Neuroimaging and Neurodevelopmental Outcomes in Preterm Infants
Susan R. Hintz, MD, MS Epi,* and Michael O'Shea, MD, MPH†

Imaging of the preterm infant brain has advanced dramatically beyond the earliest era of transillumination. Computed tomography (CT), a crucial innovation during the early 1970s, allowed noninvasive visualization of intracerebral lesions, particularly hemorrhage. The capability to document brain injury in the preterm infant led to better clarification of links to developmental outcomes. With the development of cranial ultrasound (CUS), and more recently, magnetic resonance imaging (MRI), CT is used rarely for imaging the brain of preterm infants. Despite extensive experience with neonatal neuroimaging, significant questions still remain. Substantial controversies exist pertaining to when and how neuroimaging should be performed and how images should be interpreted.

Semin Perinatol 32:11-19 © 2008 Elsevier Inc. All rights reserved.

KEYWORDS cranial ultrasound (CUS), hemorrhage, magnetic resonance imaging (MRI), periventricular leukomalacia (PVL), white matter, cerebral palsy (CP)

Cranial Ultrasound

Background

CUS has been used to image the preterm brain since the late 1970s. Classic studies by Pape1 and Slovis2 reported on the use of real-time linear array and sector scanning to detect intraventricular and parenchymal hemorrhage, ventricular enlargement, and other abnormalities. CUS uses high-frequency sound waves (5-10 MHz), transmitted through the acoustic windows of open fontanelles, to detect differences in acoustic impedance—analogous to “acoustic density”—between tissues. Some of the sound waves are reflected back to the probe, allowing detection of differences in “echogenicity” or “echodensity” between tissues, and the detection of anatomic structures, hemorrhage, and fluid collections.

Early reports of CUS in preterm infants focused almost exclusively on the anterior fontanelle (AF) as the acoustic window, but the brainstem and posterior fossa are better seen through the mastoid fontanelle (MF).3-5 Cerebellar hemorrhage, which is readily distinguishable by MF but not AF view, may be a more common complication among preterm infants than previously believed.6 The posterior fontanelle (PF) view allows for better visualization of the trigone and occipital horn of the lateral ventricles, improving detection of subtle intraventricular hemorrhages.7

Soon after its advent, CUS became a routine and widely used method of neuroimaging for preterm infants. The most important advantage of CUS is that it is performed at bedside, distinguishing it from other neuroimaging modalities. In addition, CUS involves no radiation exposure. Thus, CUS is ideal for repeated and frequent imaging. However, there are also limitations to CUS. Interpretation of CUS images is variable, in part because CUS is highly operator-dependent. Further, potentially important features, such as subtle white matter injury or parenchymal abnormalities, may be difficult to detect by CUS. These limitations will be discussed below in greater detail.

What We Can See with CUS

In a seminal paper that has informed clinicians and researchers for three decades, Papile and coworkers provided an approach to grading the severity of intracranial hemorrhage in preterm infants, based on CT images.8 However, it is now evident that if one relies only on hemorrhage grading, important prognostic information can be overlooked. Periventricular parenchymal hemorrhage, with an etiology likely associated with venous infarction,9,10 may be isolated; the manner...
in which these are "graded" can vary. The size and position of hemorrhage also appear to be predictive of short-term neuromotor outcome,10,11 yet this information is not captured by the traditional CUS grading approach. Further, this approach does not consider isolated cerebellar hemorrhages which have been strongly associated with neurosensory deficits and cerebral palsy.6,12,14

Echolucent periventricular lesions representative of severe white matter injury (WMI) can be seen by CUS.15 The location and size of these lesions relate somewhat to the severity of later neuromotor impairment.16,17 However, small cystic lesions may collapse over time and go undetected if imaging is performed infrequently.16,18 Nonhemorrhagic periventricular echodense lesions may represent evolving WMI; but transient echodensities of less than 7 to 10 days duration may not portend adverse neuromotor consequences for the preterm infant.11,18 CUS underestimates diffuse WMI, which is likely to be a much more common form of WMI in the preterm infant than cystic periventricular leukomalacia (PVL), and can be better seen by MRI.10,21 Ventricular dilation (VD) can be easily seen by CUS, although quantification of ventricular size is rarely undertaken. Nevertheless, VD has been shown to be strongly associated with impaired motor performance in early and later childhood, consistent with periventricular WMI.16,22,23

