Abnormal fetal heart rate and cerebral doppler. Those with an abnormal result then undergo fetal blood sampling with the decision to perform an IUT contingent upon the blood sampling result. The IUT procedure has been described previously.2

Pregnancies where an IUT had been performed were identified from the clinic database. 70 infants from 65 mothers who had received IUT were reviewed. Cases were selected if the infant had received one or more IUT for haemolytic disease, was liveborn, and delivered at NWH between January 1991 and June 2000. Both intravascular and intraperitoneal IUT were included in the study. The four stillbirths were excluded.

For all cases both the maternal clinical record and available neonatal notes were reviewed. Maternal data collected included maternal age, parity, antibody titres and gestation at which IUT were given along with fetal blood sample results if obtained. Neonatal data collected included gestation at birth, birth weight, cord blood results, infant haemoglobin, infant bilirubin and reticuloocyte levels when recorded, exchange transfusion requirement, simple transfusion requirement and days of phototherapy. Time of discharge from hospital, medications, feeding, head ultrasound results, audiology, and development as assessed at follow-up were also recorded if available. Where infants had been transferred from NWH prior to discharge home, a letter was sent to the local paediatrician requesting information on transfusion requirement, hospital discharge, audiology and neurodevelopmental follow up. Early top up transfusion was defined as transfusion before three completed postnatal weeks, and late top up as blood transfusion required at or after three completed weeks.

Data are presented as mean ± standard deviation if normally distributed, or as median (range) as appropriate. Incidences were compared by Fisher’s exact test or by Chi squared. The groups were compared by two-way Mann Whitney U test or Student’s t-test as appropriate.

Results

37 infants from 34 pregnancies including three sets of twins, fulfilled the entry criteria for the study and were reviewed. Rhesus disease complicated 31 pregnancies and anti-Kell antibodies three. The mean ± SD gestational age (GA) at birth was 34 ± 2.5 weeks, and birth weight 2298 ± 675 g. 33 (89%) infants were born between 32 and 37 weeks GA and only four (11%) before 32 weeks GA. These infants had a combined total of 139 IUTs. 74 were intravascular, 36 were intraperitoneal, and 28 were a combination of intravascular and intraperitoneal IUTs. The median (range) number of IUT was four (1-9), with a mean GA at the first IUT of 25 ± 5 weeks, and the last IUT at a mean GA of 31 ± 2.1 weeks. The median of peak maternal antibody titres measured during each pregnancy was 1:4096 (128-8192). Postnatal testing revealed sixteen of the infants to be Coombs positive and the remaining 21 to be Coombs negative, reflecting the
transfused Rhesus negative blood. The median number of IUTs in the Coombs positive group was three (1-9) and the median number of IUTs in the Coombs negative group was four (1-6) with considerable overlap between the groups.

Exchange transfusions were required in ten (27%) of the 37 infants with a median of one (1-3) double volume exchange performed. Table 1 details the requirement for exchange and top up transfusion by Direct Coombs test. Table 2 details the top up transfusion requirement in the study group depending on whether an exchange transfusion was performed. Linear regression demonstrated a weak, non-significant trend for increased exchange transfusion requirement in infants who had had fewer IUTs (p=0.035) and the range of cord SBR results was wide with overlap between the groups. Although cord SBR correlated with exchange transfusion requirement, (p= 0.03), the range of cord SBR results was demonstrated overlap between the group who required exchange transfusion and those who did not.

Top up transfusions were required in 26 (70%) of the 37 infants. Four of the eleven infants who did not require top up transfusion had undergone an exchange transfusion and another four had anti Kell antibody. Early transfusion was required in 21 infants and late in 22 infants. The median number of early transfusions (less than 3 weeks) was one, (0-9) and late transfusions (after 3 weeks) was two (1-4). Eight infants received transfusion after ten weeks postnatal age and 9) and late transfusions (after 3 weeks) was two (1-4). Eight infants received transfusion after ten weeks postnatal age and 12 weeks postnatal age. The number of early transfusions (less than 3 weeks) was one, (0-9) and late transfusions (after 3 weeks) was two (1-4). Eight infants received transfusion after ten weeks postnatal age and 12 weeks postnatal age. The number of early transfusions (less than 3 weeks) was one, (0-9) and late transfusions (after 3 weeks) was two (1-4).

Discussion
This review of experience from a single centre performing IUT helps to confirm the overall good outcome in infants who have undergone this procedure for haemolytic disease. Exchange transfusion was required in 27% of the group, which compares favourably with data published from other centres. Rates of exchange transfusion reported from previous studies vary from 24-61%. The relatively low rate in our cohort may be due to improvements in and more aggressive use of phototherapy compared with previous

<table>
<thead>
<tr>
<th>Table 1. Outcome of infants based on Coombs test result.</th>
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<tr>
<td><strong>Direct Coombs</strong></td>
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<tr>
<td>Positive n=16</td>
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<td>Negative n=21</td>
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Mean ± standard deviation unless otherwise stated. No significant differences between groups for any parameter.

