Hematological outcome in neonatal alloimmune hemolytic disease

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Chapter 4

Neonatal morbidity after exchange transfusion for red cell alloimmune hemolytic disease

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Abstract

Background

Exchange transfusion (ET) is a high risk procedure. Type and rate of complications in neonatal red cell alloimmune hemolytic disease exclusively is not clear.

Objective

Our aim was to study type and rate of complications associated with ET in a large series of neonates with hemolytic disease of the fetus and newborn (HDFN) due to red cell alloimmunization.

Methods

All neonates with HDFN due to red cell alloimmunization admitted to our center between January 2001 and June 2011 were eligible for this study. We recorded the number and rate of complications during admission in the group of neonates treated with (ET-group) and without ET (no-ET-group). Multivariate logistic regression analysis was performed to measure independent risk of complications of ET treatment.

Results

A total of 347 infants with red cell alloimmune hemolytic disease were included, 39% (134/347) was treated with at least one ET (ET-group) and 61% (213/347) did not require ET (no-ET-group). Comparison between ET-group and no-ET-group showed that ET treatment was independently associated with: proven sepsis (8% versus 1% respectively, odds ratio (OR) 8.3, 95% confidence interval (CI) 1.7-40.3, p = 0.009), leukocytopenia (88% versus 23% respectively, OR 36.0, 95% CI 17.5-73.8, p = <0.001), severe thrombocytopenia (platelet count $<50 \times 10^9$/L) (63% versus 8% respectively, OR 31.4, 95% CI 14.0-70.4, p = <0.001), hypocalcemia (22% versus 1% respectively, OR 27.4, 95% CI 5.9-126.8, p = <0.001) and hypernatremia (8% versus 0% respectively, p = <0.001). Neonatal death did not occur in the ET-group.

Conclusion

ET in neonates with HDFN is associated with increased risk of sepsis, leukocytopenia, thrombocytopenia, hypocalcemia and hypernatremia.

Introduction

Hemolytic disease of the fetus and newborn (HDFN) due to red cell alloimmunization may lead to excessive unconjugated hyperbilirubinemia. Neonatal treatment consists of intensive phototherapy and exchange transfusion (ET) to prevent kernicterus. After introduction in the late 1940s[1] neonatal treatment with ET became one of the most commonly performed procedures. However, ET is a high-risk invasive procedure requiring the use of central lines and is associated with a significant rate of adverse events. Although the contemporary mortality rate is reported to be less than 2%, rates of morbidity and ET-related adverse events can reach 74%.[2-9] Reported adverse events include catheter-related complications, complications related to the use of blood products, metabolic derangements and cardio-respiratory reactions.[2-9]

In nearly all previous studies a heterogeneous group of infants with HDFN treated with ET was included, varying from HDFN due to red cell alloimmunization to HDFN due to ABO-incompatibility.[2-4,6,8,9] Hemolysis caused by ABO-incompatibility is usually less severe compared to red cell alloimmunization and therefore associated with a reduced rate of neonatal morbidity. Furthermore, different indications for ET were used[2,8,9] and most studies were limited by a relative small number of included patients or were not case-controlled.[2-9] The aim of this study was to evaluate type and rate of complications associated with ET in a large series of neonates with HDFN due to red cell alloimmunization exclusively.

Patients and Methods

All term and preterm neonates with HDFN due to maternal red cell alloimmunization treated with or without ET, admitted to our center between January 2001 and June 2011 were eligible for this retrospective observational study. The Leiden University Medical Center (LUMC) is the national referral center for the management and intrauterine treatment of HDFN in the Netherlands. Neonatal outcome in part of this group was reported in previous studies.[10-14] In the Netherlands no formal ethical approval by the Medical Ethics Committee or written informed consent is necessary for retrospective studies.

