

CME

# Practice parameter: Neuroimaging of the neonate

## Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society

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**Article abstract—Objective:** The authors reviewed available evidence on neonatal neuroimaging strategies for evaluating both very low birth weight preterm infants and encephalopathic term neonates. *Imaging for the preterm neonate:* Routine screening cranial ultrasonography (US) should be performed on all infants of <30 weeks' gestation once between 7 and 14 days of age and should be optimally repeated between 36 and 40 weeks' postmenstrual age. This strategy detects lesions such as intraventricular hemorrhage, which influences clinical care, and those such as periventricular leukomalacia and low-pressure ventriculomegaly, which provide information about long-term neurodevelopmental outcome. There is insufficient evidence for routine MRI of all very low birth weight preterm infants with abnormal results of cranial US. *Imaging for the term infant:* Noncontrast CT should be performed to detect hemorrhagic lesions in the encephalopathic term infant with a history of birth trauma, low hematocrit, or coagulopathy. If CT findings are inconclusive, MRI should be performed between days 2 and 8 to assess the location and extent of injury. The pattern of injury identified with conventional MRI may provide diagnostic and prognostic information for term infants with evidence of encephalopathy. In particular, basal ganglia and thalamic lesions detected by conventional MRI are associated with poor neurodevelopmental outcome. Diffusion-weighted imaging may allow earlier detection of these cerebral injuries. *Recommendations:* US plays an established role in the management of preterm neonates of <30 weeks' gestation. US also provides valuable prognostic information when the infant reaches 40 weeks' postmenstrual age. For encephalopathic term infants, early CT should be used to exclude hemorrhage; MRI should be performed later in the first postnatal week to establish the pattern of injury and predict neurologic outcome.

NEUROLOGY 2002;58:1726–1738

Despite the development of sophisticated care techniques, the incidence of neurodevelopmental disability among the survivors of newborn intensive care remains high.<sup>1–4</sup> As newborn special care enters its fifth decade, survival rates for both severely compromised

term infants and very low birth weight (VLBW) preterm (PT) infants have increased.<sup>5,6</sup> However, the incidence of cerebral palsy (CP) has not changed during the past 10 years, the number of children with school-based problems is on the rise, and the population of infants at risk for disability is increasing.<sup>7–13</sup> Because the clinical evaluation of these infants may not provide either adequate diagnostic or prognostic information, neuroimaging is frequently used.<sup>14–16</sup>

Additional material related to this article can be found on the *Neurology* Web site. Go to [www.neurology.org](http://www.neurology.org) and scroll down the Table of Contents for the June 25 issue to find the title link for this article.

This statement has been endorsed by the American Academy of Pediatrics, the American Society of Pediatric Neuroradiology, and the Society for Pediatric Radiology.

Approved by the AAN Quality Standards Subcommittee December 8, 2001. Approved by the AAN Practice Committee January 28, 2002. Approved by the AAN Board of Directors February 23, 2002. Approved by the CNS Practice Committee January 30, 2002.

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Neuroimaging plays two important roles: 1) diagnosis of brain injury in the newborn at risk so that appropriate medical management can be provided and 2) detection of those lesions associated with long-term neurodevelopmental disability. Currently, cranial ultrasonography (US), CT, and MRI are the most available means for these tasks.

**Goals.** The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society seek to develop scientifically sound, clinically relevant practice parameters for physicians for diagnostic procedures, treatment modalities, and clinical disorders. Practice parameters are strategies for patient management that might include diagnosis, symptom, treatment, or procedure evaluation. They make specific recommendations based on the analysis of evidence in the published literature.

This practice parameter provides recommendations in response to questions regarding brain imaging of PT and term infants. For PT infants: which PT infants should undergo routine screening US? When should these studies be performed? Do abnormalities shown by neonatal US require follow-up MRI? What is the ability of US to accurately predict long-term neurodevelopmental outcome for this patient population? For term infants: which imaging strategies are able to provide clinically important information for infants with neonatal encephalopathy? Can MRI provide prognostic information for these infants?

**Description of the process.** The committee consisted of neonatologists, pediatric neurologists, perinatal epidemiologists, and neonatal radiologists selected by five professional organizations (see the electronic version of this article for appendix 1 at [www.neurology.org](http://www.neurology.org)); we evaluated the quality of the evidence from the published literature. Evidence reviewed for this parameter was identified through literature searches using MEDLINE and EMBASE for the years 1990 to 2000 and CURRENT CONTENTS for 2000. This literature search was updated in June 2001. Relevant articles were chosen from the English-language literature using the following search terms: neonate, infant, brain, cerebral, MRI, MRS, diffusion-weighted imaging (DWI), diffusion tensor imaging, US, echoencephalography, Doppler ultrasonography, cranial axial tomography, near-infrared spectroscopy, SPECT, germinal matrix hemorrhage, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), stroke, ischemia, ventriculomegaly, and echodensity. Because neonatal practices and imaging strategies have changed over the past decade,<sup>12,17-21</sup> we reviewed only those references from 1990 onward.

This search produced >1,320 citations, from which 90 met the predefined inclusion criteria: original clinical articles published since 1990, review articles, and reports of meta-analyses.

Each of the selected articles was reviewed, ab-

stracted, and classified (appendix 2) by at least two reviewers. Abstracted data included patient number, mean birth weight (BW), mean gestational age (GA), age at the time of the neuroimaging study, primary neuroimaging measure, primary and secondary outcome measures, and timing of subject selection (prospective, retrospective, case-control, or case series study). We also noted both inclusion and exclusion criteria for patient selection and description of the neuroimaging strategy in addition to the results of the given study.

The strength of the evidence for each relevant article was ranked using the defined criteria shown in appendix 2. Recommendations were derived based on the strength of the evidence and stratified (level A, B, C, or U) as shown in appendix 3.

