CLINICAL BOTTOM LINE

- Overall incidence of neonatal meningitis is 0.25–1.0 per 1000 live births (grade A).
- Uncontrolled studies suggest that meningitis is very uncommon in asymptomatic babies with only perinatal risk factors for sepsis, so in this group lumbar puncture can be safely omitted from the early sepsis screen (grade B).
- In strongly suspected cases, lumbar puncture should be included in an examination of sepsis (grade B).

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Does the use of calamine or antihistamine provide symptomatic relief from pruritus in children with varicella zoster infection?

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A 2-year-old girl presents with chickenpox. The girl has typical vesicular lesions but has no evidence of complications on examination. Her mother reports that she is scratching continuously and has had very little sleep over the past few days as a result of the pruritus. Considering the therapeutic options, we wonder whether there is any evidence to support the use of either calamine lotion or antihistamines to alleviate pruritus in varicella zoster infection.

Structured clinical question

In a child with varicella zoster infection [patient], can calamine lotion or antihistamines [interventions] reduce pruritus [outcome]?

Search strategy and outcome

Cochrane Library using ''varicella *and* calamine'', ''varicella *and* antihistamine'', ''chickenpox *and* anitihistamine'' and ''chickenpox *and* calamine'': no relevant results.

PubMed (no limits set) using the search terms given above. The search produced the same results irrespective of whether ''chickenpox'' or ''varicella'' was used. Three publications related to ''varicella *and* calamine'': none were relevant (one case report and two cross-sectional surveys). Twenty two publications related to ''varicella *and* antihistamines'': only one study was relevant.[1] Table 1 summarises the report.

In addition, PubMed was searched for ''varicella'' or ''chickenpox'', respectively, in combination with (*and*) the proprietary names of all antihistamines currently licensed for use in the UK (based on *British National Formulary 51*, March 2006 and *British National Formulary for Children 2005*). For topical antihistamines: antazoline, diphenhydramine and mepyramine. For systemic antihistamines: acrivastine, alimemazine (trimeprazine), brompheniramine, chlorpheniramine (chlorphenamine), cetirizine, cinnarizine, clemastine, cyclizine, cyproheptadine, desloratidine, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, levocetirizine, loratidine, mizolastine, promethazine, terfenadine and triproledene. Fourteen studies were found: one each related to cetirizine, doxylamine, and promethazine, and 11 related to diphenhydramine—none were relevant (search date 14 April 2006).

Commentary

No studies were found that evaluated the effect of calamine lotion on pruritus associated with varicella zoster infection. Nevertheless, the drug—a basic zinc silicate—has a good safety profile and in our personal experience, many patients (or their parents) report symptomatic relief. A study investigating the effectiveness of calamine lotion in varicella zoster infection is desirable.

Only one trial has examined the use of one particular systemic antihistamine in this context—dimethindene maleate (DMM), a non-sedating H1 blocker,[2] which is not available in the UK. Two different regimens were used in this trial—a dose of 0.1 mg/kg/day, which is the standard recommended dose and a ''low-dose'' treatment with 0.05 mg/kg/day. The study showed considerable improvement in severity of itching in both treatment groups, as well as some improvement in appetite and sleep disturbance. However, neither the method of randomisation nor the blinding process is described. The blinding process seems particularly relevant, as the primary outcome measure—the itching severity score—is composed of subjective measures rated by the patient's parents.

Although other systemic antihistamines would probably produce a similar effect, there is currently no definite evidence to support their use. Given that antihistamines are a heterogenic group of drugs—with the shared property of H1 receptor binding but variable antiadrenergic, anticholinergic and antiserotoninergic properties—it is uncertain whether the results of this study can be extrapolated to the use of other antihistamines.[3]

