Adverse Events Associated With Exchange Transfusion in Healthy and Ill Newborns

J. Craig Jackson, MD

ABSTRACT. Objective. To determine the incidence of adverse events attributable to exchange transfusion during the past 15 years and compare the incidence of severe complications between healthy and ill infants.

Design. Medical records for the past 15 years from two teaching hospitals with neonatal intensive care units were reviewed. Those newborns who underwent exchange transfusions were classified as healthy or ill. Adverse events were analyzed to determine whether they were attributable to the procedure.

Results. Of the 106 patients who underwent exchange transfusion, 81 were healthy and had no medical problems other than jaundice. The remaining 25 patients were classified as ill and had medical problems ranging from mild to severe. At least 2 (2%) of the 106 patients died of complications probably attributable to exchange transfusion. None of the 81 healthy infants died, but 1 had severe necrotizing enterocolitis requiring surgery. Of the 25 ill infants, at least 3 (12%) experienced severe complications (including 2 deaths) probably attributable to exchange transfusion. Serious complications from the most common adverse events, hypocalcemia and thrombocytopenia, were limited to the group of infants already ill with other medical problems.

Conclusions. Because of the significantly greater rate of severe complications in ill infants, exchange transfusion should be delayed until the risk of bilirubin encephalopathy is as high as the risks of severe complications from the procedure itself (12%). These results do not support recommendations to use lower exchange levels in ill infants compared with healthy infants. Pediatrics 1997;99(5). URL: http://www.pediatrics.org/cgi/content/full/99/5/e7; exchange transfusion, whole-blood; adverse events, jaundice, neonatal; kernicterus, infant, newborn.

ABBREVIATION. NICHD, National Institute of Child Health and Human Development.

The bilirubin level at which exchange transfusion is indicated remains controversial.1-3 This is because it is very difficult to define the risk of bilirubin encephalopathy in various categories of patients, such as those with or without hemolysis, healthy or ill, term or premature. The recommendations attempt to balance the benefits of preventing bilirubin toxicity with the risks of exchange transfusion. However, there are few recent reports of the complication rates from exchange transfusion or attempts to stratify the risk of adverse events based on clinical condition.

Mortality rates attributable to exchange transfusion ranged from .65% to 3.2% in studies performed in the 1960s4-7 and from .4% to 3.2% during the 1970s and 1980s.8-10 Causes of death ascribed to exchange transfusion included cardiovascular collapse during the transfusion, and the subsequent complications of necrotizing enterocolitis, bacterial sepsis, and pulmonary hemorrhage.

The most frequently cited review of adverse events from exchange transfusion is from the 1974 to 1976 prospective National Institute of Child Health and Human Development (NICHD) phototherapy study. Keenan et al11 reported that 190 infants underwent 331 exchange transfusions. Adverse clinical problems were observed in 6.7% of the exchange transfusions, and the observed rate of serious morbidity was 5.2%. Based on one death attributed to the procedure, they calculated mortality rate to be .53 per 100 patients and .3 per 100 procedures. Only 2 of the 14 serious adverse events occurred in infants defined as being in good condition at the initiation of the exchange transfusion.

Most of the published experience regarding adverse events from exchange transfusions comes from studies performed more than 15 years ago. There have been many advances in neonatal intensive care since that time that may have reduced the incidence of adverse events. For instance, the 1985 report by Hovi and Simoes8 indicated that electronic monitors were not routinely used, and that only in the final year of their study—and only in some cases—did they use continuous monitoring of electrocardiogram, blood pressure, or transcutaneous oxygen tension.