For the purposes of this practice parameter, a screening neuroimaging study was defined as one that is routinely applied to identify infants at sufficient risk of a specific disorder who would benefit from further investigation or direct action but who have no specific neurologic signs or symptoms requiring medical attention (e.g., infants born before 28 weeks of gestation).

**Neuroimaging strategies.** Although neuroimaging has proven to be extremely helpful for the assessment of injury to the PT brain and may provide useful information for evaluating the infant with neonatal encephalopathy, there are significant problems associated with imaging of the critically ill infant.<sup>14,22,23</sup> These include the choice of imaging technique, the timing of the imaging study, and regional variations in maturation of the developing brain. Further, transporting acutely ill neonates, many of whom require ventilatory assistance, multiple indwelling catheters, infusions, vasopressor support, and warming lights, represents a major challenge.

Currently, US, CT, and MRI represent the major imaging modalities most widely available for evaluating critically ill infants.

**VLBW PT infants.** Birth weight (BW) remains one of the most important predictors of infant mortality and morbidity. VLBW infants (BW <1,500 grams) now represent 1.45% of all live births in the United States.<sup>5,6,24</sup> In addition, the survival rates for this population are steadily increasing. In contrast, the handicap rates for surviving infants—particularly those with the lowest BW—are high. At 8 years of age, >50% of children with BW of <1,000 grams are educated in special education classrooms or resource rooms, 20% have repeated a grade in school, and 10% to 15% have spastic motor handicaps.<sup>1,9,13</sup>

Hemorrhage, hypoxia, and ischemia are the major causes of injury to the PT brain, and multiple studies over the past decade have used neuroimaging techniques to assess these injuries.<sup>24-28</sup>

*US screening of the VLBW PT infant.* Although cranial US of VLBW PT infants is routinely performed

**Table 1** Classification of cranial ultrasound findings for the preterm infant

Classification		Findings
Intraventricular hemorrhage*	Grade 1	Germinal matrix hemorrhage
	Grade 2	Blood within the ventricular system but not distending it
	Grade 3	Intraventricular hemorrhage with ventricular dilatation
	Grade 4	Parenchymal involvement
Preterm white matter injury†	Cystic lesions	Periventricular
Ventriculomegaly‡	Mild	0.5–1.0 cm§
	Moderate	1.0–1.5 cm§
	Severe	>1.5 cm§

\*Reference 30.

†References 29, 31–35.

‡References 36, 37.

§ Measurements at the midbody of the lateral ventricle on sagittal scan.

in newborn intensive care units, the target populations, number of examinations, and timing of these studies vary widely. Further, different institutions use different systems of nomenclature to describe IVH, white matter injury, and ventriculomegaly, the three major findings for the PT infant. For this parameter, the grading system for IVH of Papile et al.<sup>29</sup> will be used (table 1). In addition, because there is controversy surrounding the meaning of the periventricular echodensities routinely reported in US studies of PT infants,<sup>28,30–32</sup> injury to the PT white matter will include only periventricular cystic lesions.<sup>14,115</sup> There is a consensus in the field that the degree of ventriculomegaly (see table 1) predicts long-term neurodevelopmental outcome for PT infants studied at or near term.<sup>33,34</sup>

**Correlation of US findings with neuropathologic data.** Before reviewing data pertinent to the practice parameter questions, the committee reviewed the evidence correlating clinical US findings with neuropathologic data. In four class II studies<sup>35–38</sup> reporting results of a total of 87 autopsies performed on PT infants, US was 76% to 100% accurate in detecting grade 1 lesions of >5 mm and grade 3 and grade 4 hemorrhages (see the electronic version of this article for table 4 at www.neurology.org). Detection of grade 2 hemorrhages was much less accurate.

Correlation of US findings of cystic PVL with neuropathologic data was evaluated in three class II studies.<sup>38–40</sup> Each study found 100% correlation between US findings and neuropathologic data.

**Which PT infants should undergo routine screening cranial US? Evidence.** Seven class II studies evaluated the need for screening cranial US in low BW PT infants.<sup>25,27,28,41–44</sup> Review of these studies (ta-

ble 2; see the electronic version of this article for table 5 at www.neurology.org) suggests that although cranial US of 12% to 51% of infants with BW of <1,500 grams or GA of <33 weeks shows some abnormalities in the first 2 weeks of life, major US abnormalities such as grades 3 and 4 IVH or bilateral cystic PVL occur in ≤20% of infants. Furthermore, more severe abnormalities occur in those infants with the lowest BW.

Because infants with grades 3 and 4 IVH are at considerable risk for metabolic abnormalities, post-hemorrhagic hydrocephalus, and its sequelae (e.g., apnea and obtundation), such a US finding would in all likelihood alter the infant's care and thus was considered clinically significant.<sup>16</sup> In addition, cystic PVL and ventriculomegaly are risk factors for CP. These US findings might not only provide critical prognostic information but also influence long-term care strategies. Therefore, it is important to determine which infants are at high risk for grades 3 and 4 IVH, cystic PVL, and/or ventriculomegaly.

In only four studies, the data were presented by specific GA and/or BW groups.<sup>25,28,41,43</sup> In these studies, grades 3 and 4 IVH was noted in 11% of infants with BW of <1,000 grams and in 5% of infants with BW of 1,000 to 1,250 grams; when infants were compared by GA groups, 16% of those with GA of ≤25 weeks and 1% to 2% of infants with GA of >25 weeks had grades 3 and 4 IVH (see the electronic version of this article for table 5 at www.neurology.org). Likewise, cystic PVL was noted in 5% to 26% of infants weighing <1,000 grams, compared with 1% to 5% of infants with BW of >1,000 grams. Ventriculomegaly was described in 5% to 7% of infants weighing <1,000 grams. **Conclusions.** Twelve percent to 51% of infants with BW of <1,500 grams and/or GA of 33 weeks have cranial US abnormalities (class II evidence). However, major abnormalities such as grades 3 and 4 IVH, cystic PVL, and ventriculomegaly, which might alter treatment or provide prognostic information, are considerably more common (20%–25%) in infants with GA of <30 weeks.