Guidelines for ET used in our neonatal center were revised in December 2005.[10,11] Before December 2005, criteria for ET included: (1) bilirubin level at birth >3.5 mg/dL and/or (2) total serum bilirubin level above ET thresholds (rise of bilirubin value >0.5 mg/dL/h despite intensive phototherapy). In neonates not treated with IUT, a hemoglobin level at birth of <12.9 g/dL was also considered as a criterion for ET. Criteria for ET after December 2005

were: (1) total serum bilirubin above (higher) ET thresholds and/or (2) rise of bilirubin >0.5 mg/dL/h despite intensive phototherapy, and/or (3) clinical symptoms of acute bilirubin encephalopathy regardless of bilirubin level.[15]
ET was performed with double-volume transfusion (160 mL/kg) with citrated plasma (citrate 12-19 mEq/L) from a non-transfused male donor, lacking irregular erythrocyte-antibodies, added to irradiated, leukocyte-depleted (<1 × 10^6/L) and thrombocyte-reduced red cell concentrate, compatible with maternal antibodies. Citrated plasma contains nearly no free calcium, physiologic levels of potassium and glucose and an increased concentration of sodium (168 mEq/L) (Sanquin Bloodbank, The Netherlands). According to our guidelines no standard calcium supplementation is used during ET.
Primary outcome of this study was the rate of complications during admission in the group treated with ET (ET-group) and without ET (no-ET-group).

The following adverse events (complication occurring during admission) were recorded: hypocalcemia (<8 mg/dL), hypoglycemia (<46.8 mg/dL), hyperkalemia (>6.5 mEq/L), hypokalemia (<3.0 mEq/L), hypernatremia (>150 mEq/L), hyponatremia (<130 mEq/L), metabolic acidosis (pH <7.25, bicarbonate <22 mEq/L requiring treatment with bicarbonate), respiratory failure (respiratory support with continuous positive airway pressure and/or mechanical ventilation), apnea (cessation of respiration >20 seconds), pulmonary hemorrhage, cardiac arrest, hypertension (requiring antihypertensive medication), hypotension (requiring intravenous fluids or vasopressors), necrotizing enterocolitis,[16] proven sepsis (clinical and/or biochemical signs of infection (leukocytes <24 hours after birth <9 × 10^9/L and >24 hours <5 × 10^9/L or leukocytes >25 × 10^9/L and/or band forms >20% of leukocytes and/or C reactive protein >10mg/L) with positive blood culture), suspected sepsis (clinical and/or biochemical signs of infection without positive blood culture), disseminated intravascular coagulation (DIC) (requiring fresh frozen plasma), seizures (treated with anti-epileptic medication), leukocytopenia (<24 hours after birth <9 × 10^9/L and >24 hours <5 × 10^9/L) thrombocytopenia (<150 × 10^9/L; severe if platelet count <50 × 10^9/L and very severe if platelet count <20 × 10^9/L), intraventricular hemorrhage[17], or other cerebral hemorrhage and neonatal death. Platelet transfusions are given when platelets are: 1) <100 × 10^9/L before planned ET and 2) <50 × 10^9/L after ET.

We recorded the following obstetric and neonatal data: type of red cell alloimmunization, number of intrauterine red cell transfusions (IUT), gestational age at birth, birth weight, presence of hydrops at birth, hemoglobin level, reticulocyte count, leukocyte count and bilirubin level at birth, days of admission on our neonatal intensive care unit, occurrence

of complications during admission and time of occurrence in relation to ET, number of ETs and presence of umbilical venous catheter (UVC). Before ET-guideline change in 2005 a UVC was inserted directly after birth in all neonates. After 2005 a UVC was inserted when bilirubin levels increased towards ET-threshold. UVCs were left in place until bilirubin levels were decreased towards or below phototherapy threshold. According to our guidelines ultrasound to detect portal vein thrombosis (PVT) after ET was not performed standard but only in the presence of clinical signs of thrombosis.

Data are reported as means and standard deviations (SD) or as medians and interquartile ranges (IQR). Statistical analysis was performed using Student-t test and Mann-Whitney test for continuous variables. Chi-square and Fisher's-exact test were used for categorical variables. A p-value <0.05 was considered to indicate statistical significance. Of all statistically significant complications identified with univariate analysis a multivariate logistic regression analysis was performed to measure independent effect of ET(s). Results of logistic regression models were expressed as odds ratios (OR) and 95% confidence intervals (CI). Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

During this 10-year study, 348 neonates with HDFN due to red cell alloimmunization were admitted to our nursery. We excluded one preterm neonate (29 weeks' gestation) because he died immediately after caesarean section due to severe perinatal asphyxia following unsuccessful IUT. 347 Patients were included, 134 (39%) in the ET-group and 213 (61%) in the no-ET-group. Baseline characteristics are summarized in Table 1. The total number of ETs in the ET-group was 207 and the median (range) number of ETs was 1 (1-9).
In the ET-group 93/134 (69.4%) neonates needed one or more top-up transfusions compared to 162/213 (76.1%) in the no-ET-group.