Improvements in outcome from advances in neonatal care may have been offset by the increased risk of adverse events attributable to inexperience with the procedure. Due to tolerance of higher bilirubin levels in term infants without evidence of hemolysis1-3 and improved obstetric management of Rh-sensitized mothers, the last 15 years have seen a much lower frequency of exchange transfusion. Furthermore, the incidence of kernicterus in preterm infants appears to be lower in recent years and exchange transfusion is frequently deferred in patients with serum bilirubin greater than the exchange levels used in the NICHD study.12

In previously published reports of the mortality and morbidity from exchange transfusion, many of...
METHODS

The computerized discharge abstract summaries of all patients admitted in the first month of life to Children’s Hospital and Medical Center during 1981 through 1995 and the University of Washington Medical Center during 1980 through 1995 were searched for the procedure code for exchange transfusion. After eliminating records for patients who underwent only partial exchange transfusion for polycythemia, the medical records of the 106 remaining patients were reviewed in detail. Those newborns admitted solely for asymptomatic hyperbilirubinemia were classified as healthy. The remaining infants—those with any other medical conditions—were classified as ill. All patients were cared for in neonatal intensive care units by University of Washington pediatric residents and neonatal fellows under the close supervision of academic and clinical neonatologists.

The cause of jaundice reported in the record was classified in the following way: Rh disease was defined as jaundice in Rh positive newborns from Rh negative mothers with elevated titers to the Rh antigen and evidence of hemolysis. ABO disease was defined as jaundice in newborns with positive direct Coombs test against the A or B antigens from type O mothers; hemolysis was often but not always documented. Other antigen sensitization was defined as hemolytic jaundice in Coombs-positive newborns from mother with antibodies to other blood group antigens.

All blood used for exchange transfusion was obtained from the Puget Sound Blood Center. Blood from volunteer donors was anticoagulated with citrate phosphate dextrose adenosine-1 and was <5 days old. Either whole blood ABO compatible with both the baby and mother, or group O red cells resuspended in compatible (usually AB) plasma, were used. Exchange transfusions were performed by the fellow or attending neonatologist, or by pediatric residents under their direct supervision. The double-volume exchange procedures were generally completed in about 2 hours by repeatedly removing and replacing small aliquots of blood (<5 mL/kg) according to standard published guidelines.

The records were reviewed for adverse events possibly attributable to exchange transfusion and classified into six prospectively defined categories of severity (Table 1). For simplicity of data presentation and because it was difficult to assign complications to a specific transfusion in those undergoing multiple procedures, rates of complications were calculated on the number of treated infants rather than the number of procedures performed.

Each infant was assigned to the one category best describing his or her most serious complications, to allow for the calculation of cumulative percentages of adverse events of decreasing severity. However, all adverse events were recorded to determine the overall frequency of the most common complications. The rate of severe complications in healthy infants was compared with that in ill infants with the Fisher’s exact test. The 95% confidence intervals for estimates of risk were determined from standard tables.13

RESULTS

During the 15-year study period, there were approximately 15,000 neonatal intensive care unit admissions. One hundred six patients underwent exchange transfusion (Table 2). Of these, 81 were healthy and had no medical problems other than jaundice. The remaining 25 patients were classified as ill because they had additional medical problems; 10 required mechanical ventilation for hyaline membrane disease and the remainder had an assortment of conditions ranging from mild to severe (Table 3).

The 106 patients underwent 140 exchange transfusions. Ill infants underwent more multiple transfusions than healthy infants (Table 4). In 77% of the healthy infants, exchange transfusion was initiated via a catheter in the umbilical vein, whereas in 58% of the ill infants, it was initiated via a catheter in the umbilical artery.

The most common cause for jaundice was hemolysis from sensitization to Rh (n=51), ABO (n=21), or other blood group antigens (n=6). Other causes of jaundice included unknown (n=18), prematurity (n=6), and one each of the following: hemolysis with polycythemia, hereditary spherocytosis, cholestasis from gastroschisis, and adrenal hemorrhage with cholestasis.

Death

Two infants died of respiratory failure that did not appear to be attributable to exchange transfusion. The deaths of five other infants were possibly related to complications from exchange transfusion (Appendix A). All of the deaths were in the group of 25 ill