<table>
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<th>Table 2. Outcome of infants based on exchange transfusion requirement.</th>
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<td><strong>Exchange transfusion</strong></td>
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<tr>
<td>No exchange n=27</td>
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<td>Exchange n=10</td>
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Mean ± standard deviation unless otherwise stated. No significant differences between groups for any parameter.
Although exchange transfusion rates are low in the Auckland cohort overall, there are variations in the criteria used for transfusion and also in the definition of early and late transfusion. An increase in the number of IUTs and the subsequent exchange transfusion requirement has been reported. In that study, 24% of infants required exchange transfusion overall, but of infants with only one IUT, 57% required exchange transfusion compared with only 21% of infants with greater than one IUT. In our experience, there was a trend towards increased exchange transfusion requirement with fewer IUT but this was not statistically significant.

Figure 1. Box and whisker plot demonstrating relationship of cord serum bilirubin and haematocrit results to exchange transfusion requirement. The median is marked by a single line, the 25th and 75th centiles as outline of the box, the 10th and 90th centiles are represented by the whiskers and observations outside 10-90th are marked as single dots. SBR = serum bilirubin; HCT = haematocrit.

The need for ongoing monitoring and possible requirement for late top up transfusion, which persists until the infant is over three months of age, is a source of great concern for families. The frequency of blood counts and who follows up the results may vary between individual infants and in some cases this responsibility will fall upon the general practitioner. Moreover, the criteria used for top up transfusion may alter depending on the individual practice and the perception of symptoms. There is literature available on transfusion for anaemia in preterm infants, based on both haematocrit and symptoms, but the natural history of anaemia due to haemolytic disease is different. In most of the literature concerning infants with haemolytic disease, criteria for when transfusion was given is not clearly stated. However, for near term infants outside the stage of acute haemolysis a haematocrit of <0.27, or <0.3 with symptoms has been used and would seem a reasonable guide. The use of a clear transfusion guideline such as this may ensure that paediatricians and general practitioners provide consistent advice to families.

The role of erythropoietin in the prevention of late anaemia associated with haemolytic disease has been explored in a small number of published reports starting treatment at or after two weeks postnatal age. Although the studies have been small, the results have been encouraging. The largest randomised controlled study of 20 infants showed a reduction in the top up transfusion requirement from a mean of 4.2 to 1.8 in the group who received erythropoietin. The data obtained from review of the Auckland cohort do not allow us to predict which infants would develop late anaemia. However, the high rate of late transfusion may justify the use of erythropoietin in all infants who receive IUT rather than attempting to further identify risk factors for late transfusion requirement.

The follow-up data acquired for this group of infants reflects the perceived low risk of morbidity in a cohort who had a low incidence of preterm delivery prior to 32 weeks. Developmental outcomes were not assessed with formal testing unless other high risk factors were present. However, the combination of low exchange transfusion rate and relatively mature gestation at delivery meant that most infants did not require intensive care. For such a population, clinical assessment by either a NWH or local paediatrician provides an effective screen for neurodevelopmental abnormality. Only one out of the 36 infants is known to have had a low incidence of preterm delivery prior to 32 weeks. Developmental outcomes were not assessed with formal testing unless other high risk factors were present. However, the combination of low exchange transfusion rate and relatively mature gestation at delivery meant that most infants did not require intensive care. For such a population, clinical assessment by either a NWH or local paediatrician provides an effective screen for neurodevelopmental abnormality. Only one out of the 36 infants is known to have had a low incidence of preterm delivery prior to 32 weeks. Developmental outcomes were not assessed with formal testing unless other high risk factors were present. However, the combination of low exchange transfusion rate and relatively mature gestation at delivery meant that most infants did not require intensive care. For such a population, clinical assessment by either a NWH or local paediatrician provides an effective screen for neurodevelopmental abnormality. Only one out of the 36 infants is known to have had a low incidence of preterm delivery prior to 32 weeks. Developmental outcomes were not assessed with formal testing unless other high risk factors were present. However, the combination of low exchange transfusion rate and relatively mature gestation at delivery meant that most infants did not require intensive care. For such a population, clinical assessment by either a NWH or local paediatrician provides an effective screen for neurodevelopmental abnormality. Only one out of the 36 infants is known to have had a low incidence of preterm delivery prior to 32 weeks. Developmental outcomes were not assessed with formal testing unless other high risk factors were present. However, the combination of low exchange transfusion rate and relatively mature gestation at delivery meant that most infants did not require intensive care. For such a population, the use of a clear transfusion guideline such as this may ensure that paediatricians and general practitioners provide consistent advice to families.
This review of the NWH experience helps to confirm the overall good outcome for infants undergoing IUT for haemolytic disease. The majority of infants were born in good condition with a birth weight above 2000g and a gestation greater than 32 weeks. Such infants may require paediatric care in the local hospital but typically they do not require prolonged neonatal intensive care and have a good neurodevelopmental outcome. Exchange transfusions are now infrequent in this group although top up transfusion is still commonly required. It is likely that, in the future, the use of erythropoietin will decrease the rate of late anaemia in these infants. Although it was not possible to identify specific factors that predicted postnatal transfusion requirement the data provided by this study may be used to counsel parents and plan postnatal care.

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