**Recommendations (level B).** Close to 25% of infants with GA of <30 weeks have significant cranial US abnormalities that trigger important changes in acute and long-term care. Therefore, routine screening cranial US should be performed on all infants with GA of <30 weeks.

**When should screening cranial US be performed? Evidence.** Multiple class II studies performed before 1990 suggested that >90% of all IVH cases in VLBW PT infants were detected during postnatal days 4 to 5.<sup>45–48</sup>

Data from recent class II studies are shown in table 2 (see the electronic version of this article for table 6 at www.neurology.org). In one study,<sup>28</sup> 248 infants with BW of <1,500 grams underwent regular US at predefined times (1–5 days, 10–14 days, 28 days, and term). Approximately 65% of IVH cases were detected within the first week. The other cases

**Table 2** Incidence and timing of ultrasound abnormalities in preterm infants

Reference no.	Class	Inclusion criteria	US abnormalities, incidence (%)	Major abnormalities, incidence (%)	No. (%) of major abnormalities	Incidence of major abnormalities by GA or BW	Timing of major abnormalities, incidence (%)
41	II	BW, <1,500 g; GA, <34 wk	IVH, 50/250 (20)	Grades 3 and 4 IVH, 13/250 (5)	13 (5)	GA of <25 wk, 9/57 (16); GA of >25 wk, 4/193 (2)	
42	II	BW, <1,500 g; <33 wk	IVH and/or PVL, 245/338 (43)	Grades 3 and 4 IVH and/or cystic PVL, 75/338 (22)	75 (22)		d 1–3, 27/75 (36); d 4–7, 36/75 (48); d 8–14, 12/75 (16)
43	II	BW, <1500 g	PVL, 14/115 (12)			BW of <1000 g, 12/46 (26)	wk 1, 6/14 (43); wk 3–15, 8/14 (57)
25	II	GA, <32 wk; BW, <1,500 g; or GA, <37 wk with ventilator	IVH, 106/800 (13)	Grades 2–4 IVH, 51/800 (6)	51 (6)	GA of <30 wk, 46/364 (13); GA of >30 wk, 5/436 (1)	
27	II	GA, <33 wk	PVL, 26/172 (15)				wk 1, 19/26 (73); wk 2–7, 7/26 (27)
44	II	GA, <36 wk	PVL, 11/53 (21)				wk 1, 10/11 (91); wk 2, 1/11 (9)
28	II	BW, <1,500 g	IVH, PVL and/or VM, 161/317 (51)	Grades 3 and 4 IVH, PVL and/or VM, 40/317 (13)	40 (12.6)	BW of <1,000 g; 13/114 (11.4); BW of >1,000 g; 4/203 (2)	BW of <1,000 g; wk 1 (52) wk 2 (12); wk 4 (16); term (20)

BW = birth weight; GA = gestational age; wk = week; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; VM = ventriculomegaly; d = day.

occurred in the second and third postnatal weeks, and one infant developed severe IVH after postnatal day 28. When BW was <1,000 grams, severe IVH was detected in 10 (77%) of 13 infants on days 1 to 5; 13 (100%) of 13 cases of severe IVH were detected on day 28.

In a study designed to assess changes in US findings across time,<sup>42</sup> 144 infants with BW of <1,500 grams or GA of <33 weeks underwent US between days 1 and 7 and then between days 10 and 14. Fifteen infants (10%) had significant changes in US findings from the first to the second scan. Thirteen infants whose first US showed normal results or grades 1 and 2 IVH were found to have major abnormalities (i.e., grades 3 and 4 IVH and/or PVL) at the time of the second scan. For two infants, US findings changed from a major abnormality during the first US (i.e., PVL) to either normal results or a minor abnormality (i.e., grade 2 IVH) during the second US.

Cystic PVL has been detected in infants without previous US abnormalities as late as postnatal day 104.<sup>27,43,44</sup> In one report,<sup>28</sup> cystic PVL and ventriculomegaly were found in 8 (3%) of 256 neonates after previously normal US findings. For infants weighing <1,000 grams, 3 (50%) of 6 cases of PVL were noted at 36 to 40 weeks' postmenstrual age.

**Conclusions.** The timing at which US can detect injury in the developing brain may be changing. Grades 3 and 4 IVH, which may alter medical management and prognostic information, may be detected as late as the third postnatal week. Cystic PVL and ventriculomegaly, which may alter prognostic

and treatment programs, may be first seen by US at term. Furthermore, these lesions may be detected in many infants after previously normal US findings.

**Recommendation (level B).** Screening cranial US should be performed on all infants with GA of <30 weeks at 7 to 14 days of age and should be optimally repeated at 36 to 40 weeks' postmenstrual age. This recommendation is designed to detect both clinically unsuspected IVH, which may require additional clinical and/or radiologic monitoring and changes in management plans, and evidence for PVL and/or ventriculomegaly, which are useful for prognosis and best seen when the infants are examined at term.

*Do abnormalities of screening cranial US for the PT infant require follow-up MRI either to obtain information for patient management or to provide long-term prognostic data?* **Evidence.** Three recent class II studies (see the electronic version of this article for table 7 at [www.neurology.org](http://www.neurology.org)) compared results of cranial US and MRI performed during the newborn period for PT infants.<sup>26,49,50</sup> Maalouf et al.<sup>26</sup> performed paired MRI and US studies on the same day for 32 infants with GA of <30 weeks. US accurately detected the presence of germinal matrix, IVH, and parenchymal hemorrhage confirmed by MRI (positive predictive values of 0.8, 0.85, and 0.96, respectively). However, in this study and others,<sup>49,50</sup> white matter injury detected by MRI was less well predicted by US (sensitivity of 0.56–0.89). Additional information provided by MRI included depiction of hemorrhagic lesions in 64% of infants and more numerous or extensive cysts in infants with

PVL diagnosed by US.<sup>50</sup> To date, there has not been correlation with neurodevelopmental follow-up.

