Objective: To establish the evidence of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

Data Sources: Cochrane Central Register of Controlled Trials, Oxford Database of Perinatal Trials, MEDLINE, EMBASE, and previous reviews.

Study Selection: Randomized controlled trials that compared therapeutic hypothermia to normothermia for newborns with HIE.

Intervention: Therapeutic hypothermia.

Main Outcome Measures: Death or major neurodevelopmental disability at 18 months.

Results: Seven trials including 1214 newborns were identified. Therapeutic hypothermia resulted in a reduction in the risk of death or major neurodevelopmental disability (risk ratio [RR], 0.76; 95% CI, 0.69-0.84) and increase in the rate of survival with normal neurological function (1.63; 1.36-1.95) at age 18 months. Hypothermia reduced the risk of death or major neurodevelopmental disability at age 18 months in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81) and in newborns with severe HIE (0.83; 0.74-0.92). Both total body cooling and selective head cooling resulted in reduction in the risk of death or major neurodevelopmental disability (RR, 0.75; 95% CI, 0.66-0.85 and 0.77; 0.65-0.93, respectively).

Conclusion: Hypothermia improves survival and neurodevelopment in newborns with moderate to severe HIE. Total body cooling and selective head cooling are effective methods in treating newborns with HIE. Clinicians should consider offering therapeutic hypothermia as part of routine clinical care to these newborns.

The primary objective of this review was to use all the available data, including those from the most recently published randomized trials, to evaluate the effectiveness of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

METHODS

DATA SOURCE

To identify all the relevant studies, the search strategy of the Cochrane systematic review, “Cooling for Newborns With Hypoxic Ischaemic Encephalopathy” (last edited in June 2007), was reproduced from June 2007 to May 2011. Relevant studies were identified from the Cochrane Central Register of Controlled Trials, the Oxford Database of Perinatal Trials, MEDLINE, and EMBASE using the following strategy: (Silver Platter–June 2007 to May 2011: Infant, Newborn (explode) [MeSH heading] and Asphyxia (explode) [MeSH heading] or Hypoxic Ischaemic Encephalopathy and Hypothemia (explode) [MeSH heading]). References from previous reviews were cross-referenced. No language restrictions were applied.

ELIGIBILITY CRITERIA

Randomized controlled trials that compared therapeutic hypothermia (either systemic or selective head cooling) to normothermia to treat newborns with HIE were included. Studies were selected only if they included data on death or disability at 18 months or older. Randomized controlled trials that had significant methodological limitations were excluded.

STUDY IDENTIFICATION AND DATA EXTRACTION

All titles and abstracts identified as potentially relevant by the literature search were assessed for inclusion in the review. The full texts for potentially eligible studies were reviewed against the predefined criteria. Data were extracted on a predefined data extraction form by the primary author (M.A.T.). The selection of relevant studies was by consensus. Whenever necessary, additional information and clarification of published data were requested from the authors of the individual trials.

CRITICAL APPRAISAL

The methodological quality of the studies was assessed using the risk of bias assessment tool as recommended by the Cochrane Neonatal Review Group except for the criterion of blinding of intervention (methods of cooling cannot be masked).

RESULTS

Fourteen trials were evaluated for eligibility (eFigure 1; http://www.archpediatrics.com). Seven trials fulfilled the inclusion criteria; their details are shown in Table 1, with additional details noted in the eAppendix. The 7 studies that were excluded along with reasons for exclusion are shown in Table 2; 5 excluded on the basis of basic eligibility criteria; their details are shown in eAppendix. Fourteen trials were evaluated for eligibility (eFigure 1; http://www.archpediatrics.com). Seven trials fulfilled the inclusion criteria; their details are shown in Table 1, with additional details noted in the eAppendix. The 7 studies that were excluded along with reasons for exclusion are shown in Table 2; 5 excluded on the basis of basic eligibility criteria; their details are shown in eAppendix.