Complications
Detailed information on complications during admission in both groups is summarized in Table 2.

Table 1. Baseline characteristics in ET-group and no-ET-group

	ET (n = 134)	**no-ET** (n = 213)	**p-value**
Type of red cell alloimmunization			
Rh D, n (%)	122 (91)	138 (65)	<0.001
Rh c, n (%)	11 (8)	16 (8)	0.813
Kell, n (%)	1 (1)	46 (22)	<0.001
Other types than Rh D, Rh c or Kell, n (%)	0 (0)	13 (6)	
Neonates treated with IUT, n (%)	99 (74)	141 (66)	0.131
Number of IUTs per neonate[a]	2 (2-3)	3 (2-4)	0.009
Gestational age at first IUT, weeks[a]	30 (25-33)	26 (23-31)	0.001
Birth weight, kg[b]	2.9 ± 0.6	2.9 ± 0.6	0.591
Gestational age at birth, weeks[a]	36 (36-37)	36 (36-37)	0.247
Male, n(%)	89 (66)	130 (61)	0.311
Hydrops at birth, n (%)	2 (2)	4 (2)	1.000
Hemoglobin level at birth, g/dL[b]	11.6 ± 2.6	12.7 ± 2.9	<0.001
Reticulocyte count at birth, ‰[a,c]	49 (6.8-83.3)	39 (3-75.5)	0.089
Leukocyte count at birth, 10^9/L[b,d]	14.1 ± 5.6	13.4 ± 5.7	0.270
Thrombocytopenia at birth, n (%)	39 (29)	48 (23)	0.169
Bilirubin level at birth, mg/dL[b]	7.1 ± 3.1	4.8 ± 2.3	<0.001
Umbilical venous catheter, n (%)	133 (99)	64 (30)	<0.001
Days of admission on NICU[b]	6.6 ± 3.8	6.2 ± 3.9	0.009

[a] Value given as median (IQR), [b] Value given as mean ± SD, [c] assessed in 78/134 and 149/213 neonates, [d] assessed in 130/134 and 207/213 neonates, NICU = neonatal intensive care unit

Univariate analysis

Metabolic derangements/complications

Hypocalcemia (22% versus 1%) and hypernatremia (8% versus 0%) occurred significantly more in the ET-group. Four of 31 (13%) neonates with hypocalcemia needed calcium supplementation and 3/11 (27%) needed treatment (additional sodium-free intravenous fluid) for hypernatremia. Severe symptoms of hypernatremia (seizures) did not occur.

Cardio-respiratory complications

No significant differences were seen in respiratory support, apneas, cardiac arrest and hypotension (Table 2). No cases of cardiac rhythm disorders, pulmonary hemorrhage and hypertension occurred.

Table 2. Complications during admission in ET-group and no-ET-group

			univariate analysis		multivariate analysis	
	ET-group (n = 134)	**no-ET-group** (n = 213)	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Hypocalcemia	29 (21.6)	2 (0.9)	29.1 (6.8-124.5)	<0.001	27.4 (5.9-126.8)	<0.001
Hypoglycemia	14 (10.4)	28 (13.1)		0.453		0.848
Hyperkalemia	1 (0.7)	0		0.386		NC
Hypokalemia	3 (2.2)	1 (0.5)		0.303		0.220
Hypernatremia	11 (8.2)	0	NC	<0.001	NC	NC
Hyponatremia	1 (0.7)	2 (0.9)		1.000		0.949
Metabolic acidosis	2 (1.5)	7 (3.3)		0.491		0.103
Respiratory support	17 (12.7)	18 (8.5)		0.202		0.425
Apneas	7 (5.2)	3 (1.4)		0.050		0.137
Cardiac arrest	0	2 (0.9)		0.525		NC
Hypotension	2 (1.5)	4 (2)		1.000		0.356
NEC	1 (0.7)	2 (1.9)		1.000		1.000
Proven sepsis	11 (8.2)	3 (1.4)	6.3 (1.7-22.9)	0.002	8.3 (1.7-40.3)	0.009
Suspected sepsis	9 (6.7)	16 (7.5)		0.780		0.466
Leukocytopenia	118 (88.1)	49 (23.0)	24.7 (13.4-45.5)	<0.001	36.0 (17.5-73.8)	<0.001
Thrombocytopenia	132 (98.5)	67 (31.5)	143.8 (34.6-598.6)	<0.001	146.9 (34.3-629.1)	<0.001
Severe	85 (63.4)	16 (7.5)	21.4 (11.5-39.7)	<0.001	31.4 (14.0-70.4)	<0.001
Very severe	14 (10.4)	3 (1.4)	8.2 (2.3-29.0)	0.001	11.5 (2.5-53.2)	0.002
DIC	0	1 (0.5)		1.000		0.982
Seizures	2 (1.5)	1 (0.5)		0.562		0.931
Death	0	1 (0.5)		1.000		NC