While many studies have related neurodevelopmental outcome to the presence of severe grades of hemorrhage and cystic PVL on CUS, considerably more can be visualized with carefully performed CUS. Thus, it is reasonable to ask: can a more comprehensive and descriptive system for reporting CUS findings be developed, tied with recommendations for more complete imaging protocols and more frequent serial scans? Or do the challenges to interpretation and the inability to delineate some types of injury inherently limit the prognostic utility of this method of neuroimaging?

CUS and Neurodevelopmental Outcomes
Very low birth weight (VLBW; <1500 g BW) preterm infants are at high risk for neurodevelopmental impairment. Neuroimaging is often used to counsel families about prognosis and the need for early intervention. Strong associations between major CUS abnormalities and adverse neurodevelopmental outcomes among preterm infants have been described in numerous single-center, multi-site, and population-based analyses. However, inconsistencies in CUS protocols and study design make comparisons challenging.

Vohr and coworkers24 reported 18 to 22 month corrected age outcomes of ELBW infants born 1993 to 1998 in the NICHD Neonatal Research Network (NRN). No specific CUS protocol was required for this multi-center cohort, thus the number of CUS obtained during hospitalization and routine views included in each CUS varied among patients. Data on PVL were collected only if cystic changes were noted. After adjusting for numerous confounding variables, the authors found that cystic PVL (OR 10.5, 95% CI 7.2-15.2) and grade 3 or 4 IVH (OR 2.4, 95% CI 1.8-3.1) were strongly associated with moderate to severe CP. Cystic PVL and severe IVH were also independently associated with Bayley Scales of Infant Development II (BSID) Mental Developmental Index (MDI) scores <70, a marker of delayed early cognitive function. However, patients with severe neuromotor or neurosensory impairment were included in this group; thus some of this association may be explained by impairments other than cognitive. Another recent analysis from the NICHD NRN focused on changes in neurodevelopmental outcomes at 18 to 22 months among extremely preterm infants <25 weeks EGA, and also found that IVH grade 3 or 4 and cystic PVL were strongly associated with CP.25

In the EPIPAGE study,26 infants 22 to 32 weeks EGA born in 9 French regions during 1997 were followed to 2 years of age. CUS was usually obtained 1 to 3 times in the first 2 weeks, then every 1 to 2 weeks; however, neither timing of scanning nor scanning views were standardized across study sites. PVL was defined as periventricular echodensity (“flaring”) lasting >14 days or any periventricular cystic changes. CP was ascertained by questionnaires sent to pediatricians or other care providers.27 WM abnormalities, defined as PVL, ventricular dilation, or intraparenchymal hemorrhage or cyst, were associated with CP. Of the 344 children with a history of WM abnormalities (18% of the total follow-up group), 24.4% were diagnosed with CP; of 76 with cystic PVL (less than 4% of the total follow-up group), 57% were diagnosed with CP. Among those with no CUS abnormalities, CP was diagnosed in just over 4%.

The EPIcure study was a population-based study of all infants 20 to 25 + 6/7 weeks EGA born in the UK and Ireland from March 1995 to January 1996; neurodevelopmental follow-up occurred at 30 months and beyond.28 Severe CUS abnormalities, defined as parenchymal hemorrhage, cystic changes, or ventricular dilation on the last CUS, were associated with CP (classified retrospectively as nonprogressive disorder of movement and posture) (OR 4.95, 95% CI 2.25-10.85), and with severe motor disability (defined as highly likely to need physical assistance to perform tasks) (OR 7.15, 95% CI 2.73-18.74). Of note, when children with motor disability were excluded, severe CUS abnormality was not significantly correlated with BSID MDI score.

