmental delay or cognitive impairment are listed by these categories in Table 1; laboratory findings that contribute to the prediction of outcome are listed in Tables 2, 3, and 4 and all are discussed below.

Abnormal development of the fetus (disorders intrinsic to the fetus), whether associated with chromosomal anomalies, biochemical defects, or structural defects may result in death or developmental delay. The laboratory
Table 1. Examples of causes of abnormal development.

1. Disorders intrinsic to the fetus
   - Congenital malformation
   - Chromosomal anomalies
   - Inborn errors of metabolism
   - Hypothyroidism
2. In utero insults
   - Infection
   - Drugs
   - Malnutrition
   - Hypoxia
3. Peripartum and postnatal insults
   - Hypoxic–ischemic insults
   - Intracranial hemorrhage
   - Infection/meningitis
   - Biochemical abnormalities
   - Seizures
   - Prematurity
   - Severe illness
4. Postneonatal insults
   - Low socioeconomic status
   - Inadequate parenting
   - Child abuse or neglect
   - Parental mental illness
   - Medical illnesses (e.g., meningitis)
   - Traumatic brain injury

plays a crucial role in determining prognosis by providing a diagnosis in chromosomal, biochemical, and endocrine abnormalities that may result in an abnormal fetus. Testing for these disorders may be performed in asymptomatic populations (i.e., prenatal screening for chromosomal abnormalities for women with an advanced maternal age and newborn screening for phenylketonuria and hypothyroidism) or for fetuses or newborns with known congenital anomalies. Imaging studies are necessary in cases in which prognosis is based on structural defects such as brain malformations.

The fetus, in utero, is particularly vulnerable to insults. Drugs such as thalidomide, mercury, phenytoin, and alcohol may cause congenital malformations especially when taken in the first trimester. Illicit drugs taken later in pregnancy can cause withdrawal and subsequent behavior problems and learning disabilities. Congenital infections such as the TORCH infections (Toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus) and others such as syphilis and varicella-zoster virus, may cause congenital malformations and multiorgan involvement frequently associated with long-term neurologic injury. These are just a few examples. The indications for doing laboratory tests to assess for the above problems vary from the presence of risk factors in an asymptomatic baby to clinical symptoms (see Table 3).

Labor, delivery, and the first week of life are a time of great transition for the fetus. Problems may become apparent at this time because some organ systems such as the lungs become essential for life just after birth; some babies may have been chronically stressed and do not have the reserve to tolerate the added stress of delivery. Previously well fetuses may face premature delivery, obstetrical complications, difficulties in making the transition to life ex utero, and several disease states in the newborn period that may lead to death or long-term impairment. Important among these causes are prematurity, hypoxic–ischemic injury, intracranial hemorrhage (especially in the premature baby), seizures, infection, and biochemical abnormalities such as hypoglycemia, hyperbilirubinemia, and electrolyte disturbances. In the neonatal intensive care unit setting, the ability of the laboratory to use microtechniques to analyze blood samples and thereby allow for closer biochemical monitoring has been one of the many advances that has contributed to the decline in the low birth weight mortality rate.

Conditions with laboratory abnormalities such as hypoxia, acidosis, hypoglycemia, and hyperbilirubinemia that occur in isolation frequently enough for the outcome to be reasonably well known will now be discussed (Table 4). The diagnosis of these conditions by the laboratory provides prognostic information.

Hypoxia and acidosis may occur in the fetus for many reasons. If not relieved, this will be reflected in abnormal cord blood gas results and other evidence of fetal distress. A clinical picture of hypoxic–ischemic encephalopathy may ensue and may vary from mild to moderate or to severe. The outcome is related to the severity of the hypoxic–ischemic encephalopathy. With mild injury, almost all babies are expected to survive and be normal. Severe injury has a mortality of 75%, and 100% of survivors have neurologic sequelae [5]. Hence, the severity of the illness, which is determined clinically and augmented by neuroimaging and other neurological tests, is crucial in determining prognosis.