The primary outcome was a composite of death or long-term (≥18 months) major neurodevelopmental disability (cerebral palsy; developmental delay [<2 SDs below the mean in Mental Developmental Index (MDI) score in Bayley Scales of Infant Development II [BSID-II], a Cognitive Scale score or a Language Composite Scale score on the BSID-III, Griffiths assessment, Brunet-Lézine quotient, or Gesell Child Development Age Scale; or intellectual impairment [IQ <2 SDs below the mean], blindness [vision <6/60 in both eyes], or sensorineural deafness requiring amplification]. Secondary outcomes included examining each component of the primary outcome independently, survival with normal neurological function (no cerebral palsy, normal development [not <1 SD below the mean on the aforementioned standardized tests], normal vision, and normal hearing). Furthermore, we determined if the severity of encephalopathy or the method of cooling modified the effect of hypothermia on the composite outcome of death or major disability. Grade of encephalopathy was assessed on the basis of clinical examination or amplitude-integrated electroencephalography (aEEG), both of which were considered equivalent.

DATA ANALYSIS

Meta-analysis was performed with Review Manager software (RevMan, version 5.0; Nordic Cochrane Centre) using the Mantel-Haenszel method and a fixed-effect model. Risk ratios (RRs) and the number needed to treat (NNT) values were calculated. The χ² test was applied to detect between-study heterogeneity, and I² values were calculated to assess statistical heterogeneity.

Fourteen trials were evaluated for eligibility (eFigure 1; http://www.archpediatrics.com). Seven trials fulfilled the inclusion criteria; their details are shown in Table 1, with additional details noted in the eAppendix. The 7 studies that were excluded along with reasons for exclusion are shown in Table 2; 5 excluded on the basis of basic eligibility criteria; their details are shown in eAppendix.

CLINICAL HETEROGENEITY ASSESSMENT AMONG INCLUDED STUDIES

A total of 1214 newborns with moderate to severe HIE were randomized in the included trials. Newborns who were reported to have mild HIE were excluded from this review. The included trials had similar enrollment criteria including evidence of birth asphyxia and moderate to severe HIE (Table 1). Three trials also included abnormal aEEG as an enrollment criterion. Newborns were at least 35 weeks gestation in 1 trial, at least 36 weeks in 4 trials, and at least 37 weeks in the other 2 trials. Four trials used total body cooling and 3 trials used selective head cooling with mild systemic hypothermia. In all the included trials,
random allocation and hypothermia were initiated within 6 hours after birth. Therapeutic hypothermia was maintained for 72 hours except in the trial by Gunn et al,22 in which cooling was discontinued between 48 and 72 hours if the newborn recovered neurologically. Rewarming was gradual at no more than 0.5°C per hour until the temperature was normalized in 5 trials,10,12,13,20,21; passive rewarming was allowed in 1 trial.22 The rewarming temperature was normalized in 5 trials10,12,13,20,21; passive gradual at no more than 0.5°C per hour until the newborn recovered neurologically. Rewarming was unclear in the trial conducted by Gunn et al.32