In a large single-center cohort study, Hack and coworkers described the outcomes of ELBW infants at 20 months of age corrected for prematurity.29 Severe CUS abnormality, defined grade 3 or 4 IVH, PVL, or persistent ventricular dilation on any CUS during hospitalization, was strongly associated with neurologic abnormality (OR 8.1, 95% CI 3.7-17.7) but not with poor cognitive outcome.

Studies of later childhood outcomes have also found associations between severe CUS findings and neurodevelopmental sequelae. Long-term follow-up of the National Brain Hemorrhage Study (NBHS) cohort showed that parenchymal lesions or ventricular enlargement (PLVE) on neonatal CUS were significantly associated with disabling CP at 2 years and with poor motor abilities at 6 and 9 years.22 Severe cognitive impairment also was related to PLVE.30 but the association was not significant after controlling for differences in motor ability and perinatal factors.22 Isolated germinal matrix hemorrhage and IVH without VE were not associated with out-
come at 6 and 9 years. In an 8-year follow-up of the Victorian Infant Cohort Study (VICS), Sherlock and coworkers described a linear relationship between increasing grade of IVH and rates of CP and neurosensory disability. Increasing grade of IVH was also related to decreasing IQ, but this finding was explained primarily by the severe cognitive impairments among the small number with grade 4 IVH (n = 6).

Taylor and coworkers described a stepwise decrement in abnormal CUS findings for cognitive impairment is substantially lower than for other neurodevelopmental outcomes. The typical timing and frequency of CUS screening of preterm infants may be inadequate. The primary guideline for CUS screening in the United States is the Practice Parameter for Neuroimaging of the Neonate in 2002, which recommends screening with CUS for all infants with EGA <30 weeks at 7 to 14 days, and, “optimally,” again at 36 to 40 weeks. However, more frequent and detailed surveillance protocols, using high-resolution techniques and with attention to subtle findings, probably increase the sensitivity of CUS for identifying infants at high risk for adverse outcomes.

Factors That May Contribute to CUS as an “Imperfect Predictor” of Neurodevelopmental Outcome

Prospective neurodevelopmental outcome studies rarely have considered interobserver reliability of CUS interpretations, but low reliability could attenuate associations between CUS abnormalities and outcomes. A recent retrospective analysis of CUS data from the NICHD trial of inhaled nitric oxide for premature infants assessed interobserver reliability between two central readers, and accuracy of local compared with central readers (regarded as the “gold standards”). The level of agreement between central readers was high for major CUS findings, such as grade 3 or 4 IVH and degree of ventriculomegaly (kappa = 0.84 and 0.75, respectively), but much worse for lower grade IVH (kappa = 0.4) and for PVL alone. The sensitivity of local reader interpretation was also excellent for grade 3 or 4 IVH (88–92%), but was poor for grade 1 or 2 IVH (48–68%). These results, similar to the few previous large analyses in the literature, raise significant concerns about the validity of interpretations about mild to moderate hemorrhage by CUS. Despite the conventional focus on severe IVH, lower grade hemorrhage may also be associated with neurodevelopmental impairment; ELBW infants with uncomplicated grade 1 or 2 IVH appear to have poorer neurodevelopmental outcomes at 20 months than those with normal CUS, even after adjusting for confounding risk factors. Furthermore, compared to preterm infants without IVH, those with a history of uncomplicated IVH have been shown to have significantly reduced cortical gray matter volume at near-term. These studies underscore the potential importance of reliable ascertainment of even subtle hemorrhage.

The typical timing and frequency of CUS screening of preterm infants may be inadequate. The primary guideline for CUS screening in the United States is the Practice Parameter for Neuroimaging of the Neonate in 2002, which recommends screening with CUS for all infants with EGA <30 weeks at 7 to 14 days, and, “optimally,” again at 36 to 40 weeks. However, more frequent and detailed surveillance protocols, using high-resolution techniques and with attention to subtle findings, probably increase the sensitivity of CUS for identifying infants at high risk for adverse outcomes.

