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

Table 1 Is supplementary iron useful when preterm infants are treated with erythropoietin?

First author, year, country	Patient group	Study type (level of evidence)	Outcome	Key results	Study weaknesses
Carnielli *et al*,[1] 1998, Italy	63 preterm infants with birth weight ⩽1750 g and gestational age ⩽32 weeks were randomised to three groups: group 1 received 400 IU rHuEPO/kg, 3 times/week and 20 mg/kg/week of IV iron; group 2 received 400 IU rHuEPO/kg, 3 times/week; group 3 control	Individual double-blind RCT (level 1b)	Number of transfusions	Fewer transfusions with those receiving IV iron	Quality score Jadad scale 3; the data in this study were difficult to interpret as mean data and logarithms of data were reported
Fujiu *et al*,[2] 2004, Japan	24 preterm infants with birth weight 750–1499 g, postnatal age 14–28 days and Hb <12 g/dl were randomised to two groups: group 1 received 200 IU rHuEPO/kg twice weekly and 4 mg/kg/day oral iron; group 2 received 200 IU rHuEPO/kg twice weekly	Individual RCT (level 1b)	Number of transfusions	No transfusions given in either group	Quality score Jadad scale 2; methods of randomisation were not well described; the sample size was small, so the significance that could be attached to the findings of the study is uncertain
Kivivuori *et al*,[3] 1999, Finland	41 preterm infants with birth weight <1500 g were randomised to three groups: group 1 received 300 IU rHuEPO/kg, 3 times/week and 6 mg/kg/day of oral iron; group 2 received 300 IU rHuEPO/kg, 3 times/week and 12 mg/kg/day of IM iron; group 3 received 12 mg/kg/day of IM iron	Multicentre RCT (level 1b)	Number of transfusions	No statistical difference between groups (p=0.2)	Quality score Jadad scale 2; randomisation method was not well described
Meyer *et al*,[4] 1996, South Africa	42 preterm infants with birth weight <1500 g, gestational age<33 weeks and postnatal age 7–30 days were randomised to two groups: group 1 received 600 IU rHuEPO/kg, 3 times/week and 6 mg/kg/week of IV iron; group 2 received 600 IU rHuEPO/kg, 3 times/week and 12 mg/kg/day of oral iron	Individual RCT (level 1b)	Number of transfusions	No difference between groups, concludes that oral iron is sufficient	Quality score Jadad scale 2; randomisation method was inadequately described
Bader *et al*,[5] 2001, Israel	30 preterm infants with birth weight <1750 g, gestational age <34 weeks and postnatal age 3–5 weeks were randomised to two groups: group 1 received 900 µg rHuEPO/kg/week and 8 mg/kg/day of oral iron; group 2 received 900 µg rHuEPO/kg/week and 16 mg/kg/day of oral iron	Multicentre double-blinded RCT (level 1b)	Number of transfusions	No significant difference between groups, concludes that oral iron is sufficient	Quality score Jadad scale 2; randomisation method was not well described
Nazir *et al*,[6] 2002, USA	52 preterm infants with gestational age ⩽32 weeks and postnatal age >7 days were randomised to three groups: group 1 received 1200 IU rHuEPO/kg/week and 6 mg/kg/day of oral iron; group 2 received 1200 IU rHuEPO/kg/week and 12 mg/kg/day of oral iron	Individual double-blinded RCT (level 1b)	Number of transfusions	No difference between the two groups	Quality score Jadad scale 5

Hb, haemoglobin; IM, intramuscular; IV, intravenous; rHuEPO, recombinant erythropoietin; RCT, randomised controlled trial.

mean values and logarithms, making statistical analysis difficult. Fujiu *et al*[2] found that no infants in either arm of their study required a blood transfusion. Although this may suggest that there was no difference between the groups, the sample size was small, with only 24 infants in total, and the clinical equivalence could not be shown. In addition, the authors state that losses due to phlebotomy in their study were lower than those in other similar studies. This may be relevant, as one of the most common causes of the anaemia of prematurity is iatrogenic blood loss.

Kivivuori *et al*[3] and Meyer *et al*[4] compared rHuEPO treatment and parenteral iron supplementation with rHuEPO treatment and oral iron supplementation. Combined data from the two studies showed that there was no significant difference between the groups for the number of blood transfusions given (odds ratio (OR) 1.65, 95% confidence interval (CI) 0.41 to 6.64). This seems to suggest that oral iron supplementation is at least sufficient. However, one study used intravenous iron supplementation whereas the other used intramuscular iron supplementation. Differences in absorption of these two different routes may be relevant, but no study has been carried out comparing intravenous with intramuscular iron supplementation.

Bader *et al*[5] and Nazir *et al*[6] compared infants receiving rHuEPO treatment and high-dose oral iron supplementation with those receiving rHuEPO treatment and low-dose oral iron supplementation. There was no significant difference between the two groups, when combining data for the two studies, regarding the number of blood transfusions (OR 0.46, 95% CI 0.04 to 5.75).

Preterm infants on special-care baby units frequently become anaemic and require top-up blood transfusions. Preterm infants often have low iron stores; this becomes more evident if they do not receive transfusions or iron supplementation. Erythropoietin is used occasionally to stimulate red cell production and prevent anaemia, and the increased erythropoiesis that occurs as a result of rHuEPO treatment will deplete iron stores. The studies currently available do not give an

adequate answer to the question as to which is the best mode and dose of iron supplementation with rHuEpo treatment. On the basis of the principle of using the lowest effective dose and the least invasive mode of administration, at present, low-dose oral iron would seem appropriate for supplementation when rHuEpo is used in preterm infants.

CLINICAL BOTTOM LINE

- Evidence available to strongly support any specific recommendation for iron supplementation with recombinant erythropoietin treatment in premature infants (grade D) is insufficient.
- Low-dose oral iron supplementation is not inferior to other treatment regimens (grade B).

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