**Table 1. Details of Included Trials**

<table>
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<tr>
<th>Source</th>
<th>Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azopradi et al,19 2009</td>
<td>Inclusion GA=36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG</td>
<td>Hypothermia group (n=163): cooling blanket to maintain rectal temperature 33°C-34°C Control group (n=162): radiant heaters to maintain rectal temperature 37.0°C±0.2°C</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital abnormalities or &gt;6 h of age</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Death or severe neurodevelopmental disability in survivors at 18 mo of age</td>
</tr>
<tr>
<td></td>
<td>group (n=163)</td>
<td>GA=36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital abnormalities, &gt;5.5 h of age, received propylphylactic anticonvulsants, BW&lt;1800 g, HC&lt;2 SD for gestation if BW and length≥2 SD, or critically ill and unlikely to benefit from intensive care</td>
<td>Hypothermia group (n=116): cooling cap to maintain rectal temperature 34°C-35°C Control group (n=118): radiant warmer to maintain rectal temperature 36.8°C-37.2°C</td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Mortality and severe neurodevelopmental disability in survivors at 18 mo of age</td>
</tr>
<tr>
<td></td>
<td>group (n=118)</td>
<td>GA=37 weeks with PHI and encephalopathy</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital abnormality or metabolic diseases</td>
<td>Hypothermia group (n=18): cooling cap with sequential randomization of rectal temperature to 36.0°C-36.5°C (n=6), then to 35.5°C-35.9°C (n=6), then to 34.5°C-35.4°C (n=6) Control group (n=13): radiant warmer to maintain rectal temperature 36.8°C-37.2°C</td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Acute adverse effects, long-term neurodevelopmental outcomes were also reported</td>
</tr>
<tr>
<td></td>
<td>group (n=110)</td>
<td>refrigerated gel packs to maintain rectal temperature 33°C-34°C</td>
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<tr>
<td>Exclusion</td>
<td>Major congenital abnormalities, &gt;6 h of age, BW&lt;2 kg, overt bleeding, required &gt;80% oxygen, death was imminent, or therapeutic hypothermia had commenced before assessment</td>
<td>Hypothermia group (n=110): refrigerated gel packs to maintain rectal temperature 33°C-34°C Control group (n=111): radiant warmer to maintain rectal temperature 36.8°C-37.3°C</td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Mortality or major sensorineural disability in survivors at 2 y of age</td>
</tr>
<tr>
<td></td>
<td>group (n=102)</td>
<td>GA=36 weeks with PHI, &lt;6 h of age, and encephalopathy or seizures</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital abnormalities, BW&lt;1800 g, or &gt;6 h of age</td>
<td>Hypothermia group (n=102): cooling blanket to maintain esophageal temperature 33°C-34°C Control group (n=106): standard care to maintain esophageal temperature 36.5°C-37.0°C</td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Death or moderate or severe disability in survivors at 18 to 22 mo of age</td>
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<tr>
<td></td>
<td>group (n=111)</td>
<td>GA=36 weeks with PHI, encephalopathy, and abnormal EEG or aEEG findings</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital malformations, &gt;5.5 h of age, received anticonvulsant therapy, BW&lt;1800 g, HC less than the third percentile for GA if BW and length are greater than the third percentile, imperforate anus, or gross hemorrhage</td>
<td>Hypothermia group (n=64): cooling mattress to maintain rectal temperature 33°C-34°C Control group (n=65): an open care unit to maintain rectal temperature 36.5°C-37.5°C</td>
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<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Death or severe disability in survivors at 18 to 21 mo of age</td>
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<td>group (n=110)</td>
<td>GA=37 weeks, BW&gt;2500 g, PHI, and encephalopathy</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Major congenital abnormalities, signs of infection, other causes of encephalopathy or severe anemia</td>
<td>Hypothermia group (n=119): cooling cap to maintain nasopharyngeal temperature 34°C±0.2°C and rectal temperature 34.5°C-35°C Control group (n=116): radiant warmer to maintain rectal temperature 36.0°C-37.5°C</td>
</tr>
<tr>
<td>Intervention</td>
<td>Hypothermia</td>
<td>Death and severe disability at 18 mo of age</td>
</tr>
<tr>
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<td>group (n=110)</td>
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</tbody>
</table>

Abbreviations: aEEG, amplitude-integrated electroencephalogram; BW, birth weight; EEG, electroencephalogram; GA, gestational age; HC, head circumference; PHI, peripartum hypoxia-ischemia.