Magnetic Resonance Imaging Background

Brain MRI has been increasingly used for research and clinical purposes since the 1980s, but has been applied relatively infrequently to premature infants. However, with optimization of MR methods for detecting neonatal brain injury...
and greater availability of MR scanners closer to neonatal intensive care units (NICU), MRI has become a more routine advanced neonatal neuroimaging approach. Recognition of the excellent MR safety profile and reduction of barriers to nonsedated scanning has facilitated expanded utilization. MR-compatible monitoring devices, ventilators, and warming equipment can now be used during transport from the NICU and during the scan itself. Scanning without sedation is now possible with simple feeding and swaddling, and by using polystyrene bead-filled “huggers.” Finally, although much more expensive, MRI-compatible isolettes with integrated head coil allow for transfer and scanning within the safety and comfort of the incubator, and reduce the potential for motion artifact. Using these approaches, at least two-thirds of patients can be scanned without sedation.

**What We Can See With MRI**

**Brain Areas of Special Interest**

Compared with CUS, where views of the brain are limited to what can be seen through the acoustic windows of the fontanelles, MRI offers more complete visualization of anatomic features and injury. However, to what extent this added detail can improve neurodevelopmental outcome prediction is an area of active research. For example, among preterm infants, MRI evidence of cerebellar injury has been associated with adverse developmental outcomes, including motor, cognitive, communication, and behavioral impairments.

The cerebellum can be visualized by CUS, using mastoid fontanelle views, but MRI allows delineation of cerebellar lesion topography and identification of supratentorial injury, which may help predict severity of neuromotor delays. Barkovich and Sargent described thalamic, basal ganglia, and brainstem abnormalities in a small group of preterm infants after asphyxia. Although the authors noted that injury could be detected by MRI, CT, or CUS, CUS findings were transient in some cases. Several groups have reported on the ability to recognize basal ganglia and thalamic hyperechogenicity by serial CUS, but the association of this particular finding with adverse neurodevelopmental outcome is variable. MRI may demonstrate basal ganglia injury more clearly and frequently than CUS, but MRI studies have also suggested a strong relationship of these lesions with other types of brain injury.

**White Matter Injury**

CUS detects severe WMI, such as cystic PVL and ventriculomegaly due to periventricular WM loss. On the other hand, CUS does not detect diffuse WM or “minor” WM lesions as well as MRI. Comparing 62 paired CUS and MRI performed on the same day in preterm infants, Maalouf and colleagues showed that IVH by CUS predicted IVH by MRI, and large WM echogenicity by CUS predicted hemorrhagic parenchymal injury or punctate hemorrhage by MRI very well (predictive probability (PP) 0.85 and 0.96, respectively). However, mild or no WM echogenicity by CUS poorly predicted normal WM by MRI (PP = 0.54) and moderate to severe WM echogenicity by CUS poorly predicted WM hemorrhage or diffuse excessive high signal intensity (DEHSI) of the WM by MRI (PP = 0.54). The finding of abnormal CUS cerebellar or basal ganglia echogenicity did not agree well with MRI findings.

In a study comparing MRI at 1 to 42 days to CUS performed within 72 hours of the MRI, no infants without periventricular WM injury by MR had lasting CUS periventricular echodensities. However, CUS failed to detect WMI in nearly all of those with the most subtle WMI pattern by MRI, half of those with moderate WMI, and 20% of those with moderately severe WMI. A relatively low sensitivity of CUS for detection of noncystic WM abnormalities has been found in multiple studies. This more subtle form of WMI is considerably more prevalent than the cystic form; Inder and coworkers found that 55% of VLBW infants had some evidence of WMI by MRI at near-term, but only 4% had cystic changes. Noncystic WMI in preterm infants is associated with reduced total brain volumes, reduced cerebellar volume, reduced cortical and deep gray matter volume at near term, further, regional brain volume reduction is associated with long-term neurodevelopmental and cognitive impairments in middle to late childhood.