Glucose is the primary metabolic fuel for the brain and inadequate glucose delivery may lead to neuronal cell death. Glucose delivery depends on cerebral blood flow as well as blood glucose concentrations. Other noxious stimuli may make the brain more vulnerable to permanent brain injury. Though hypoglycemia may cause seizures acutely, long-term intellectual deficits, motor impairments, and seizure disorders may result without any symptoms having occurred at the time of the hypoglycemia. These factors have made it difficult to define hypoglycemia.

Erythroblastosis fetalis, before the treatment of Rh-negative mothers with anti-Rh immune globulin, provided us with experience with hyperbilirubinemia and its effect on the brain. It is not certain that similar degrees of hyperbilirubinemia from other causes have the same
Kernicterus is an acute bilirubin encephalopathy that presents in the first days of life. As the child grows, survivors typically develop uncontrolled abnormal writhing movements, abnormal eye movements, hearing loss, and usually some intellectual deficit.

Another example is ototoxicity documented with high aminoglycoside concentrations. The laboratory is also important for the diagnosis of meningitis, which in the newborn may result in full recovery, developmental delay, and hearing loss. Laboratory results may indicate an increased risk for other conditions that are associated with abnormal outcomes. Though typically multifactorial, intracranial hemorrhage may be caused by an isolated severe thrombocytopenia or a coagulopathy that may result in motor (cerebral palsy) or intellectual impairments.

Normal development cannot be confirmed at birth but only with the passage of time. It is therefore necessary to be familiar with postneonatal factors that may alter development to ensure that these developmental problems are not incorrectly attributed to the fetal or newborn period.

**Use of Multiple Variables in Predicting Outcome**

Studies with multiple regression analyses have been performed to predict mortality and long-term outcome [e.g., nursery neurobiologic risk score (Brazy et al. [6]) and the clinical risk index for babies (CRIB) ([7])]. Brazy’s revised score is composed of seven domains (ventilation, pH, seizures, intraventricular hemorrhage, periventricular leukomalacia, infection, and hypoglycemia), each of which can receive a score from 0 (normal) to 4 (reflecting the most severe derangement). It was developed for use in very-low birth weight babies (<1500 g) and is most useful when scored at the time of discharge from the neonatal intensive care unit. In logistic regression analyses, it demonstrates a significant contribution to the prediction of neurodevelopmental outcome at age 6, 15, and 24 months. Recognizing the limitations of a sample size of 58, a cutoff score of ≥6 gives a sensitivity of 0.60, specificity of 1.00, positive predictive value of 1.00, and negative predictive value of 0.68 in the very-low birth weight population.

The CRIB was also developed for premature babies with a birth weight of <1500 g or <31 weeks of gestation. It is simple, with only six items (nonlethal congenital malformations, birth weight, gestational age, oxygen requirement, and base deficit), which are assessed at age 12 h. It has been shown to predict in-hospital death, with an area under the ROC curve of 0.90, and is undergoing further confirmation of other outcomes.

The SNAP score (score for neonatal acute physiology) [8] is designed to measure severity of illness in all neonatal intensive care unit patients by measuring the severity of derangement in multiple organ systems. The 34 items, scored in the first 24 h of admission, include

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**Table 2. Examples of disorders intrinsic to the fetus.**

<table>
<thead>
<tr>
<th>Lab finding</th>
<th>Symptoms in the newborn</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal karyotype</td>
<td>Dysmorphic features</td>
<td>Abortion, death, multisystem disorders</td>
</tr>
<tr>
<td>Hyperphenylalaninemia</td>
<td>None</td>
<td>Mental retardation if untreated</td>
</tr>
<tr>
<td>Low thyroxine, high thyrotropin</td>
<td>Often none</td>
<td>Clinical hypothyroidism with mental retardation if untreated</td>
</tr>
</tbody>
</table>

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**Table 3. Examples of in utero insults to the fetus.**

