Challenges of managing children with severe anaemia

Severe anaemia is a leading cause of hospital admission in children in sub-Saharan Africa. Children admitted to hospital with severe anaemia have poor outcomes, with around 9-10% dying while in hospital, and 12% dying within 6 months of admission. Children admitted to hospital with severe anaemia are also at high risk (18%) of having to be re-hospitalised following in the 6 months following the initial hospital discharge.

Supplies of safe blood for transfusion in sub-Saharan Africa are very limited, and not enough to meet the high demand for blood. Children and child-bearing woman receive up to 75% of all blood transfusions.

The WHO guidelines for managing common childhood illness recommend a restricted approach to blood transfusions for children with severe anaemia, to preserve the scarce resource and reduce the risk of transfusion-transmitted infections. For stable children with haemoglobin 4-6g/dl and no complications, they recommend not transfusing. The guidelines do not specify what clinical or haemoglobin monitoring should be carried out.

Immediate vs no immediate transfusion strategies for children with uncomplicated severe anaemia

Key points

• Severe anaemia is common and life-threatening for children in sub-Saharan Africa.
• There is often more demand for than supply of safe blood for transfusions in these settings.
• WHO recommendations, based on expert opinion, recommend conservative blood transfusion strategies, to preserve scarce resource and reduce risk of transfusion-transmitted infections. These conservative strategies recommend not transfusing children with uncomplicated anaemia (haemoglobin of 4-6g/dl).
• For children with uncomplicated severe anaemia and haemoglobin 4-6g/dl, the TRACT trial tested immediate vs no immediate transfusions but with transfusion triggered by new severity signs or post-randomisation haemoglobin <4g/dl.
• For children who followed WHO guidelines (no immediate transfusion), 49% met the criteria triggering a transfusion during their primary admission: 76% of those were because their haemoglobin dropped below 4g/dl, and 15% had a new clinical severity sign. Clinical and haemoglobin monitoring is important to identify children who require transfusions post-admission.
• TRACT found no evidence of differences in 28 day mortality, 180 day mortality, or readmissions between immediate and triggered transfusion strategies. We can exclude the possibility of a small benefit in terms of readmissions, but cannot exclude the possibility of a small mortality benefit.
• Overall mortality was lower than expected (28-day mortality was less than 2% overall), perhaps due to the closer surveillance and repeated haemoglobin monitoring of children in the trial.
• Haemoglobin recovered faster in children who had immediate transfusions, but by 180 days there was no evidence of differences in average haemoglobin between the two groups.
• The triggered transfusion strategy reduced blood requirements by ~60% compared to immediate transfusion in uncomplicated severe anaemia, preserving blood transfusion supplies for emergencies.
• The triggered transfusion strategy was considerably less costly than immediate transfusions (mean cost of $66.46 per child in the triggered group, compared to $72.09 in the immediate group), despite the longer length of stay in hospital (around 24 hours, on average).
The TRACT trial
The TRACT trial was carried out in Uganda and Malawi. Within the trial, 1566 children with uncomplicated severe anaemia (haemoglobin 4-6g/dl) were randomised to receive either:
• immediate transfusion
• no immediate transfusion, but with transfusion triggered by drop in haemoglobin to <4g/dl or new severity signs developing (impaired consciousness or increased work of breathing)
(The trial also included other children who did not contribute to this randomised comparison.)
It was decided to compare an immediate transfusion vs no immediate transfusion, but with transfusion triggered by drop in haemoglobin to <4g/dl or new severity signs developing, rather than immediate vs no transfusion at all, as it was felt unethical to withhold transfusions from children who deteriorated while in hospital.
Children were followed up for 180 days.
• The median age of children taking part was 26 months
• The median haemoglobin was 5.1g/dl
• 33% had a fever
• 14% were in shock
• 63% had malaria
• 2% were HIV positive
• 2% had severe malnutrition
• None reported having Sickle Cell Disease at screening, but 22% were found to have Sickle Cell Disease on testing at the end of the trial

Immediate vs no immediate transfusion
Half of children in the no immediate transfusion group received a transfusion in their primary admission, mostly because their haemoglobin had dropped to <4g/dl. The median hospital stay was 3 vs 4 days in immediate vs no immediate transfusion groups. Although small, this difference in length of hospital stay was not likely to be due to chance. During the primary admission, children in the immediate group received a mean of 314 ml blood vs 142 ml in the no immediate transfusion group.