**Conclusions.** Compared with US performed on the same day, MRI of PT neonates detects more white matter abnormalities in the first week of life, more hemorrhagic lesions, and more numerous or extensive cysts. There are insufficient data from follow-up studies to indicate whether these additional findings provide more information about the neurodevelopmental prognosis.

**Recommendation (level C).** Currently, available data from class II studies do not provide sufficient evidence that routine MRI should be performed on all VLBW PT infants for whom results of screening cranial US are abnormal.

*What is the ability of neonatal cranial US to predict long-term neurodevelopmental outcome for VLBW PT infants? Evidence.* VLBW PT infants are at high risk for neurodevelopmental handicap. Depending on the GA of the cohort and the year of birth, the previously reported incidence of mental retardation and/or CP among PT infants ranged from 7% to almost 50%.<sup>1,4,51,52</sup> Further, the timing of cranial US used to predict outcome in the reported literature varied from the first 2 weeks of life through term. For this reason, the lesions reported and the predictive values for these lesions were difficult to compare. Finally, in several studies, children deemed excessively impaired were omitted from the follow-up assessments, and in many, the outcome measures were reported in broad categories. Therefore, it was difficult to assess the nature of CP or mental retardation across cohorts.

Only reports containing the following data were included: GA and/or BW of the study population, postmenstrual age of the "predictor" US when recorded, neurodevelopmental follow-up rate, age at assessment, and outcome variables.

The six class II studies<sup>34,53-57</sup> (see the electronic version of this article for table 8 at [www.neurology.org](http://www.neurology.org)) compared US findings with the incidence of CP for almost 2,250 VLBW PT children at ages 2 to 9 years. Significant associations between grade 4 IVH, PVL, and/or ventriculomegaly and CP were noted in all six studies. In the largest of these studies,<sup>58</sup> both grade 4 IVH and PVL were associated with CP (odds ratio [OR], 15.4; 95% CI, 7.6-31.1); any grade IVH alone was also associated with CP (OR, 3.14; 95% CI, 1.5-6.5). Similar data were available from one class III study and three class IV studies (see the electronic version of this article for table 8 at [www.neurology.org](http://www.neurology.org)).<sup>59-62</sup>

When the same groups from class II and class III studies<sup>53-55,57-59,63,64</sup> assessed the correlation of neonatal US findings with the developmental quotient, grade 4 IVH and moderate to severe ventriculomegaly were strongly associated with the risk of mental retardation at 2 to 9 years of age (see the electronic version of this article for table 8 at [www.neurology.org](http://www.neurology.org)). In these prospective studies, OR

ranged from 9.97 to 19.0. In addition, Whitaker et al.<sup>65</sup> demonstrated that for infants with BW of 500 to 2,000 grams who had grade 4 IVH and/or moderate to severe ventriculomegaly, the OR for the development of any neuropsychiatric disorder at the age 6 years was 4.4.

**Conclusions.** Grades 3 and 4 IVH, cystic PVL, and moderate to severe ventriculomegaly determined by US have all been shown to be significantly associated with CP at 2 to 9 years of age in VLBW PT infants (class II evidence). In addition, class II evidence, grade 4 IVH, and ventriculomegaly have been significantly associated with mental retardation and neuropsychiatric disorders at the same time points. The OR, which vary depending on the population under study, the lesion, and the outcome measure, all indicate at least a 10-fold elevation in the risk of adverse outcome for VLBW PT infants with US evidence of grades 3 and 4 IVH, cystic PVL, and moderate to severe ventriculomegaly.

**Recommendation (level A).** For VLBW PT infants, US should be used to predict long-term neurodevelopmental outcome. The findings of grades 3 and 4 IVH, periventricular cystic lesions, and moderate to severe ventriculomegaly are all associated with adverse outcome.

### **Term infants with neonatal encephalopathy.**

Clinical examination of the term infant with signs and symptoms of neonatal encephalopathy is often unable to determine the severity or extent of cerebral damage and frequently provides little information regarding the etiology of the insult. Although numerous reports suggest that hypoxic-ischemic encephalopathy (HIE) is a common cause of neonatal encephalopathy, the differential diagnosis of this condition is extensive, including a spectrum of abnormalities ranging from infectious to metabolic abnormalities and congenital malformations.<sup>66,67</sup> Even in those infants with documented HIE, the clinical presentation may vary widely.<sup>68</sup> Of those neonates with moderate to severe HIE, almost one-quarter have mental retardation, seizures, and CP, and promising intervention strategies are now becoming available.<sup>69-71</sup> Therefore, for diagnostic and prognostic reasons, early assessment and diagnosis of infants with neonatal encephalopathy is important.

For the definition of neonatal encephalopathy, the committee used the criteria set forth by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists in *Guidelines for Prenatal Care*.<sup>72</sup> For results of a study to be rated as class I evidence, infants described therein must meet all of the following conditions:

1. Profound metabolic or mixed acidemia (pH < 7.00 [umbilical cord artery blood sample if obtained]).
2. Apgar score of 0 to 3 for >5 minutes.
3. Neonatal neurologic manifestations (e.g., seizures, coma, or hypotonia).
4. Multisystem organ dysfunction (e.g., cardiovascu-

lar, gastrointestinal, hematologic, pulmonary, or renal system).