<table>
<thead>
<tr>
<th>TABLE 1. Classification of Adverse Event Severity</th>
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<tbody>
<tr>
<td>Asymptomatic lab abnormalities</td>
</tr>
<tr>
<td>During or immediately after exchange transfusion, previously normal value for sodium, potassium, glucose, or calcium values fell outside the normal range, or platelets fell below 50,000/μL. No symptoms and no treatment given.</td>
</tr>
<tr>
<td>Asymptomatic complications, treated</td>
</tr>
<tr>
<td>Asymptomatic patients whose laboratory values were judged severe enough to require additional treatment (platelet transfusion, antibiotics) or who had complications of management (eg, clotting of catheter).</td>
</tr>
<tr>
<td>Serious, transient complications</td>
</tr>
<tr>
<td>Serious complications that resulted in permanent bodily alterations.</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Died due to adverse events, regardless of the interval after the transfusion.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>TABLE 2. Gestational Age and Body Weight (Mean ± SD and Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infants</td>
</tr>
<tr>
<td>(n=106)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Body weight, g</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>
increase the risk of catheter thrombus and because curred even if the exchange transfusions had not oc-
cPeriventricular hemorrhage
Systemic lupus erythematosus

Serious, Prolonged Complications
In the group of 81 healthy newborns, 4 additional infants developed serious prolonged complications probably attributable to exchange transfusion. One developed *Staphylococcus aureus* bacteremia 2 days after exchange transfusion, and two others developed omphalitis in association with umbilical catheter placement for exchange transfusion; all required prolonged courses of antibiotics. One developed a serious purpuric eruption similar to porphyria, thought to be secondary to exchange transfusion. Adverse events in all 4 infants were considered probably attributable to exchange transfusion.

Table 5

<table>
<thead>
<tr>
<th>Complication</th>
<th>Previously Healthy (n = 81)</th>
<th>Previously Ill (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Permanent serious sequelae</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Serious, prolonged complications</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Serious, transient complications</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Asymptomatic, treated</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Asymptomatic lab abnormalities</td>
<td>18%</td>
<td>18%</td>
</tr>
</tbody>
</table>
of the 25 ill infants, 6 had only asymptomatic complications, including administration of calcium for hypocalcemia (n = 3), clotting of umbilical catheter requiring replacement (n = 2), and 1 who was treated for both hypocalcemia and thrombocytopenia.

**Asymptomatic Laboratory Abnormalities**

Of the 81 healthy infants, 10 had only asymptomatic and untreated laboratory abnormalities, including hypocalcemia (n = 6), thrombocytopenia (n = 2), hypocalcemia and thrombocytopenia (n = 1), and hyponatremia and thrombocytopenia (n = 1). Of the 25 ill infants, 1 had only hypocalcemia.

**Implications for Laboratory Monitoring**

The most common adverse events were related to hypocalcemia and thrombocytopenia (Table 6 and Table 7). Only two infants had hypoglycemia during or after exchange transfusion (mild and asymptomatic in both cases) and one had asymptomatic hyponatremia (121 mEq/dL).

**Estimates of Risk for Severe Complications**

For statistical comparisons between healthy and ill infants, death and permanent serious sequelae were combined and defined as severe complications. The 12% rate of severe complications in the ill infants (3 of 25) is significantly greater \( (P < .05) \) than the 1.2% observed in the healthy infants (1 of 81). Based on the number of infants in this review, the 95% confidence interval for the 12% estimate of severe complications in ill infants is 3% to 31%. The 95% confidence interval for the 1.2% estimate in healthy infants is 0% to 7%.

**DISCUSSION**

Despite improvements in neonatal intensive care in the past two decades, exchange transfusion remains a high-risk procedure. Two of the 106 patients in this study (2%) died of complications probably attributable to exchange transfusion, similar to previous reports. In this study, none of the 81 healthy infants undergoing exchange transfusion died. This observation, and the paucity of reports of transfusion-related deaths in healthy infants, suggests that the mortality rate for the procedure in this population is well below 1%. The rate of permanent serious sequelae from exchange transfusion is also very low, approximately 1%, and both this study and prior reports indicate that necrotizing enterocolitis is the most common severe complication. Thus, the bilirubin exchange level for healthy infants should be set at a level at which the risk of bilirubin encephalopathy is no higher than 1%.