Table 1 Antihistamines in children with pruritus in varicella zoster infection

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Englisch and Bauer[1]	128 paediatric patients (age 1–6 years) with chickenpox randomised to DMM 0.1 mg/kg/day or 0.05 mg/kg/day or placebo (1/3 of the dose given at am 2/3 given at pm) Duration of treatment: 7 days	Double-blind randomised controlled trial, multicentre study (level 1b)	Change in ISS from baseline ISS composed of severity of itching during daytime rated on 4-point scale by parents (''no itching'' to ''itching is dominant'') and disturbance of sleep during the first 8 days of the illness	DMM groups showed significant reduction of ISS compared with placebo group No significant difference between the two different DMM dosages Secondary outcome measures: better appetite and less sleep disturbance in DMM groups (significance not calculated), no difference regarding skin superinfection	All patients additionally received topical treatment (astringent lotion—active ingredient: tannin) Process of randomisation not described Methods of blinding not described Only minor adverse events (tiredness in 2 cases), no serious adverse events

DMM, dimethindene maleate; ISS, itching severity score.

Despite the fact that no serious adverse events were observed in this study, there are several publications reporting adverse effects in children with varicella zoster infection treated with diphenhydramine, including ataxia,[4] urinary retention,[4] clouding of consciousness,[5] behavioural abnormalities and hallucinations.[5–7] The side effects are thought to be related to the anticholinergic properties, are usually short lived and have been reported in association with systemic,[4 6 8] as well as topical use[6 7] of diphenhydramine. The decision to use systemic antihistamines should therefore be based on the potential benefit of symptomatic relief weighed against possible side effects on an individual basis.

Clinical bottom lines

- No published evidence is available to support the use of calamine to alleviate pruritus in varicella infection (grade D).
- Only limited evidence is found to support the use of systemic antihistamines in this context and benefits have to be weighed against potential risks (grade B).

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Is supplementary iron useful when preterm infants are treated with erythropoietin?

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A preterm baby on the neonatal intensive care unit develops anaemia of prematurity, requiring a blood transfusion. The parents of the baby are Jehovah's Witnesses and do not believe in blood transfusions. They do agree to allow their baby to have recombinant human erythropoietin (rHuEPO) treatment instead. However, the clinical staff are unsure whether giving coexisting iron supplementation with rHuEPO treatment will further reduce the requirement for transfusion, and if so in what dose and form should the iron supplement be given?

Structured clinical question

In a preterm infant who is receiving rHuEPO therapy [patient], does iron supplementation [intervention] reduce the requirement for blood transfusion [outcome]? If so, what method of administration and dose [intervention] reduces it most successfully [outcome]?

Search strategy

Primary sources: Medline was searched for articles published from 1966 to 2005, Embase from 1996 to 2005, Cinahl from 1982 to 2005, and also the Cochrane Library Controlled Trials Register 1900 to 2005. The search was carried out in May 2005 using the keywords {neonate(s) *or* infant(s) *or* newborn(s) *or* preterm(s)} *and* {erythropoietin *or* EPO *or* rHuEPO *or* recombinant human erythropoietin} *and* {an(a)emia *or* iron deficiency *or* iron *or* Fe *or* ferric compounds *or* ferrous compounds *or* ferrous sulphate *or* ferrous sulfate *or* ferrous fumarate} *and* {red cell transfusion}) *limit* to randomized controlled trials.

We found seven articles, six of which were relevant (table 1).[1–6] Jadad score was calculated in all of these.[7]

Commentary

Anaemia in premature infants is a common problem. Although erythropoietin is not used widely in neonatal practice, there is evidence of its efficacy in reducing the need for transfusion in preterm infants,[8] especially if they are not extremely small or sick.[9] It is regularly used in situations where blood transfusion is unacceptable. Iron supplementation has been a standard in neonatal care for preterm infants for many years and helps to reduce late anaemia[10] if given with vitamins, especially vitamin E.[11] However, when stimulating erythropoiesis with rHuEpo to reduce the need for transfusion, iron availability becomes critical. Several studies have investigated rHuEpo efficacy in preterm infants and most of them have used supplementary iron in either the oral or parenteral routes.

The literature on the use of rHuEpo and iron mostly consists of studies on dose variation of rHuEpo rather than variation in the iron supplementation. Our search yielded seven studies, but one[12] was excluded owing to poor methodological quality. Two studies by Carnielli *et al*[1] and Fujiu *et al*[2] compared rHuEpo and oral iron supplementation with rHuEpo alone; however, the interpretation of the data is difficult because Carnielli *et al*[1] reported their results only as