response to treatment did not contribute to the failure to receive intraperitoneal therapy — an assumption that is potentially flawed.

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Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy

TO THE EDITOR: Shankaran et al. (Oct. 13 issue)[1] report improved neurologic outcomes and reduced mortality in newborns with perinatal asphyxia treated with mild hypothermia. This confirms previous observations from one randomized trial and eight nonrandomized studies.[2,3]

The accompanying editorial by Papile[4] concludes that brain cooling for neonates with hypoxic–ischemic encephalopathy should be considered an experimental technique and that widespread application would be premature. Papile suggests that longer-term follow-up will be needed to confirm the benefits in terms of neurologic performance. We feel strongly that this conservatism is misplaced. No other effective treatments for encephalopathy after hypoxia are available; with two randomized trials and eight nonrandomized studies all showing benefits from hypothermia without significant adverse events, and with supporting evidence from studies of other conditions,[3,5] particularly encephalopathy after hypoxia subsequent to cardiac arrest, how much more evidence is needed?

The effectiveness of hypothermia depends on speed of induction[3,5]; indeed, "time is brain." Obtaining informed consent will cause a loss of precious time. Although obtaining consent is unavoidable for unproven treatments, it should no longer apply to the treatment of encephalopathy after hypoxia. Physicians caring for patients with hypoxic encephalopathy should begin offering this treatment immediately.

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TO THE EDITOR: Shankaran and colleagues report that whole-body hypothermia reduces the risk of death or disability in infants with hypoxic–ischemic encephalopathy. Their article, however, may have contributed to perpetuating misinterpretations about the etiology of encephalopathy in newborns.

Their chief criterion for study entry was marked acidosis, which can be due to hypoxia or ischemia but can have other antecedents. Only a small proportion of cases of encephalopathy in term infants is attributable to identifiable perinatal catastrophes.[1,2] The neutral term "neonatal encephalopathy" does not claim more than the evidence supports and is clearly more suitable than "hypoxic–ischemic encephalopathy" when the etiology is uncertain.

Appropriate terminology matters. Methods of prevention are likely to differ according to the etiology of the encephalopathy. In addition, the diagnosis of hypoxic–ischemic encephalopathy by the physician can be used to blame obstetrical caregivers, even when the processes leading to

brain injury were present some time before birth and were not recognizable or alterable by the obstetrician. A diagnosis of hypoxic–ischemic encephalopathy should be made only when there is clear evidence to justify it. The preferable term is neonatal encephalopathy.

(The views expressed are those of the authors and do not necessarily represent those of the National Institutes of Health or the Department of Health and Human Services.)

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TO THE EDITOR: The article by Shankaran et al. about systemic hypothermia in newborns adds critical weight to previous reports that post-injury hypothermia may improve the recovery of infants with neonatal encephalopathy. Although the magnitudes of the effect, adjusted for the severity of clinical encephalopathy, are similar in the present report and in a trial we reported previously,[1] it is intriguing to note one apparent difference. In the trial of head cooling, there was no effect on mortality in the first week of life, whereas neuromotor disability at 18 months was reduced; in the trial of systemic cooling, a substantial component of the overall improvement in final outcome was a reduction in early mortality. There is some evidence from early magnetic resonance imaging (MRI) of infants cooled by both methods that suggests that the cortex is much better protected by head cooling than by systemic hypothermia, although deep-brain structures appeared similarly protected.[2]

Thus, it may be that long-term follow-up will demonstrate a difference in cognitive or other outcomes. Further work is essential to identify the optimal methods of applying hypothermia and selecting infants who may benefit from treatment.

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THE AUTHORS REPLY: As noted by Polderman and Girbes, treatment for hypoxic–ischemic encephalopathy currently is limited to supportive intensive care, and our study demonstrated the efficacy of whole-body cooling in reducing the rate of death or disability in infants with moderate or severe encephalopathy. We are currently cooling infants in our network centers if the infants meet the same criteria as for study entry. We also use a protocol identical to the study protocol. We believe, however, that caution must be exercised before whole-body hypothermia can be used in routine clinical practice. Use of the equipment requires skilled personnel, and the infants require continuous monitoring during the cooling and rewarming process.