Values in columns 2 and 3 represent n (%). Respiratory support = continuous positive airway pressure and/or mechanical ventilation, NEC = necrotizing enterocolitis, DIC = disseminated intravascular coagulation, NC = not calculated

Infectious complications

Proven sepsis and leukocytopenia occurred significantly more often in the ET-group (8% versus 1% and 88% versus 23%, respectively). All ET-treated neonates with proven sepsis had leukocytopenia during admission and in 55% (6/11) leukocytopenia occurred after ET. In the 14 neonates from both groups with proven sepsis, bacterial cultures were positive for Staphylococcus aureus (7/14), coagulase-negative Staphylococcus (3/14), beta-hemolytic Streptococcus (1/14), Klebsiella pneumonia (1/14), Escherichia coli (1/14) and Bacillus cereus (1/14). This last patient developed a sepsis with brain abscesses after an ET performed through a UVC.[18]

Hematological complications

The rate of thrombocytopenia was significantly higher in the ET-group (99% versus 32%). Seventy-five of 134 ET-treated neonates were treated with at least one platelet transfusion. One near-term neonate (36 weeks' gestation) received a platelet transfusion after ET on day one because of post-ET platelet count 39 × 10^9/L. On day 2 cranial ultrasonography showed a hemorrhage in the right parieto-occipital periventricular white matter, which was not observed antenatally. Magnetic resonance imaging (MRI) showed no sinus thrombosis and coagulation was normal. At one year of age, the infant had no neurologic sequelae. In the no-ET-group 3 neonates had intracerebral hemorrhage on cranial ultrasound and/or MRI of whom one neonate had severe thrombocytopenia for which he received 4 platelet transfusions. This neonate died during admission (see below).
In both study-groups no cases of bilirubin encephalopathy or PVT were observed.

Neonatal mortality

Only one of 347 neonates died during admission. This neonate from the no-ET-group (30 weeks' gestation) had severe fetal hydrops. On day 2 bilirubin levels increased above ET threshold, however due to intravenously access problems ET could not be performed. Subsequently, bilirubin levels decreased below ET threshold with phototherapy. He died on day 11 due to respiratory failure, pulmonary hypertension, bilateral intraventricular hemorrhage grade 2 and renal failure.

ET guideline change

To measure the possible effect of ET guideline change[10] on the rate of the previously mentioned complications we performed a sub-analysis of ET-treated neonates before and after guideline change. Rates of complications were not significantly different between both groups (data not shown).

Multivariate analysis

Complications during entire admission

We corrected for the following covariates: hemoglobin level at birth, type of red cell alloimmunization, days of admission and gestational age at birth. We corrected for the first two because of significant differences at baseline (Table 1) and for the latter because preterm neonates are more susceptible for ET-related complications.[8,19] Since the presence of UVC and ET are correlated (Spearman correlation coefficient r = 0.680, p = <0.001), we did not correct for the presence of a UVC. Proven sepsis (OR 8.3), severe thrombocytopenia (OR 31.4), leukocytopenia (OR 36.0) and hypocalcemia (OR 27.4), had a higher incidence in the ET-group.