All the included studies used appropriate methodology following the Cochrane review guidelines.23 Assessment of the risk of bias among the included studies is reported in Table 3. Overall, the methodology of the 7 studies was strong, particularly in the 3 largest completed trials10,12,13 and the 2 trials that were stopped early due to the loss of clinical equipoise as assessed by independent data monitoring committees.20,22 Two trials had moderate methodological quality. The trial by Gunn et al19 was limited by a small sample size. It also had addi-
tional newborns randomized in other reports. The trial by Zhou et al. may not be generalizable because of the higher proportion of males included (87% in the selective head-cooling group and 83% in the control group) and is weakened by high attrition (17% lost to follow-up). Also in the trial report by Zhou et al., the outcome of 5% of the subjects was assessed by pediatricians in local hospitals rather than by blinded-certified neurologists. In none of the trials were caregivers blinded to the treatment assignment. The study protocol was violated in 2 trials with the inclusion of 19% to 20% of newborns with mild HIE. The assessment of publication bias in 2 trials with the inclusion of 19% to 20% of newborns with mild HIE. The assessment of publication bias using funnel plots indicated no substantial evidence of publication bias in the primary outcome of death or severe disability in newborns with moderate or severe HIE (Figure 1). More details about the methodological quality of the included trials are reported in the eAppendix.

**PRIMARY OUTCOME: COMPOSITE OF DEATH OR MAJOR NEURODEVELOPMENTAL DISABILITY AT 18 MONTHS**

The primary outcome was assessed in all 7 trials included in this review, representing 1214 newborns (Table 1). Therapeutic hypothermia reduced the risk of the composite outcome of death or major neurodevelopmental disability at age 18 months (RR, 0.76; 95% CI, 0.69-0.84; and NNT, 7; 95% CI, 5-10; I² = 0%; Figure 2).

**SECONDARY OUTCOMES**

Each component of the composite primary outcome was examined. Hypothermia reduced the risk of death at age 18 months (RR, 0.75; 95% CI, 0.63-0.88; NNT, 11; 95% CI, 7-26; I² = 0%; Figure 3). Among newborns who survived to 18 months, those treated with hypothermia had significantly lower rates of major disability (RR, 0.68; 95% CI, 0.56-0.83; NNT, 8; 95% CI, 5-16; I² = 12%; Figure 3), cerebral palsy (0.62; 0.49-0.78; 8; 6-16; 33%; Figure 3), developmental delay (0.66; 0.52-0.82; 8; 5-18; 25%; Figure 3), and blindness (0.56; 0.33-0.94; 23; 12-207; 0%; Figure 3). The rate of deafness was 3.7% in newborns treated with hypothermia and 5.8% in newborns treated normothermia, suggesting a protective effect of hypothermia that was not statistically significant (RR, 0.64; 95% CI, 0.32-1.27; I² = 0%; Figure 3). Therapeutic hypothermia increased survival with normal neurological function (RR, 1.63; 95% CI, 1.36-1.95; NNT, 7; 95% CI, 5-11; I² = 0%; Figure 4). Hypothermia reduced the risk of death or major disability both in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81; NNT, 6; 95% CI, 4-11; I² = 0%; Figure 5) and in newborns with severe HIE (0.83; 0.74-0.92; 7; 5-16; 0%; Figure 5). The risk of mortality or major neurodevelopmental disability was reduced by both total body cooling (RR, 0.75; 95% CI, 0.66-0.85; NNT, 6; 95% CI, 4-11; Figure 6) and selective head cooling (0.77; 0.65-0.93; 7; 4-21; Figure 6) when compared with normothermia. Statistical heterogeneity by I² was not significant for any of the analyses, indicating homogeneity among the included studies.

**SENSITIVITY ANALYSES**

The trial conducted by Simbruner et al. was terminated early due to ethical concerns regarding controls (normothermia group); 14% of the randomized subjects were not included in the final analysis of this trial. Therefore, sensitivity analysis was performed assuming an extreme scenario (all newborns lost to follow-up in the hypothermia group were affected with the primary outcome and all the newborns lost to follow-up in the normothermia group were unaffected). In this extreme scenario, the evidence remained in favor of the hypothermia group (RR, 0.76; 95% CI, 0.59-0.99).