Haemoglobin increases in the first 48 hours were greater in the immediate versus no immediate transfusion groups, with children in the immediate group having a mean +2.42g/dl greater haemoglobin at 48 hours.
Children in the no immediate transfusion group who were transfused after 12 hours had similar post-transfusion haemoglobin increases to those transfused within 12 hours. During admission, haemoglobin recovery to >9g/dl occurred faster and new profound anaemia (Hb<4g/dl) more slowly in immediate vs no immediate transfusion groups. These differences are unlikely to be due to chance. However, the differences in haemoglobin reduced as time went on, and by day 180 there was no evidence of any difference in mean haemoglobin, or proportions of children with haemoglobin >9g/dl between the two groups.
Overall, mortality was lower than anticipated (28 day mortality was 1% in the immediate transfusion group and 2% in the no immediate transfusion group: 180 day mortality was 4% in the immediate transfusion group and 6% in the no immediate transfusion group). At these low mortality rates, we did not find evidence of differences in mortality between the groups at either at day 28 or day 180. 10 of the 13 children who died by day 28 in the no immediate transfusion had received a transfusion relatively shortly (median 9h) after entering the trial. Among children who died, the cause of death could not be assigned in 44/82 children, as most deaths occurred outside hospital. The most common known primary causes of death were haematological conditions (16/82). 10 deaths were attributed to septicaemia/meningitis.
By day 180, 122 (16%) immediate and 108 (14%) no immediate transfusion children had been readmitted to hospital. This difference could be due to chance. Most readmissions were related to anaemia, malaria and/or sepsis.

out post-admission to identify deterioration in children not initially receiving a transfusion.
The evidence upon which these guidelines are based is weak. Adherence to the WHO guidelines on transfusion for severe anaemia is poor, as clinicians are concerned that the guidelines undertreat children. This briefing paper explores the results of the TRACT trial, which compared immediate transfusions vs no immediate transfusions but with transfusion triggered by new severity signs or post-randomisation haemoglobin <4g/dl (for children with uncomplicated severe anaemia and haemoglobin 4-6 g/dl).
Costs of immediate vs triggered transfusions

The main differences in costs between the two strategies were:

- **Hospital stay**: as children in the no immediate transfusion group were in hospital longer than children in the immediate group, these costs were higher (mean $34.30 in the no immediate transfusion group compared to $29.70 in the immediate group).

- **Blood transfusion**: As fewer children in the no immediate transfusion group received a blood transfusion, the average cost-per child was lower in the no immediate transfusion group ($11.78 in the no immediate transfusion group compared to $22.20 in the immediate group).

The costs of haemoglobin tests were similar between the two groups. Overall, the mean cost-per-child was $66.46 in the no immediate transfusion group compared to $72.09 in the immediate group. The no immediate transfusion strategy was considerably less costly than the immediate strategy.

Implications of these results

These results suggest that, for children with uncomplicated severe anaemia, a "no immediate transfusion" strategy, with transfusions given if children’s haemoglobin drops below 4g/dl or a new severity sign occurs, can reduce costs and blood requirements compared to giving immediate transfusions.

As mortality was lower than predicted, the TRACT trial cannot rule out the possibility that immediate transfusion may offer a small mortality benefit, but it is able to rule out a benefit from immediate transfusions on hospital readmissions. Given the burden of paediatric severe anaemia in sub-Saharan Africa, immediate transfusion in uncomplicated severe anaemia risks overburdening the blood transfusion services compared with close monitoring and targeted transfusion. Even within the TRACT trial, recruitment was halted regularly due to lack of blood supplies.

Implementing the strategy of not giving immediate transfusions to children with uncomplicated severe anaemia safely depends on haemoglobin tests and monitoring for severity signs being carried out regularly, to identify children who go on to require a transfusion. This close monitoring may help improve outcomes for children with severe anaemia.
There was no evidence that children with undiagnosed sickle cell disease in the no immediate transfusion group were more likely to go on to require a transfusion than children without sickle cell disease. This means that children with sickle cell disease do not need a separate protocol for management of anaemia, even if identified within an admission.

A substantial proportion of children in TRACT were readmitted to hospital within 180 days. This suggests that future trials should focus on strategies to prevent the need for readmission.

Further reading


How much blood should children with complicated severe anaemia receive? MRC CTU at UCL briefing paper no. 25.

Acknowledgements
This briefing paper was written by A South, S Walker, D Gibb and K Maitland on behalf of the TRACT trial team.

The TRACT trial was funded by the UK Medical Research Council (MRC) [MR/J012483/1].