Complications after first ET

Since our main interest is in ET-related complications, we performed a sub-analysis excluding all complications in the ET-group that were observed before (first) ET (adjusted-ET-group, Table 3). Similar to the entire data set, neonates undergoing ET were more likely to experience sepsis, leukocytopenia, thrombocytopenia, hypocalcemia and hypernatremia.

Table 3. Complications during admission in Adjusted Exchange Transfusion (ET) and No Exchange Transfusion group

			Univariate analyses		Multivariate analyses	
	Adjusted ET group n = 134	**No ET group** n = 213	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Hypocalcemia	25 (18.7)	2 (0.9)	24.2 (5.6-104.1)	<0.001	21.9 (4.7-101.7)	<0.001
Hypernatremia	10 (7.5)	0	NC	<0.001	NC	NC
Proven sepsis	8 (6.0)	3 (1.4)	4.4 (1.6-17.1)	0.030	5.30 (1.0-27.1)	0.046
Leukocytopenia	91 (70.5)[b]	49 (23.0)	8.0 (4.9-13.2)	<0.001	9.0 (5.1-15.9)	<0.001
Thrombocyto-penia	90 (67.2)	67 (31.5)	4.5 (2.8-7.1)	<0.001	3.90 (2.4-6.4)	<0.001
Severe	71 (53)	16 (7.5)	14.9 (8.0-27.8)	<0.001	16.3 (7.8-34.1)	<0.001
Very severe	14 (10.4)	3 (1.4)	8.2 (2.3-29.0)	<0.001	11.5 (2.5-53.1)	0.002

Values in columns 2 and 3 represent n (%). For the adjusted ET group, only complications which occurred after first ET were analyzed. [b] Assessed in 129/134 neonates

Discussion

This study demonstrates that treatment with ET in neonates with HDFN is associated with an increased risk of sepsis, thrombocytopenia, leukocytopenia, hypocalcemia and hypernatremia. Treatment with ET was not associated with neonatal death in our cohort. Several studies have been published on neonatal morbidity due to treatment with ET.[2-9] One of the known risk factors associated with ET is development of invasive bacterial infections. The reported incidence of ET-related sepsis ranges from 0% to 11%.[4,6,8] The incidence of proven sepsis detected in this study (8%) is in accordance with these previous reports.
We found that the independent risk of sepsis was more than eight times higher in the ET-group. The exact cause of increased risk of infection is not fully understood, but is most probably related to the use of UVCs for ET. UVCs are a well-known risk factor for nosocomial infection.[20] Sepsis in the ET-group may also be caused by administration of infected blood products. Although the current risk of transmission of infectious diseases is relatively low, it is not completely negligible.[5,21] Furthermore, ET-related wash out of leukocytes may also play a role in the higher incidence of sepsis in the ET-group, since in double volume ET more than 90% of circulating blood is replaced by leukocyte-depleted donor-blood.[21,22] Finally, limited data on leukocytopenia in neonates with HDFN due to red cell alloimmunization show that the risk of leukocytopenia is increased in severe Rhesus HDFN.[23,24] In this study 86% (12/14) of neonates with proven sepsis had leukocytopenia of whom 11 were treated with ET. In 55% (6/11) leukocytopenia occurred after treatment with ET. In the remaining 45% leukocytopenia might be caused by bone marrow suppression due to increased erythropoiesis.
Another important ET-related complication is PVT. Risk factors for PVT include umbilical catheterization and ET.[25] However, none of the included infants in our study was diagnosed with PVT, probably because in this retrospective study no standard ultrasound to detect PVT after umbilical catheterization and/or ET has been performed.
Another reported risk associated with ET is thrombocytopenia due to the use of a thrombocyte-free blood product.[26] Previous studies reported incidences of ET-related thrombocytopenia ranging from 6% to 44%.[2-4,6,8,9] In our study, the incidence of thrombocytopenia in the ET-group was much higher, almost all neonates (99%) had low platelet counts and 63% had severe thrombocytopenia. Differences in incidence can be explained by differences in methodology and study population. We only included neonates with red cell alloimmune HDFN which is known to be associated with an increased risk for thrombocytopenia, even without ET.[14,27,28] Because other studies included neonates with ABO-incompatibility, their incidence of thrombocytopenia should be lower. In this study,