Due to the methodological concerns in the trial by Zhou et al. discussed earlier, a sensitivity analysis excluding the data from this study was carried out. The conclusion did not change in that the combined rate of death or major disability was lower in the hypothermia group compared with the normothermia group (RR, 0.77; 95% CI, 0.70-0.86; NNT, 7; 95% CI, 5-12) (eFigure 2). The sensitivity of the results to the exclusion of this trial was also examined in the subgroup analysis in newborns with moderate (n=557) and severe HIE (n=480); the results remained significantly in favor of hypothermia in newborns with moderate HIE (RR, 0.70; 95% CI, 0.58-0.84; NNT, 6; 95% CI, 4-13) (eFigure 3) and in newborns with severe HIE (0.84; 0.75-0.94; 8; 5-21) (eFigure 4).

**COMMENT**

This updated systematic review of the randomized controlled trials conducted in newborns with HIE supports that therapeutic hypothermia is effective in reducing the risk of death or major disability at age 18 months in newborns with either moderate or severe HIE. An important outcome of this review is that hypothermia re-
duced the mortality rate without increasing the disabil-
ity rate in asphyxiated newborns. This outcome was
indicated by a decrease in the rate of major disability
and an increase in the rate of survival with normal neu-
rological function.

The homogeneity of the included studies (patient
inclusion and exclusion criteria, study design, method-
ological quality, and length of follow-up) increases the con-
fidence that therapeutic hypothermia improves the long-
term outcomes at 18 months in different clinical settings.

Experimental and clinical evidence had previously sug-
gested that outcomes after hypothermic treatment were
strongly influenced by the severity of HIE, with less ef-
ective neuroprotection following severe HIE.41,42 Se-
vere HIE is associated with a shorter latent phase (the
period between reestablishment of apparently normal ce-
rebral metabolism after HIE and the start of secondary
energy failure and its irreversible neurotoxic cascade),
worst secondary energy failures and more cortical-gray
matter neuronal death.43 The extensive brain injury in
severe HIE involving the basal ganglia and thalami are
often associated with abnormalities in specific cortical
and subcortical white matter.43 Moderate and severe le-
sions in the basal ganglia and thalami and severe white
matter lesions are associated with cerebral palsy.44-46 Al-
though the evidence from this review suggests that new-
borns with severe HIE will benefit, therapeutic hypo-
thermia seems to be more beneficial to newborns with
moderate HIE than newborns with severe HIE (relative
risk reduction, 33% vs 17%). The diversity in the timing
and magnitude of the brain injury in newborns with mod-
erate and severe HIE may have led to a differential treat-
ment effect.

Although hypothermia decreases rates of death or dis-
ability, newborns who are profoundly asphyxiated will
not likely benefit from hypothermic therapy. Identify-
ing newborns who are untreatable can be a challenge;
therefore, early predictors of nonresponders are re-
quired to individualize treatment decision. Six moder-
ately asphyxiated newborns or 7 severely asphyxiated
newborns need to be treated to save 1 newborn from death
or major disability.

Edwards et al19 in a recent meta-analysis estimated that
the RR of composite outcome of death or major disability
reached statistical significance in newborns with moder-
ate HIE (RR, 0.73; 95% CI, 0.58-0.92) and did not reach
statistical significance in newborns with severe HIE (0.87;
0.75-1.01). Based on their results, these authors recom-
mended that “... clinicians make individual decisions on
whether to treat newborns with severe encephalopa-
thy.”19 Their review did not include 3 recent trials.20-22 With
the inclusion of these trials and the higher number of new-
borns available for analysis, it is clear that newborns with
severe HIE also benefit from therapeutic hypothermia.

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</table>

Table 3. Risk of Bias Assessment Among the Included Studies

The homogeneity also allowed us to use the fixed-effects
model in the analysis where it was appropriate. Had the
included studies been heterogeneous, the random-effects
model would have been a more appropriate method.