In ill infants, the incidence of procedure-related complications leading to death was 8% and the rate of severe complications (death or permanent serious sequelae) was 12%. Clinicians and parents should be aware of the much greater incidence of severe complications in this population when judging whether to perform an exchange transfusion. The bilirubin exchange level for ill infants should be at a point where the risk of bilirubin encephalopathy is approximately 12%. It is commonly assumed—although with limited evidence—that infants with risk factors such as prematurity, asphyxia, acidosis, and respiratory distress syndrome are at higher risk for bilirubin encephalopathy. Unless their risk is more than 10-fold greater than for healthy infants at any given level of bilirubin, the exchange levels for ill and healthy infants should be the same. Unfortunately, we probably have better data on the risks of exchange transfusion than on the risks of hyperbilirubinemia.

Unless the procedure can be made safer in this high-risk population, severe complications are inevitable. Overuse of the procedure may reduce the incidence of bilirubin encephalopathy at the cost of increased incidence of severe procedure-related complications. If exchange transfusions are delayed until the risks of severe complications from the procedure are equal to the risks of bilirubin encephalopathy, the number of patients with each will be roughly equal. A review of the medical records from our neurodevelopmental clinics indicated that only three children cared for in our nurseries during the past 15 years have been diagnosed as having bilirubin encephalopathy or kernicterus. Thus, during 15 years, four infants suffered severe complications from exchange transfusion in order to prevent a disease that developed in only three children.

Uncertainty regarding the figure of 12% incidence of severe complications in the ill infants is due first to the small size of the population, only 25 patients. The 95% confidence interval for three events out of a total of 25 is 3% to 31%. Second, there is uncertainty in ascribing complications in already ill infants to exchange transfusion. The estimate is too high if none of the severe complications outlined in Appendices A and B were attributable to exchange transfusion, and too low if all of them were. The results of this study have implications for monitoring both healthy and ill infants who undergo exchange transfusion. The most common serious morbidities included symptomatic hypocalcemia,

### TABLE 6. Complications Associated With Hypocalcemia

<table>
<thead>
<tr>
<th></th>
<th>81 Healthy Infants</th>
<th>25 Ill Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Serious, transient complications*</td>
<td>4 (5%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Asymptomatic hypocalcemia (treated)</td>
<td>15 (19%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Asymptomatic hypocalcemia (untreated)</td>
<td>13 (16%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Normal calcium or not measured</td>
<td>49 (60%)</td>
<td>13 (52%)</td>
</tr>
</tbody>
</table>

* ECG changes, pedal spasm, irritability, marked jitteriness.
bleeding from thrombocytopenia, catheter-related complications, and apnea and bradycardia with cyanosis requiring resuscitation. These complications are common enough that exchange transfusion, even in healthy newborns, should be performed only in nurseries prepared to respond to these adverse events. Because 5% of healthy infants in this study developed symptomatic hypocalcemia, such infants should at a minimum have blood-ionized calcium checked at the first signs of hypocalcemia. However, it should be noted that the administration of supplemental calcium during exchange transfusion is usually ineffective and unnecessary.14 Because 10% of healthy infants had platelet counts decrease to <50,000 per microliter, such infants should at a minimum be observed closely for petechiae or other signs of bleeding. Invasive procedures such as lumbar puncture or surgery should be delayed until a safe level of platelets has been achieved. Furthermore, both calcium and platelet counts should be checked before repeat transfusions. Catheters should be removed as soon as appropriate, and there should be a high index of suspicion for thrombotic complications. Although apnea, bradycardia, and cyanosis occur rarely during exchange transfusion of healthy infants, cardiorespiratory and oxygen saturation monitoring appear indicated. In ill infants, in addition to the above precautions, routine measurement of both ionized calcium and platelet count after exchange transfusion is indicated, given the occasionally severe complications associated with hypocalcemia and thrombocytopenia in this population.

Because many of the complications of exchange transfusion are probably unavoidable, the best way to reduce complications is to prevent the need for exchange transfusion. The use of effective phototherapy, including optimization of the wavelength and power of the lamps, and maximization of skin light exposure including use of fiberoptic pads, can greatly reduce the need for exchange transfusion. Other innovative approaches for treating jaundice include intravenous gammaglobulin in Rh-sensitized newborns and the administration of tin mesoporphyrin.

In summary, this report indicates that adverse events remain common after exchange transfusion. Some complications are as severe as, or worse than, the bilirubin encephalopathy the exchange transfusion was intended to prevent. These severe complications must be balanced against the benefits of lowering serum bilirubin. Because of the much higher rate of complications in ill infants, the results do not support recommendations to use lower exchange levels in ill infants compared with healthy infants.

