In a preterm infant, does blood transfusion increase the risk of necrotizing enterocolitis?

Report by
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An otherwise well 3 week old infant born at 28 weeks gestation has a haemoglobin level of 68 g/l and is prescribed a blood transfusion. The departmental protocol states feeds should be withheld during the transfusion to decrease the risk of development of necrotising enterocolitis (NEC). What is the evidence that blood transfusion increases the risk of NEC?

Structured clinical question

In a preterm infant [patient] does blood transfusion [intervention] increase the risk of NEC [outcome]?

Search strategy and outcome

Search words: ''transfusion'' AND ''necrotizing enterocolitis'' (excluding exchange transfusion).

Secondary sources—Cochrane Library (Issue 3, 2003): no relevant systematic review.

Pub Med (1975–2003). Limits: newborn. Search outcome: 85 articles, of which two were relevant.

Pub Med (1975–2003) using clinical queries with methodology filters (category aetiology, emphasis: sensitivity). Limits: newborn. Search outcome: 34 articles, of which one was relevant (already retrieved by Pub Med).

Embase (1974–2003). Search outcome: 111 articles, of which one relevant (already retrieved by Pub Med).

Cinahl (1982–2004). Search outcome: 15 articles, none relevant.

Sum Search. Search outcome: 29 articles, none relevant.

See table 2.

Commentary

In the two reported studies,[1 2] the indications for transfusion were not standardised, the time interval between transfusion and NEC was not available, and any transfusion at any time between birth and NEC was analysed.

The results of the ecological study[1] are difficult to interpret as the association found between transfusion and NEC was at the level of the NICU but was not studied at the individual neonate level.

Bias in the published results of the two studies is possible, as the findings may be related to other practices in the specific neonatal intensive care unit (e.g. restricted transfusion policy). It may also reflect confounding by the indication for transfusion (e.g, infants who have NEC may require more transfusions). It could also be that the anaemia for which a blood transfusion was requested was an independent risk factor for NEC, or an early manifestation of NEC still developing, which then becomes recognised several hours later (during or after the transfusion).

While anecdotal reports suggest that NEC has developed quickly after a blood transfusion, such information is not available in published studies. However, neonatal exchange transfusion[3 4] and intrauterine transfusion,[5] both via umbilical vessels, have been shown to be associated with an increased incidence of NEC.

Further studies minimising bias and confounding are needed to prove or disprove an association between blood transfusion and the risk of NEC, but even then, association is not necessarily synonymous with causality. It should be possible to undertake randomised controlled studies on the

Table 2 Blood transfusion and necrotising enterocolitis

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Bednarek *et al* (1998)	Prospective analysis of blood transfusions and outcomes (including NEC) in 825 very low birth weight (<1500 g) infants in 6 neonatal units over 1 year, with adjustment for birth weight and illness severity. The 6 units were categorized into low, medium and high transfusion units based on the mean number of transfusions per infant	Prospective ecological study (level 2c)	Incidence of NEC	Adjusted OR (95% CI) for the: High transfusing units: 1.1 (0.5–2.2) Medium units: 1 (reference) Low transfusing units: 0.3 (0.1–0.08) $p<0.05$ The low transfusing NICU group showed a significantly lower incidence of NEC compared with the middle and high transfusing units.	Association difficult to interpret in ecological studies as the association found between transfusion and NEC is at the level of the units but was not studied at the individual neonate level Findings may be related to other practices in the specific NICU (e.g. restricted transfusion policy) or reflect confounding by indication for transfusion (e.g. infants who have NEC may require more transfusions). Time interval between transfusion and NEC not available (any transfusion at any time before NEC was counted)
McGrady *et al* (1987)	Case-control study of 33 neonates with NEC during an outbreak, and 40 controls matched on birth weight, duration of stay in the unit and approximate date of admission. Median birth weight of cases = 1360 grams, median gestational age = 32.5 weeks	Individual case-control study (level 3b)	Risk factors for NEC	Transfusion was highly and significantly associated with NEC, crude OR = 15.5 (95% CI = 2.59–92.51); RR = 8.98 (95% CI = 1.08–74.6) after adjustment for therapy with caffeine, theophylline and furosemide. There was no association with type or timing of feeding	This study was that of an outbreak of NEC and not the endemic form of NEC. Epidemic NEC may be importantly very different from endemic NEC

effect of withholding feeds versus feeding during blood transfusions on the rate of NEC, although blinding would be impossible and the sample size required for adequate power would likely be extremely large.

CLINICAL BOTTOM LINE

- Low quality evidence has shown an association between neonatal blood transfusion and the development of NEC.
- Withholding enteral feeds for a few hours during a blood transfusion may have theoretical benefits, but there is no published evidence to support this practice.
- Despite a lack of direct evidence, we continue to withhold feeds during blood transfusion.