Although these criteria were originally developed for those infants thought to have HIE, they also describe any infant who requires immediate neonatal evaluation—both to determine the underlying cause of encephalopathy and to provide therapeutic interventions, when available.<sup>67,73,74</sup> Studies in which the entry criteria of the infants evaluated were less rigorously defined received lower classification levels than did those in which infants met these conditions.

*Which neonatal neuroimaging strategies can detect cerebral abnormalities that may affect the immediate and long-term management of the infant with neonatal encephalopathy? Evidence.* One study discussed gray-scale US of the infant with neonatal encephalopathy.<sup>75</sup> A second study compared findings of gray-scale US and Doppler US with outcome,<sup>76</sup> and a third study compared results of gray-scale US and Doppler US with somatosensory evoked potentials, visual evoked potentials, and results of the cerebral function monitoring.<sup>77</sup> A fourth study compared findings of gray-scale US, Doppler US, and CT.<sup>78</sup> Three other studies compared results of gray-scale US and MRI for infants with neonatal encephalopathy.<sup>79-81</sup> Four studies reported CT findings for these infants.<sup>82-85</sup>

*Gray-scale US, Doppler US, and studies comparing US with CT and/or MRI.* In one class III study<sup>75</sup> (see the electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)), US was performed on 104 encephalopathic term neonates and 70 control term neonates on the first postnatal day. A diffuse increase in echogenicity of the cerebral parenchyma and slit-like ventricles were significantly more common in infants with encephalopathy than in controls (39% versus 1% [ $p < 0.001$ ] and 44% versus 9% [ $p < 0.001$ ], respectively), but the investigators found no correlation between US findings on the first postnatal day and neurodevelopmental status at 1 year of age. Similar results were noted in a class II study evaluating term infants with neonatal encephalopathy on the first postnatal day.<sup>76</sup>

In the same class II study,<sup>76</sup> analysis of simultaneous Doppler US demonstrated resistive indices (resistive index = peak systolic velocity minus end diastolic velocity divided by peak systolic velocity) of  $<0.60$  for all children with adverse neurodevelopmental outcome. In another class II study,<sup>78</sup> gray-scale US, Doppler US, and CT were performed on infants with neonatal encephalopathy (see the electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)). Gray-scale US was not predictive of outcome, but a resistive index of  $\leq 0.5$  in the middle cerebral artery was associated with adverse neurodevelopmental outcome at 1 to 2 years (sensitivity, 82%; specificity, 89%). In addition, CT demonstrating generalized decreased density had 91% sensitivity and 100% specificity for adverse outcomes.

Three studies compared early US and MRI studies for infants with neonatal encephalopathy (see the

electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)).<sup>79-81</sup> An abnormal MRI signal in the basal ganglia in association with an abnormal US result for the basal ganglia was most frequently associated with an adverse neurodevelopmental outcome including CP, seizures, and developmental delay at 1 year of age, while normal findings of US and CT or US and MRI had low negative predictive values.

*Conclusions.* Seven studies (classes II and III) assessed the role of gray-scale US in the diagnosis of term infants with neonatal encephalopathy. Although gray-scale US can be easily performed at the bedside, there are little data to support the use of this modality in imaging of the encephalopathic term neonate. However, two class II studies of Doppler US suggested that resistive indices of  $<0.5$ – $0.6$  are consistent with the diagnosis of HIE.

*CT studies.* CT can be performed rapidly and without sedation of the neonate. Four studies used CT to evaluate term infants with neonatal encephalopathy. One study<sup>84</sup> reported basal ganglia changes; a second study<sup>82</sup> reported both basal ganglia and thalamic changes. Two studies<sup>83,85</sup> used CT to detect intracranial hemorrhages in infants with signs and symptoms of neonatal encephalopathy who also had low hematocrit or evidence of coagulopathy; in both studies, detection of intracranial hemorrhages altered clinical care.

*Conclusions.* One class II study and three class IV studies assessed the value of CT for encephalopathic term neonates. Two studies suggested that low attenuation in the basal ganglia and/or thalami indicates severe injury consistent with HIE. The other two studies demonstrated that CT plays a role in the detection of hemorrhagic lesions.

*MRI studies.* Two studies (see the electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)) compared MRI findings with neuropathologic data for infants with neonatal encephalopathy believed attributable to HIE.<sup>86,87</sup> In the larger study,<sup>87</sup> imaging data were compared with results of neuropathologic analyses of the posterior limb of the internal capsule, thalamus, parietal cortex, hippocampus, and medulla. The posterior limb of the internal capsule was the most reliable region analyzed, and agreement of MRI findings was similar to that achieved by two pathologists reviewing the histologic sections ( $\kappa = 0.66$ ). In this study, the MRI abnormality was predictive of the pathologic abnormality with a sensitivity of 0.70 and a positive predictive value of 1.0. The predictive value of a single MRI abnormality was 0.79 (95% CI, 0.61–0.96).

In eight class II studies (see the electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)),<sup>2,88-94</sup> conventional T1- and T2-weighted MRI studies were performed for a total of 272 term neonates, most of whom were clinically suspected of having neonatal encephalopathy secondary to hypoxic-ischemic injury. Scans were obtained at ages ranging from 1 to 30 postnatal days, and the mean age range was 2 to

8 days. Three patterns of injury were detected by MRI: 1) injury to the thalami and/or posterior-lateral putamen with involvement of the subcortical white matter in the most severe injuries; 2) injury to the parasagittal gray matter and subcortical white matter, posteriorly typically more than anteriorly; and 3) focal or multifocal injury. Thalamic and basal ganglia damage was the most common abnormality reported. This pattern of injury was detected in almost 40% of infants and represented over one-half of all abnormalities (see the electronic version of this article for table 10 at [www.neurology.org](http://www.neurology.org)). In one class III study,<sup>95</sup> abnormal T1-weighted images showing hyperintensities in a characteristic distribution were demonstrated as early as 3 days after the injury; abnormal T2-weighted images showing hypointensities were demonstrated by 6 to 7 days.