The link between WMI and gray matter reduction in the developing preterm infant brain is an area of active research. Prolonged hypofusion and local or systemic cytokine-related injury. Some researchers have suggested that direct cytokine injury to gray matter could be responsible in part for gray matter volume loss. But more important may be mechanisms resulting in reduced connectivity. The premature infant is in a period of rapid axonal growth and elongation; these axons are sensitive to direct injury (eg, ischemic), as well as indirect injury secondary to oligodendroglial cell injury and loss. Subplate neurons, abundant during the preterm period, act as transition points for axonal connections to cortical and subcortical destinations and are vulnerable to injury. Reduction of these connections during a crucial period in brain development could impair neuronal differentiation and, subsequently, gray matter growth.

**MRI Findings and Neurodevelopmental Outcome**

**Specific MRI Findings and Outcomes**

Several studies indicate that MRI provides prognostic information that is complementary to that provided by CUS. In infants with IVH and associated unilateral parenchymal hemorrhage, all infants who had abnormal myelination of the posterior limb of the internal capsule (PLIC) on MRIs performed at near term developed hemiplegia at 12 to 24 months, whereas those with normal, symmetrical PLIC myelination had normal neuromotor outcomes. Early MRI (within the first four weeks of age) in patients with unilateral parenchymal hemorrhage identified additional cysts, punc-
tate white matter lesions, or posterior fossa lesions in several patients, but these early findings did not appear to directly enhance outcome prediction.88 However, in a recent study of 3 to 5 year neuromotor and functional outcomes among infants with T1 hyperintensity or cysts in the periventricular region on term equivalent MRI, the absence of T1 hyperintensity of the corona radiata related to the corticospinal tract—near the PLIC—was associated with normal neuromotor outcomes.83 Conversely, severity of MRI lesions in that same region appeared to be correlated to the severity of motor impairment. Thus, detailed image analysis and attention to specific anatomic regions are required to optimize even advanced neuroimaging methods as prognostic tools.

Among infants with CUS evidence of periventricular echodensities, Sie and coworkers84 reported that brain MRI identified WM lesions ranging from punctate to extensive, as well as cysts that were not seen by CUS. The authors subsequently reported85 that neonatal MRI accurately predicted the location and extent of brain injury on MRI at 18 months and that neonatal MRI scores (based on severity and extent of lesions) predicted motor and visual outcomes at 18 months extremely well. These researchers suggested that, particularly among infants with inhomogeneous periventricular echodensities on CUS, neonatal MRI provided additional valuable information for predicting later outcomes.

Early Neonatal MRI
Several studies have also evaluated usefulness of “early” MRI (performed before term equivalent age). Miller and coworkers86 reported that moderate–severe WMI was seen in 29% (24/83) and mild WMI in 23% of preterm infants by early MRI (performed at a median PMA of 32 weeks). Abnormal signal intensity of WM lesions was less apparent over time, but the severity of WMI remained stable. The authors found that moderate–severe WMI on early MRI was significantly and independently associated with abnormal neurodevelopmental outcome at 18 months. These findings seem to indicate that noncystic WMI associated with adverse outcome can be identified early in the postnatal course.

Another study of sequential brain MRI in preterm infants arrived at different conclusions. Dyet and coworkers58 reported that substantial changes were found when comparing early MRI (performed at a median age of 2 days) to near term equivalent scans, with less than 10% of near term MRI interpreted as normal compared with approximately 40% of early MRI. Although punctate WM lesions seen on early MRI scans appeared to resolve over time in many cases, diffuse excessive high signal intensities (DEHSI) was seen in more than 80% of near-term scans. At 18 to 36 months, lower developmental quotients appeared to be associated with DEHSI and posthemorrhagic ventricular dilation, but not with punctate white matter lesions, hemorrhage alone, or any early MRI indicator apart from cerebellar hemorrhage. However, only 82% of survivors underwent a near-term MRI, and follow-up was obtained in only 68% of survivors. Further study of very early MRI for prediction of neurodevelopmental outcomes is warranted, both to elucidate etiologic mechanisms and timing of injury and to identify early findings that are more accurate and reliable predictors of severe impairment.