Figure 1. Publication bias funnel plots for the primary outcome. A, Publication bias funnel plot for death or severe disability in newborns with moderate hypoxic ischemic encephalopathy. B, Publication bias funnel plot for death or severe disability in newborns with severe hypoxic ischemic encephalopathy.
The assessment of the severity of encephalopathy is difficult, imprecise, and subjective when based on clinical evaluation alone. Two of the included trials that used clinical criteria alone violated their protocol and included newborns with mild HIE. 20,22 Newborns with mild HIE were not expected to benefit from hypothermia. 47 None of the adverse events of death or severe disability occurred in newborns with mild HIE in the trial reported by Zhou et al. 22 However, in the trial by Jacobs et al. 20 33% and 25% of newborns with mild HIE in the control and cooled groups, respectively, died or had severe disability; the authors related the recruitment of newborns with mild HIE to the lack of a standardized neurologic assessment tool to assess encephalopathy. One may speculate that newborns may be misclassified in regard to their degree of encephalopathy and subsequently receive suboptimal treatment decisions. The combination of the aEEG and the neurological examination shortly after birth enhances the ability to identify high-risk newborns and limits the number of newborns who would be falsely identified when they are assessed with either evaluation alone. 48

The realistic therapeutic window of hypothermia is uncertain. 1,9 10 10 11 10 3 Experimental evidence suggests that the neuroprotective response of hypothermia is influenced by the timing of initiation of therapy. 50,51 In all included trials, the timing of initiation of hypothermia was no more than 6 hours after birth. Li et al. 52 suggested that delaying the onset of therapy by 6 to 10 hours after birth did not negatively affect the rate of moderate to severe disability and...
death when compared with newborns treated within 6 hours after birth. The National Institute of Child Health and Human Development is evaluating late hypothermia for newborns with HIE initiated between 6 and 24 hours of age (ClinicalTrials.gov Identifier: NCT00614744). Until further evidence is available, it seems prudent to initiate therapeutic hypothermia as soon after birth as possible for newborns with moderate to severe HIE.

The strengths of this updated systematic review are the inclusion of recent trials, increased power based on increased sample size, detailed subgroup analyses, and sensitivity analyses. The current analysis was able to re-

Figure 5. Forest plot of the primary outcome of death or major disability in survivors in newborns with moderate to severe hypoxic ischemic encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenszel test.

Figure 6. Forest plot for the primary outcome of death or major disability by method of cooling in newborns with moderate to severe encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenszel test.
fine the confidence with which clinicians should offer therapeutic hypothermia in newborns with moderate to severe HIE.

The unblinded nature of the included studies will remain the major limitation of the available evidence about therapeutic hypothermia. The current evidence is limited to 18-month follow-up data; therefore, it remains appropriate for clinicians to be conservative when counseling parents about longer-term neurological function. Long-term follow-up of the newborns in the trials reported to date will provide data to examine if neurological data recorded at 18 months accurately predict long-term neurological function.\(^\text{19}\) As the outcome of birth asphyxia is devastating, work should continue to find adjuvant therapy to hypothermia.

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Author Contributions: Drs Tagin, Vincer, and Whyte had full access to all the data in this review and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tagin. Acquisition of data: Tagin. Analysis and interpretation of data: Tagin, Woolcott, Vincer, Whyte, and Stinson. Drafting of the manuscript: Tagin. Critical revision of the manuscript for important intellectual content: Tagin, Woolcott, Vincer, Whyte, and Stinson. Statistical analysis: Tagin. Study supervision: Whyte.

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Online-Only Material: The eAppendix and eFigures are available at http://www.archpediatrics.com. This article is featured in the Archives Journal Club. Go to http://www.archpediatrics.com to download teaching PowerPoint slides. Visit http://www.archpediatrics.com to listen to an author podcast about this article.

REFERENCES