**Conclusions.** Results of class II studies indicate that characteristic MR patterns of cerebral injury can be detected using conventional T1- and T2-weighted imaging sequences performed at mean ages of 2 to 8 days for encephalopathic term infants.

**Diffusion weighted imaging.** Studies of adult arterial infarcts have shown that DWI signal changes occur within minutes of symptom onset and hours before changes become apparent on T1- or T2-weighted images.<sup>96</sup> In one class II study<sup>86</sup> and four class III studies<sup>97-100</sup> that investigated the use of DWI in the evaluation of term neonates (see the electronic version of this article for table 11 at [www.neurology.org](http://www.neurology.org)), entrance criteria were not stated in enough detail to determine which infants met strict criteria for acute neonatal encephalopathy, and neonates with focal seizures were also included. MR studies were performed a mean of 2 to 4 days after birth, and DWI findings were compared with those of standard MRI sequences. Abnormal DWI results were reported for two-thirds of infants. For 7% to 58% of infants with abnormal DWI findings, T2- and/or T1-weighted images were also abnormal. Abnormal DWI results and normal T1- and/or T2-weighted images typically occurred when imaging was performed earlier than day 2 of life or when there was diffuse white matter involvement. Robertson et al.<sup>99</sup> described one patient for whom all imaging sequences including DWI and T1- and T2-weighted imaging sequences were normal when performed at 13 hours despite development of DWI and T1- and T2-weighted imaging abnormalities by 5 days. Robertson et al. also described one other patient for whom DWI results were normal at 8 days when T1- and T2-weighted images were abnormal; this decreased sensitivity of DWI in the subacute to chronic phase has also been noted for the adult population, suggesting that the maximum sensitivity of DWI is between 2 and 8 days.

**Conclusions.** Findings of one class II study and four class III studies suggest that DWI can provide evidence of cerebral injury before conventional MRI techniques for term infants with neonatal encephalopathy. However, DWI results may be negative if it

is performed earlier than 24 hours of life or later than 8 days of life.

**Proton MRS.** A number of investigators have explored the utility of <sup>1</sup>H-MRS and <sup>31</sup>P-MRS at field strengths of  $\geq 1.5$  T, but the recommendations for this parameter will be limited to <sup>1</sup>H-MRS at 1.5 T because this is the equipment most commonly available for neonatal imaging. All of the studies that evaluated <sup>1</sup>H-MRS at 1.5 T used single-voxel point resolved spectroscopy (PRESS) or stimulate echo acquisition mode (STEAM) MRS; although multivoxel chemical shift imaging (CSI) allows high resolution evaluation of larger regions of tissue, there are no data at this time that assess the role of this modality in perinatal brain injury.

In a number of class II studies (see the electronic version of this article for table 12 at [www.neurology.org](http://www.neurology.org)), echo times of  $\approx 136$  msec and 272 msec were preferred over the shorter echo times of  $\approx 36$  msec because of the higher SD of metabolite concentrations measured at these shorter echo times.<sup>20,93</sup> An echo time of 136 msec has the additional advantage of an inverted lactate peak, making distinction from lipids (which can resonate in the same region) more accurate.

One class II study<sup>101</sup> used MRS at 1.5 T within the first 18 hours in 31 cases of suspected HIE and in 7 matched controls. Lactate/creatine ratios ranged from 0 to 0.6 (median, 0.05) for the seven controls. In contrast, the investigators demonstrated lactate/creatine ratios of  $>1.0$  for 10 (32%) of the 31 infants with suspected HIE. In three additional class II studies,<sup>93,102,103</sup> proton MRS of the basal ganglia was performed within the first 2 weeks of life on 77 infants with neonatal encephalopathy. Elevated lactate/*N*-acetylaspartate ratios were the most consistent findings, although elevated lactate/creatine and lactate/choline ratios were also reported for infants with suspected neonatal encephalopathy.

**Conclusions.** Data from class II studies suggest that MRS can play an important role in the assessment of encephalopathic term infants. Lactate/creatine ratios of  $>1$  in the first 18 hours are more common in those infants with later neurologic findings consistent with HIE. Elevated lactate/*N*AA, lactate/creatine, and lactate/choline ratios in the first 2 postnatal weeks are more common in infants with suspected neonatal encephalopathy than in age-matched controls.

#### Recommendations for diagnostic assessment.

1. For infants with a history of neonatal encephalopathy, significant birth trauma, and evidence for low hematocrit or coagulopathy:

a. Noncontrast CT should be performed to look for hemorrhage (level B).

b. If the CT findings cannot explain the clinical status of the neonate, MRI should be performed (level A).

2. For other neonates with acute encephalopathy:

a. MRI should be performed between days 2 and 8 of life (level A).

b. If single-voxel MRS is available, MRI should include MRS (level B).

c. At the time of MRI, DWI should also be performed if this modality is available (level C).

d. CT should be performed only if MRI is not available or if the neonate is too unstable for MRI (level A).

*Can MRI provide prognostic data for term infants with neonatal encephalopathy? Evidence.* Eight class II studies (table 3; see the electronic version of this article for table 9 at [www.neurology.org](http://www.neurology.org)) assessed the ability of conventional MRI performed between 2 and 8 days of age to predict neurodevelopmental handicap at postnatal ages of 12 to 24 months.<sup>2,88-94</sup> Although results of several studies suggested that abnormalities of the cerebral white matter are associated with adverse outcome in term infants with neonatal encephalopathy, 50% to 94% of infants with changes in the basal ganglia developed CP, mental retardation, and seizures at 1 to 2 years of age.<sup>2,88,91,94</sup> Barkovich et al.<sup>89</sup> correlated cognitive and motor outcome with timing of conventional MRI. Proton density MRI scans correlated best during the first 3 postnatal days, proton density and T1-weighted im-

ages correlated best during the first 7 postnatal days, and T2-weighted images correlated best after 7 to 8 postnatal days. Overall, proton density images during the first 7 postnatal days were the best predictor of outcome in this study.