Comparing CUS and Term Age Equivalent MRI in the Prediction of Neurodevelopmental Outcomes
Several studies have attempted to specifically compare the predictive capabilities of MRI with CUS, with most focusing on CP or motor delay as a primary outcome. Most of these were small, primarily single-center efforts. Among the most frequently cited studies, Valkama and coworkers87 compared MRI with CUS, both performed at term equivalent, in 51 VLBW, preterm infants (<34 weeks); 12 infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity, whereas CUS at term predicted CP with 67% sensitivity and 85% specificity. As discussed earlier, both de Vries81 and Roelants-van Rijn and coworkers82 found term-equivalent MRI delineation of PLIC to be complementary to CUS in predicting neuromotor impairments when particular brain injuries are present. Mirmiran and colleagues49 performed a prospective observational study of MRI versus CUS to predict CP at 18 and 30 months in 62 preterm infants (<1250 g, <30 weeks EGA). CUS was obtained twice during the first 2 weeks of life, and the most abnormal findings were used for analysis. The sensitivity and specificity of MRI to predict CP at 18 to 22 months were 71% and 91%, respectively. The sensitivity of MRI for CP at 30 months of age increased to 86% with the specificity remaining high at 89%. The sensitivity of CUS to predict CP was only 29% at 18 and 43% at 30 months.

The largest study to date50 compared findings on term equivalent MRI with serial CUS (assessed for IVH and cystic PVL or WM echolucencies) and their association to 2-year neurodevelopmental outcomes in a cohort of 167 preterm survivors (<30 weeks EGA). The authors demonstrated: (1) that the presence of moderate–severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; (2) a significant correlation between white and gray matter abnormalities; (3) increasing severity of WMI was linearly related to worse Bayley MDI scores, but an independent association of “moderate–severe WMI” with “severe cognitive delay” was not found; and (4) gray matter abnormality on neonatal MRI was not significantly associated with later neuromotor or cognitive impairments after adjusting for CUS findings. Although sensitivities of moderate–severe WMI to predict CP (65%), neurosensory impairment (82%), and severe cognitive delay (41%) were greater than that of CUS abnormalities CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n = 29) or severe (n = 6) WMI was small. Importantly, approximately half of those with moderate–severe WMI by neonatal MRI did not have neurodevelopmental impairment at 2 years.

Challenges to Interpretation of MRI Versus CUS Studies
The substantial differences among these studies preclude a single, uniform clinical conclusion. CUS timing and protocols differ among studies, as do the definitions of an “abnor-
mal” finding. Some would argue that the frequently used characterization of an abnormal CUS (grade 3 or 4 IVH or cystic periventricular changes) is extremely coarse at best, and does not use all information available from this tool. Thus, it is reasonable to ask whether protocols requiring more detailed CUS interpretation, a more complete imaging protocol, and frequent serial CUS would provide information with predictive value similar to that of MRI. And might more quantitative MR evaluations, such as diffusion tensor imaging (DTI) and volumetric assessments, enhance the predictive capability of MRI beyond the level described in previous comparisons with CUS?40,41

Optimally, we would be able to identify high-risk preterm patient subgroups for whom MRI would unambiguously improve outcomes prediction. Results of some studies have suggested that near-term MRI may be valuable in the setting of specific CUS findings, including cerebellar echogenicity, diffuse persistent periventricular echogenicities, and unilateral parenchymal hemorrhage.10,53,81,82 Uncomplicated grade 1 or 2 hemorrhage is associated with reduced cortical volumes at near term, suggesting a potential benefit of further neuroimaging for patients with these lesions.40,41 Given the high risk for neurodevelopmental impairment, one might speculate that delineation of injury by MRI could be useful for preterm infants after certain perinatal and neonatal clinical courses or complications40,74,90,93 or for extremely low gestational age infants at term.25,28

Where Do We Go From Here?

Is It Time for Routine MRI in Preterm Infants?