We agree with Nelson and Leviton that only a proportion of newborn encephalopathy is attributable to hypoxia and ischemia. The subgroup of neonates with encephalopathy after hypoxia and ischemia comprises infants who may benefit from hypothermia, given the efficacy of this intervention in studies in animals.[1-3] The eligibility criteria for this trial were designed to be consistent with acute hypoxic–ischemic encephalopathy supported by profound fetal acidosis or acute perinatal events and resuscitation at birth. We reviewed the diagnosis at discharge or death of the 205 study infants with primary outcome data, and 4 infants (2 in the hypothermia group and 2 in the control group) were confirmed after randomization to have sepsis. No metabolic or major congenital abnormalities that contributed to encephalopathy were diagnosed in any study infant.

We respectfully disagree with the statement by Gluckman et al. that a substantial component

of the overall improvement in the final outcome of our study was a reduction in early mortality. The rate of the primary outcome of our study (death or moderate or severe disability at 18 to 22 months of age) was significantly lower in the hypothermia group than in the control group. For the secondary outcome of death before 18 months, the relative risk in the hypothermia group, as compared with the control group, was 0.68 (95 percent confidence interval, 0.44 to 1.05; P=0.08). The frequency of neuromotor impairment was similar in our study and the Cool Cap study by Gunn et al.[4] In our study, disabling cerebral palsy occurred in 19 percent of infants in the hypothermia group and 30 percent of infants in the control group. In the Cool Cap study, severe neuromotor disability occurred in 19 percent of the cooled infants and 31 percent of the control infants. Our study differs from the Cool Cap study in the following areas: eligibility criteria (we did not use the amplitude-integrated electroencephalograph), method of cooling (whole body in our study as compared with selective head cooling in the Cool Cap study), and the target temperature (33.5°C in our study as compared with 34° to 35°C in the Cool Cap study). We also suggest that patterns of brain injury on MRI for infants undergoing head or body cooling remain unresolved; MRI shows that systemic hypothermia provides protection of the cortex with cooling.[5] We will examine our study subjects at school age to determine the long-term effects of cooling therapy.

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Deaths from *Clostridium sordellii* after Medical Abortion

TO THE EDITOR: Since its approval in France in 1988, a regimen of mifepristone (RU 486) and a prostaglandin has been used to terminate more than 1.2 million pregnancies of up to seven weeks of gestation. Most women have received oral mifepristone (at a dose of 600 mg), followed by oral misoprostol (at 400 or 800 μg).[1,2] Success rates have exceeded 95 percent, and uterine infection (endometritis) has been rare (≤1 percent), less than the rate of infection after surgical abortion.[3] No case of *Clostridium sordellii* has been reported. Mifepristone has also appeared to be safe when it has been used (without misoprostol) for long-term treatment of other indications (i.e., Cushing's syndrome and meningiomas).

In the cases reported by Fischer et al. (Dec. 1 issue)[4] and discussed in the accompanying Perspective article by Greene,[5] misoprostol was vaginally administered. This method has been shown to be highly efficacious (more effective than oral administration for the termination of pregnancy from day 49 to day 63),[6,7] and its use after the administration of 200 mg of mifepristone has been recommended by the World Health Organization. However, such use has not been approved by any regulatory agency. It is possible that this regimen (which involves vaginal insertion under nonsterile conditions) may predispose patients to infection with *C. sordellii* or other bacteria while the cervix is open. In the United Kingdom and Sweden, antibiotic prophylaxis is routinely prescribed when this regimen is used, and no severe infection has been reported after approximately 350,000 cases of use (data provided by Exelgyn).

One additional precaution should be noted. Early studies (without secondary administration