Similarly, three studies using DWI (table 3; see the electronic version of this article for table 11 at [www.neurology.org](http://www.neurology.org)) performed at a mean age of 2 days in neonatal encephalopathy demonstrated a significantly elevated risk of adverse neurologic outcome, although the small sample sizes make predictions unreliable.<sup>97-99</sup>

Finally, review of the class II studies using proton MRS (table 3; see the electronic version of this article for table 12 at [www.neurology.org](http://www.neurology.org)) within the first 11 days of life demonstrated that lactate/creatine ratios of >1.0 and elevated lactate/NAA or lactate/choline ratios were highly predictive of adverse neurodevelopmental outcome at 1 to 2 years of age.<sup>93,101-103</sup> Infants with lactate/creatine ratios of >1.0 were found to have adverse neurodevelopmental outcome at 1 year of age (OR, 13.2; sensitivity, 66%; specificity, 95%; positive predictive value, 86%; negative predictive value, 88%).<sup>101</sup> Similarly, ele-

**Table 3** MRI studies of term neonatal encephalopathy

Reference no.	Class	Number	Follow-up	Predictor study	Time study	Outcome measures	Age	Data
88	II	15	15/15	MRI	newborn	CP	1 yr	only BG predict CP (3/3)
102	II	31	31/31	MRS	newborn	CP, MR	1 yr	BG lac/CHO & lac/NAA associated with MR and/or CP p < 0.003 for all
90	II	25	25/25	MRI	>7 days	DQ	1 yr	6/6 N MRI—Normal 12 abn BG—12/12 MR/CP
117	III	16	16/16	MRS	d 18	exam	1 yr	no significant differences
101	II	31 HIE & 7N	31/31	MRS	newborn	CP, MR	1 yr	if Lac/creat >1.0, OR 13.2; sens 66%, spec 95%
97	II	26	26	DWI	newborn	exam	6 mo	abn DWI: 10/12 abn examN DWI: 12/14 N exam
98	II	4	4 of 4	DWI	d 2	exam	3–21 mo	abn DWI: 4/4 abn exam
91	II	43	43/43	MRI	d 6	MR, CP		abn BG predict CP or MR p < 0.01
2	II	52	52/52	MRI	d 8–30	head growth	1 yr	N MRI: 11/12 N outcome abn WM: 5/5 abn outcomeabn BG: 5/7 abn outcome
93	II	21	18/18 survivors 3 deaths	MRI/MRS	d 8	outcome	2 yrs	N MRI: 8/9 N; abn MRI: 5/11 abn; abn BG/MRI: 4/7 abn; Lac/NAA assoc with outcome p < 0.05
99	II	43	43/43	MRS	<1 mo	outcome	1 yr	lac/creat predict outcome p = 0.001
94	II	75	73/75	MRI	d 1–17	DQ	1 yr	abn BG: sens 90%; spec 100%
104	II	18 HIE & 3 N	14/14 survivors 4 deaths	MRI	d 6	outcome	1–2 yrs	Lac/NAA predict outcome p = 0.05



vated lactate/NAA and lactate/choline or lactate/creatine ratios in the region of the basal ganglia were significantly associated with CP and mental retardation ( $p < 0.001$  for all studies).<sup>102,103</sup> In another report, abnormalities of NAA/creatine, NAA/choline, and choline/creatine ratios in the occipital gray/parietal white matter regions were predictive of adverse outcome at a mean age of 15 months in infants with HIE.<sup>104</sup> Positive predictive values for abnormal neurodevelopmental outcome based on these metabolites were 0.64, 0.68, and 0.75 for values  $>2$  SD from those of controls.

**Conclusions.** Class II MRI studies demonstrated that the incidence of neurodevelopmental handicap among those infants with abnormalities of the thalami and basal ganglia at mean postnatal ages of 2 to 8 days is significant at 1 to 2 years of age. Limited and predominantly class III DWI evidence demonstrates abnormalities in infants with neonatal encephalopathy at a time when results of conventional MRI are normal. Class II studies of proton MRS performed within the first 8 postnatal days also suggest good to excellent predictive values for this measure for neurodevelopmental outcome at 1 to 2 years of age.

**Recommendation.** MRI should be performed within the first 2 to 8 days of life to provide predictive data for neurodevelopmental outcome in encephalopathic term infants (level A). DWI (level C) and MRS (level B), when available, should also be performed within the first 2 to 8 days to provide additional prognostic data concerning neurodevelopmental outcome.

**Future directions.** As the number of infants cared for in neonatal intensive care units grows and survival statistics steadily increase, neuroimaging has become critical technology. Imaging of the developing brain is no longer a research goal; it has become clinically relevant. Neuroimaging can provide diagnostic information but also data used for clinical decision making as well as information on treatment efficacy and prognosis. This becomes particularly important in the anticipation of potential preventive, protective, and rehabilitative strategies for the management of critically ill newborn infants.

Several ongoing clinical trials are assessing the impact of neuroprotective strategies on long-term neurodevelopmental outcome.<sup>105</sup> For these studies, neuroimaging is critical—not only to provide diagnostic entry criteria but also to assess the effect of the intervention and to provide prognostic neurologic information.