<table>
<thead>
<tr>
<th>Lab finding</th>
<th>Symptoms in the newborn</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive serology for a TORCH infection</td>
<td>Growth retardation, hepatitis, chorioretinitis, malformations</td>
<td>Death, developmental delay, deafness, organ dysfunction</td>
</tr>
<tr>
<td>Positive serology for parvovirus 19</td>
<td>Anemia</td>
<td>Hydrops fetalis with death or resolution to normal</td>
</tr>
<tr>
<td>HIV positive</td>
<td>Asymptomatic</td>
<td>AIDS, death, not infected (maternal antibody transmission only)</td>
</tr>
<tr>
<td>Low platelets</td>
<td>None or bleeding</td>
<td>Cerebral palsy if intracranial bleed</td>
</tr>
<tr>
<td>Positive drug screen for illicit drugs</td>
<td>None, obstetrical complications, withdrawal, intracranial hemorrhage</td>
<td>Normal, behavioral problems, developmental delay</td>
</tr>
</tbody>
</table>

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**Table 4. Examples of peripartum and postnatal insults.**

<table>
<thead>
<tr>
<th>Lab finding</th>
<th>Symptoms in the newborn</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia/acidosis</td>
<td>Hypoxic–ischemic encephalopathy</td>
<td>Normal, developmental delay, death</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Seizures</td>
<td>Normal, developmental delay</td>
</tr>
<tr>
<td>High aminoglycoside concentrations</td>
<td>None</td>
<td>Normal, hearing loss</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Kernicterus</td>
<td>Hearing loss, developmental delay, choreoathetosis</td>
</tr>
<tr>
<td>Thrombocytopenia/coagulopathy</td>
<td>None or bleeding</td>
<td>Cerebral palsy if intracranial bleed</td>
</tr>
<tr>
<td>Cerebrospinal fluid leukocytosis</td>
<td>Meningitis</td>
<td>Normal, developmental delay, hearing loss</td>
</tr>
</tbody>
</table>
The best measure of development for a specific research question may vary from a very specific outcome measure to broad medical diagnostic categories, or to measures of how children function in their community. Specific outcome measures are indicated when the pathophysiology is well understood. For example, dietary fat influences membranes in the brain and retina, and differences in the fatty acid composition of formulas for pre-mature infants might affect visual development [9]. Electroretinography and visual acuity are therefore appropriate outcome measures. If one is assessing the effect of newborn intensive care as an entity on the future of children, rates of major impairments (defined as medical diagnostic categories such as cerebral palsy, blindness, and intellectual impairment) are often chosen. However, for parent counseling, whether a child can walk, talk, function in a regular school, and other such functional outcomes are needed.

AGE AT ASSESSMENT OF OUTCOME
Neonatal follow-up studies face various intrinsic problems. The results are always out of date to some degree because of the time required to reach the age of assessment. The earlier the age at assessment, the less predictive the results are of future outcome. Testing older children is essential to discern how they will eventually function in society, but loss to follow-up and postdischarge confounding factors, especially the environmental factors listed in Table 1, make it harder to make causal links with variables in the newborn period.

In practice, follow-up studies at ages 12–24 months from the expected date of delivery are used to determine the rate of major impairments. Early school age is used to determine the incidence of learning disabilities and functional outcomes.

CONFOUNDING VARIABLES
The multiple factors that influence development make it difficult to prove causality between newborn events and subsequent abnormal development. In an impaired child who was sick with multiorgan derangements in the newborn period, it is often difficult retrospectively to determine which neonatal events caused or contributed to the subsequent developmental problem. As discussed above, the SNAP and other scores may improve our ability to predict outcome prospectively.

Outcomes of the Extremely Premature Neonate
The extremely premature neonate is an example of a population at high risk for developmental delay.

MORTALITY
It is important to discuss mortality in the context of developmental delay because death used to be inevitable for these babies, and death from discontinuation of intensive care support is considered an alternative for some.

With the introduction of neonatal intensive care in the
1960s, mortality rates for the infant weighing <1000 g at birth fell from 96% in the early 1950s to 20–50% in the 1980s and 1990s [10]. The limit of viability has been pushed ever lower, with survival now possible for 16–24% of all liveborns in some perinatal centers at 23 weeks of gestation [11, 12] and 24% at 500–599 g [10].