### APPENDIX A. DEATHS POSSIBLY ATTRIBUTABLE TO EXCHANGE TRANSFUSION

Infant 1 was a 26-week gestation, 824-g infant with hyaline membrane disease who was improving until sudden respiratory failure 36 hours after exchange transfusion. The infant died of *Pseudomonas* sepsis 2 days after exchange transfusion, possibly attributable to infectious complications of exchange transfusion.

Infant 2 was a 30-week gestation, 900-g infant with gastrochisis whose exchange was performed through a Broviac catheter in the superior vena cava. After the exchange transfusion, a clot was noted on the catheter. The infant subsequently developed *Staphylococcus aureus* sepsis, *Escherichia coli* sepsis, superior vena cava syndrome, *Candida tropicalis* fungemia, and died 1 month later.

Infant 3 was a 24-week gestation, 630-g infant with severe asphyxia, hyperkalemia, and hypernatremia. During the exchange transfusion, the patient suffered cardiac arrest associated with severe hypocalcemia, and died several days later due to intraventricular hemorrhage and intractable seizures.

Infant 4 was a 33-week gestation, 2435-g infant with respiratory failure from hydrops fetalis. During the exchange transfusion, the infant suffered respiratory deterioration necessitating discontinuation of the exchange transfusion. After the infant died a few days later of respiratory failure and heart block, an autopsy was performed. Necrosis of the cardiac conduction system possibly related to emboli from the exchange transfusion was observed.

Infant 5 was a 35-week gestation, 3380-g infant with mild hyaline membrane disease. Several weeks after two exchange transfusions, the patient developed chronic hepatitis, possibly acquired from blood transfusion, and later died of hepatic encephalopathy.

### APPENDIX B. PERMANENT SERIOUS SEQUELAE POSSIBLY ATTRIBUTABLE TO EXCHANGE TRANSFUSION

Infant A was a 34-week gestation, 2030-g healthy infant whose umbilical venous catheter was replaced several times for clotting during the exchange transfusion. The next day the infant developed massive pneumoperitoneum, acidosis, and perforation of the splenic flexure of the bowel. The infant underwent resection of necrotic bowel and creation of colostomy, and later underwent surgery for bowel reanastomosis and closure of the colostomy. The infant also developed necrosis of the thumb; this complication and the bowel injury were classified as probable thrombotic complications of exchange transfusion.

Infant B was a 27-week gestation, 1080-g infant who developed chronic aortic obstruction from exchange transfusion through the umbilical artery catheter (and later died of causes unrelated to exchange transfusion).

Infant C was a 27-week gestation, 700-g infant who developed *Staphylococcus epidermidis* sepsis after the third exchange transfusion. The infant required repeated platelet transfusions due to severe thrombocytopenia from multiple exchange transfusions and then suffered intraventricular bleeding, hydrocephalus, and developmental delay.

Infant D was a 32-week gestation, 2630-g infant who had erythroblastosis fetalis, but did not require mechanical ventilation. The infant developed severe thrombocytopenia after exchange transfusion, had a sudden and severe respiratory deterioration attributable to pulmonary hemorrhage, and required intubation and mechanical ventilation. Subsequent tracheal injury resolved after bronchoscopy, but the infant was noted to have global developmental delay.

### TABLE 7. Complications Associated With Thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>81 Healthy Infants</th>
<th>25 Ill Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or permanent serious sequelae*</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Serious transient complications†</td>
<td>2 (2%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Asymptomatic, but received platelet transfusion</td>
<td>2 (2%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Asymptomatic thrombocytopenia (not treated)</td>
<td>5 (6%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Normal platelet count or not measured</td>
<td>72 (99%)</td>
<td>10 (40%)</td>
</tr>
</tbody>
</table>

* Symptomatic pulmonary hemorrhage, intraventricular hemorrhage.
† Petechial rash, rectal bleeding, hematuria, bleeding umbilicus.
REFERENCES
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Pediatrics 1997;99:e7
DOI: 10.1542/peds.99-5-e7

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