Two sets of difficulties must be overcome to more fully incorporate neuroimaging into the newborn intensive care unit. MRI holds great promise; however, this imaging modality and others that may be soon developed must become more infant friendly, and imaging strategies should be developed to provide maximum information in minimum time. This would include the following: improved magnet technology

that would allow easy placement of affordable MRI devices in newborn intensive care units, software and hardware advances that would minimize imaging time and allow DWI and/or MRS sequences to be easily performed on critically ill neonates, and MRI-compatible devices that improve our ability to monitor and maintain critically ill neonates. Further, it is important that results of these imaging studies, including processed DWI and MRI data, be available immediately for viewing by all involved specialties.

To provide more accurate information, these MR techniques must be optimized and standardized in terms of types of sequence, parameters for each imaging sequence, regions of brain evaluated, and timing of evaluations. Prospective imaging studies with centralized, blinded readers and well-defined cohorts of infants and matched controls should be performed to determine accurate diagnostic criteria. Similarly, prognostic data can be determined only from blinded standardized follow-up assessments of all infants imaged by the modality under study.

Although there is some recent control data on DWI for neonates,<sup>106,107</sup> the numbers of patients studied are small. There is also a strong need for MRS control data for neonates. For both of these modalities, serial studies are generally lacking, and the impact of timing of the study and regional variation on its result remains unknown. For example, although elevated lactate/NAA, lactate/creatine, and lactate/choline ratios are reported to be more common for infants with suspected HIE, more studies are required to determine the upper limits of these ratios for the normal population at various postnatal ages and to determine the sensitivity, specificity, and predictive values of these ratios. Studies are also needed to determine not only the optimal timing of DWI and MRS evaluation for term infants with neonatal encephalopathy but also the optimal region for investigation for MRS. Long-term follow-up data on the disability rate are of critical importance. Control data, timing studies, neuropathologic correlations, and ultimately outcome assessments are also needed before MRI becomes the standard of care for the VLBW PT neonate. MRS and DWI for this age group have the potential to provide much needed information concerning the timing of white matter injury in the developing brain and may lead to injury-specific interventions.<sup>108</sup>

Preliminary studies suggest that the more aggressive and timely use of advanced structural and functional prenatal imaging techniques to detect and characterize abnormalities may allow intervention to prevent postnatal neurologic morbidity and mortality.<sup>109,110</sup> Prenatal imaging may provide information for consideration of corrective prenatal surgical or medical interventions where appropriate and can assist with the planning of surgical or medical interventions in the intrapartum and postpartum periods. Therefore, studies that correlate prenatal US and MRI findings with results of postnatal neuroimaging and outcome are needed.

Near infrared spectroscopy, nuclear medicine (SPECT and PET), and fMRI are other major imaging technologies not discussed in this parameter because of lack of data; these technologies are under evaluation for use in the assessment of the developing brain.<sup>111-115</sup> The challenge is to develop and implement effective applications of these advanced neuroimaging techniques and to perform studies evaluating their diagnostic and predictive ability. As evidence becomes available,<sup>116</sup> it must be reviewed on a regular basis, and the practice parameter must be modified accordingly.

**Disclaimer.** This statement is provided as an educational service of the American Academy of Neurology and the Child Neurology Society. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology and the Child Neurology Society recognize that specific patient care decisions are the prerogative of the family and the physician caring for the patient.

## Appendix 1

*Professional Organizations Represented:* American Academy of Pediatrics, American Academy of Neurology, American Society of Pediatric Neuroradiology, Child Neurology Society, Society for Pediatric Radiology.

*AAN Quality Standards Subcommittee Members:* Gary Franklin, MD, MPH (Co-Chair); Catherine Zahn, MD (Co-Chair); Milton Alter, MD, PhD (ex-officio); Stephen Ashwal, MD; Rose M. Dotson, MD; Richard M. Dubinsky, MD; Jacqueline French, MD; Gary H. Friday, MD; Michael Glantz, MD; Gary Gronseth, MD; Deborah Hirtz, MD (facilitator); Robert G. Miller, MD; David J. Thurman, MD, MPH; and William Weiner, MD.

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## Appendix 2

### Definitions for classification of diagnostic evidence

*Class I:* Evidence provided by a prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

*Class II:* Evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or a well designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

*Class III:* Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

*Class IV:* Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

### Definitions for classification of prognostic evidence

*Class I:* Evidence provided by a prospective study of a broad spectrum of persons who may be at risk for developing the outcome (e.g., target disease, work status). The study measures the predictive ability using an independent gold standard for case definition. The predictor is measured in an evaluation that is masked in a clinical presentation and the outcome is measured in an evaluation that is masked to the presence of the predictor.

*Class II:* Evidence provided by a prospective study of a narrow spectrum of persons who may be at risk for developing the outcome, or by a retrospective study of a broad spectrum of persons with the outcome compared to a broad spectrum of controls. The study measures the predictive ability using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.

*Class III:* Evidence provided by a retrospective study where either the persons with the condition or the controls are of a narrow spectrum. The study measures the predictive ability using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.

*Class IV:* Any design where the predictor is not applied in a masked evaluation OR evidence provided by expert opinion or case series without controls.

## Appendix 3

### Definitions for strength of recommendations

*Level A:* Established as useful/predictive or not useful/predictive for the given condition in the specified population (requires at least one convincing class I study or at least two consistent, convincing class II studies).

*Level B:* Probably useful/predictive or not useful/predictive for the given condition in the specified population (requires at least one convincing class II study or at least three consistent class III studies).

*Level C:* Possibly useful/predictive or not useful/predictive for the given condition in the specified population (requires at least two convincing and consistent class III studies).

*Level U:* Data inadequate or conflicting. Given current knowledge, test/predictor is unproven.

### Acknowledgment

The authors thank Wendy Edlund, Alison Nakashima, Vicki Glasgow, Marjorene Ainley, and Nancy DiMaio for bibliographic and editorial support and Karol Katz for computing assistance.

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*Neurology* 2002;58;1726-1738

DOI 10.1212/WNL.58.12.1726

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