**RISK FACTORS FOR ABNORMAL NEURODEVELOPMENT**

Several complications of prematurity are associated with a poorer neurodevelopmental outcome. Foremost among these are cerebral injuries as documented on head ultrasound or other neuroimaging. This may either occur as an intraventricular hemorrhage (IVH), especially if associated with intraparenchymal hemorrhage (occurs in 7% of <1500 g birth weight babies) or as the symmetric white matter hypoxic injury, periventricular leukomalacia (8% of <1500 g babies) [12]. Whereas a small IVH limited to the subependymal region is associated with only a slight increase in major neurological sequelae, larger bleeds with ventricular dilatation results in 30–40% sequelae, and when accompanied by intraparenchymal injury, 80–100% of survivors have major neurological impairments [13].

The premature brain is more vulnerable to injury by other factors such as hyperbilirubinemia and thrombocytopenia than the term brain.

Retinopathy of prematurity in its most severe form, grade 4, results in retinal detachment and blindness. This may affect 3–8% of extremely low birth weight survivors (birth weight <1000 g), with higher rates in the even smaller babies. Retinopathy of prematurity can usually be detected by age 6 weeks, or 32 weeks corrected age, by indirect ophthalmoscopy. Blindness is clearly an important developmental sequela.

Bronchopulmonary dysplasia (BPD) has different definitions but in general is a lung injury with abnormal chest x-ray and prolonged oxygen need in a baby who had hyaline membrane disease. BPD or other forms of chronic lung injury occurs in 79% (defined as oxygen need at age 28 days) or 9% (defined as oxygen need at postmenstrual age 36 weeks) of babies weighing 501–750 g at birth. It may result in prolonged ventilator or oxygen dependence, prolonged hospitalization, and poor growth. These factors may result in transient developmental delay, but these sick infants are also at risk for long-term neurodevelopmental delay (odds ratio 4.5 [14]).

**MAJOR IMPAIRMENTS**

The impairment rate varies inversely with gestational age and birth weight. Because definitions of impairments vary and patient populations are heterogeneous it is difficult to compare centers. Major impairments may be classified as intellectual, motor (these two may be combined under neurological), auditory, and visual.

Sample size is generally small among the tiniest. Of 129 survivors born at 23–25 weeks of gestation, 36% had at least one major impairment (34% had a motor impairment, 20% scored below 2 SDs on the Bayley Scales of Infant Development, 19% were legally blind, and 4% were deaf requiring hearing aids) [11].

In a review of the literature, for babies born in 1970 or later with birth weights of <1001 g, 41–75% of survivors were normal. Of these babies, 12–32% had severe or major handicaps and 0–12.7% had severe visual problems [15]. The incidence of major neurosensory impairments has not changed over time in most studies despite the increase in survival (e.g., 19%, 21%, and 22% in <800-g survivors born in 1977–1980, 1983–1985, and 1986–1990 [10].

**MINOR IMPAIRMENTS**

The association of disabilities in school-age children and prematurity was made as early as 1961 [16], with only 24% of the children (birth weight <3 lbs.) able to attend regular school and only 22% free of behavioral problems. More recently Hack et al. showed that a birth weight of <750 g was associated with inferior cognitive ability (21% had low mental scores and 45% required special education), psychomotor skills, low academic achievement, and more behavioral and attention problems than larger premature (birthweights 750–1499 grams) and term children [14].

Many variables in the newborn period may influence mortality and long-term outcome. The laboratory plays a role in the prediction of outcome in some babies by aiding in diagnosis and the identification of risk factors, but no single laboratory test at present can be used to predict neurodevelopmental outcome. In the at-risk newborn, blood gases, glucose, and bilirubin are examples of variables that should be monitored because abnormal results correlate with adverse outcomes. The laboratory needs to provide diagnostic facilities for conditions such as inborn errors of metabolism, congenital hypothyroidism, and meningitis, in which a diagnosis is prognostic, and this needs to be timely, especially for conditions in which early diagnosis improves the outcome. More accurate prediction, especially in ill newborns with multiple problems, requires the consideration of multiple variables including laboratory results, clinical parameters, and imaging studies. The SNAP is one score that incorporates many variables to predict mortality that might prove useful for generalized use in intensive care unit patients. Further research is needed in the area of evaluation of different methods of providing laboratory services.

**References**