Although clear evidence exists that MRI is superior to CUS in identifying and defining subtle WMI and other abnormalities, it is not yet clear whether this information can improve prediction of patient outcomes. The largest, most comprehensive study to date demonstrated that moderate to severe WMI on MRI was associated with neurodevelopmental impairment independent of severely abnormal CUS. However, 50% of those with moderate to severe WMI did not have neurodevelopmental impairment, whereas approximately 22% of those with none or mild WMI did have neurodevelopmental impairment. Multiple factors certainly influence neurologic, sensory, and cognitive outcomes of preterm infants24-28; whether neuroimaging proof of the impact of these factors can even be expected is not yet known. To date, only relatively short-term neurodevelopmental follow-up has occurred for studies comparing predictive capabilities of neonatal CUS and MRI. Study cohorts must be followed to school-age and later childhood to determine whether differences in neonatal neuroimaging findings will be associated with more subtle challenges to development, cognitive and executive function.

When, or if, MRI would be “routinely” recommended is thus a complicated question, and discussion cannot be limited to research results alone. Even as more hospitals obtain technology and equipment, the “real-life” challenges to performing a term equivalent age MRI for every preterm infant are not trivial. There is no doubt that the cost of preterm birth is enormous and growing, and a single MRI may be unlikely to meaningfully impact this already huge financial burden. Could improved quality, and more complete and frequent CUS, provide the same prognostic advantage as the addition of a neonatal MRI?

A Need for Further Studies

If the primary goal in obtaining an MRI is to better delineate brain injury or suspected anatomical abnormality, there is no doubt that MRI will meet the objective and should be undertaken. However, the advantage of MRI for predicting of neurodevelopmental outcome after carefully performed CUS is not clear. The NICHD Neonatal Research Network is currently in the midst of a multi-center, prospective study of early CUS, term equivalent CUS and MRI among infants <28 weeks EGA who are participating in a randomized controlled trial of ventilation and oxygen strategies (The SUPPORT trial, ClinicalTrials.gov NCT00233324). All survivors will receive comprehensive neurodevelopmental assessment at 18 to 22 months of age corrected for prematurity. Unlike many other previous reports, this study will have central reader interpretation for MRI as well as all CUS. This study is likely to be the largest of its kind to date; an additional advantage is that the cohort will consist exclusively of extremely preterm (<28 week) infants, arguably the highest risk group. Predictive modeling analyses will assess the value of early CUS, late CUS, and term MRI findings, alone and in combination, to predict 18 to 22 month neurodevelopmental outcomes over and above the value of numerous traditional risk factors alone. Due to large patient numbers expected in this study, ancillary analyses may also be able to identify risk subgroups in which MRI may be particularly useful. But beyond further large, prospective studies with relatively short-term neurodevelopmental endpoints, follow-up should also be extended in existing cohorts at least to school age. In fact, it would seem appropriate and prudent to consider incorporation of longer-term follow-up into all randomized controlled trials and prospective cohort studies involving premature infants. As we have learned time and again from experts in the field,22-28 18- to 22-month outcomes certainly do not provide a complete picture of the neurologic, functional, or cognitive future for these high-risk infants.

Unfortunately, even in the age of advanced neuroimaging, we have not yet found a single “perfect predictor” for adverse neurodevelopmental outcome in the preterm infant. Neurologic and particularly cognitive outcomes are influenced by a multitude of variables. At the present time, brain MRI is likely to be used in most institutions as a complementary tool to CUS in the preterm infant, with this easily repeatable bedside technology serving as the primary neuroimaging method.95 But, there is still much to be gained by optimization of our current institutional protocols, and continued rigorous research evaluation and comparison of neuroimaging methods.

Our research efforts should continue to strive toward understanding how clinical events and processes affect the preterm brain and how that injury is linked with outcome, with the
ultimate goal of working toward well-conceived studies of neuroprotective strategies.

**References**

89. Arzoumanian Y, Mirmiran M, Barnes PD, et al: Diffusion tensor brain
imaging findings at term-equivalent age may predict neurologic abnormalities in low birth weight preterm infants. AJNR Am J Neuroradiol 24:1646-1653, 2003