REFERENCES

1 **Bednarek FJ,** Weisberger S, Richardson DK, *et al*. Variations in blood transfusions among newborn intensive care units. SNAP II Study Group. *J Pediatr* 1998;**133**:601–7.
2 **McGrady GA,** Rettig PJ, Istre GR, *et al*. An outbreak of necrotizing enterocolitis. Association with transfusions of packed red blood cells. *Am J Epidemiol* 1987;**126**:1165–72.
3 **Jackson JC.** Adverse events associated with exchange transfusion in healthy and ill newborns. *Pediatrics* 1997;**99**:E7.
4 **Tan KL,** Phua KB, Ang PL. The mortality of exchange transfusions. *Med J Aust* 1976;**1**:473–6.
5 **Musemeche CA,** Reynolds M. Necrotizing enterocolitis following intrauterine blood transfusion. *J Pediatr Surg* 1991;**26**:1411–12.

Are routine urine cultures helpful in the management of asymptomatic infants or preschool children with a previous urinary tract infection?

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An asymptomatic 18 month old boy, undergoing radiological investigations after a urinary tract infection (UTI) diagnosed few months earlier, is reviewed at the clinic. According to departmental protocol, a three monthly urine culture should be submitted in infants and young children as, until the age of 4 years, they remain at risk of developing renal scars after UTIs. You wonder as to the value of this routine culture.

Structured clinical question

In an asymptomatic infant or preschool child with a history of UTI under 4 years of age [patient] does the detection and management of asymptomatic bacteriuria (ABU) on routine urine culture [intervention] decrease the incidence of symptomatic UTI or renal scarring [outcomes]?

Search strategy and outcome

Secondary sources—Cochrane Library (Issue 3, 2003): search words: (1) ''urine culture'' OR (2) ''asymptomatic bacteriuria'' OR (3) ''urinary tract infection''. Database of systematic reviews: 32, 24, and 135 articles (for 1, 2, and 3 respectively), with 24, 14, and 101 complete reviews (for 1, 2, and 3 respectively). No relevant systematic review for under 4s.

PubMed (1975–2003): search words—(''urine culture'' OR ''asymptomatic bacteriuria'' OR ''urinary tract infection'') AND (''prognosis'' OR ''renal scar*''). Limits: child <4 years. Search outcome: 12 papers, of which two were relevant (under 4 years of age).

SumSearch: 43 articles, two relevant (already retrieved by PubMed).

See table 3.

Commentary

As infants and young children are thought to remain at risk, until the age of 4 years, of developing renal scars after UTIs, some paediatric departments carry out periodical urine culture in this group, even in the absence of symptoms. In addition to the fact that urine collection and culture in preschool children under 4 years of age is not always technically easy and is associated with an unsatisfactory high risk of bacterial contamination, detection of ABU in this group would be of value if its treatment results in decreased risk of renal scarring and symptomatic UTI, without adverse effects of the therapy.

Previous reports have shown that the development of new renal scars or the progression of existing scars are very uncommon after the age of 4 years,[3] and, although new scars may occasionally develop after the age of 4 years, they generally occur in the context of symptomatic UTI or acute pyelonephritis but not after ABU.[4] Although there is evidence of progression of scarring in relation to ABU, there is no evidence of benefit from treatment. Studies of ABU in schoolchildren have shown that absence of treatment does not increase the risk of subsequent renal scarring after the age of 5 years[5] and that bacterial strains in ABU do not commonly cause symptomatic pyelonephritis.[6] However, changes in bacterial flora have been associated with recurrences of or development of acute pyelonephritis ABU.[7] In children with ABU, the use of antibiotic therapy for intercurrent infections leads to a change in the urinary flora and is associated with an increased risk of pyelonephritis,[8] in contrast to untreated ABU where no spontaneous changes of urinary bacteria occurs.[9]

We therefore reviewed all published studies to try answering specifically the structured clinical question: What is the evidence that the detection and management of ABU in preschool children under 4 years of age decrease the incidence of symptomatic UTI or renal scarring? Unfortunately, we found no good quality randomised studies addressing that specific question. The two studies reviewed show that in children under 4 years of age, no new renal scarring occurred when bacteriuria was asymptomatic[1] and that renal scarring only occurred in children with symptomatic recurrences associated with abnormal cystograms.[2] However, both studies have obvious weaknesses: in addition to small sample sizes, there was no treatment randomisation. The first study was carried out in an unselected population of children, but not after a selected group with previous UTI which would very likely have a different natural history and prognosis. The second study was carried out exclusively in girls, who are known to have a different natural history than boys. In addition, as these studies were carried out before DMSA was available, the diagnosis of renal damage was made by intravenous urography (IVU). As DMSA is more sensitive than IVU to detect cortical scarring, some small scars may not have been recognised on IVU, although such small scars are not thought to be clinically significant. In addition, the first study did not clearly differentiate between primary and secondary (after a previous UTI) ABU.

Despite their weaknesses, which should caution about the generalisation of their findings, these studies have shown that the detection and the treatment of ABU in infants and preschool children did not decrease the risk of renal scarring. In addition,