the risk of severe thrombocytopenia is 21-fold higher in the ET-group. Neonatologists must be aware of this potentially devastating complication as massive hemorrhage may arise after ET. Complications can be prevented by prophylactic platelet transfusion. In our study, platelet transfusions were administered in 57% of neonates before, during or after ET.
A further complication of ET is hypocalcemia, resulting from the use of citrated blood which contains almost no free calcium.[26,29] Previous studies reported incidences ranging from 3% to 42%.[4,8,10,11] In our study, 22% of neonates in the ET-group had hypocalcemia, and 13% needed replacement therapy. Treatment with ET was independently associated with an almost 30-fold increased risk of hypocalcemia. If left untreated, hypocalcemia can lead to potentially devastating complications such as seizures and cardiac arrhythmias. It is therefore crucial to measure calcium levels during the ET-procedure and act accordingly.
Another metabolic complication related to ET is hypernatremia. Hypernatremia probably results from an increased level of sodium in citrated blood. Only few studies have reported on hypernatremia resulting from ET, and the exact incidence is unknown.[30,31] Because hypernatremia can lead to serious complications we recommend frequent measurements of serum sodium levels during and after ET.
Finally, previous studies have reported that ET may also lead to neonatal death. Neonatal mortality attributable to ET ranges between 0.5% and 2%.[2,6-8] In accordance with our findings, three recent studies reported no ET-related deaths.[3,4,9] However, these studies (as well as ours) were not powered to detect a difference in neonatal mortality. Differences between reported rates can be explained by methodological differences such as different sizes of study cohorts and differences in disease-severity between cohorts. Neonates included in previous studies were often more premature than our study-population.[7-9]
Another explanation could be that our center is the national referral center for intrauterine treatment of red cell alloimmunization. Consequently all severely affected neonates with HDFN are born and treated in our center. As a result, ET is a frequently performed and standardized procedure and part of routine practice. We speculate that this may have contributed to the low level of severe morbidity and mortality in the ET-group. Operator's experience ('learning curve') could also be a factor in the reduction of morbidity and mortality in the ET-group.
Future alternative treatments for hyperbilirubinemia might theoretically further reduce the rate of ET and consequently decrease morbidity and mortality rates.[32]

In conclusion, sepsis, leukocytopenia, thrombocytopenia, hypernatremia and hypocalcemia are common complications in neonates with HDFN due to red cell alloimmunization treated with ET. In experienced hands severe permanent morbidity and mortality rates due to ET-procedures can be reduced to a minimum.

References

1. Diamond LK, Allen FH, Jr., Thomas WO, Jr: Erythroblastosis fetalis. VII. Treatment with exchange transfusion. N Engl J Med 1951; 244:39-49.
2. Badiee Z: Exchange transfusion in neonatal hyperbilirubinaemia: experience in Isfahan, Iran. Singapore Med J 2007; 48:421-3.
3. Davutoglu M, Garipardic M, Guler E, Karabiber H, Erhan D: The etiology of severe neonatal hyperbilirubinemia and complications of exchange transfusion. Turk J Pediatr 2010; 52:163-6.
4. Hosseinpour SS, Gharehbaghi MM: Exchange transfusion in severe hyperbilirubinemia: an experience in northwest Iran. Turk J Pediatr 2010; 52:367-71.
5. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S et al: An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004; 114:e130-e153.
6. Jackson JC: Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997; 99:E7.
7. Keenan WJ, Novak KK, Sutherland JM, Bryla DA, Fetterly KL: Morbidity and mortality associated with exchange transfusion. Pediatrics 1985; 75:417-21.
8. Patra K, Storfer-Isser A, Siner B, Moore J, Hack M: Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr 2004; 144:626-31.
9. Steiner LA, Bizzarro MJ, Ehrenkranz RA, Gallagher PG: A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. Pediatrics 2007; 120:27-32.
10. Rath ME, Smits-Wintjens VE, Lindenburg I, Brand A, Oepkes D, Walther FJ et al: Top-up transfusions in neonates with Rh hemolytic disease in relation to exchange transfusions. Vox Sang 2010; 99:65-70.
11. Rath ME, Smits-Wintjens VE, Lindenburg IT, Brand A, Van Kamp IL, Oepkes D et al: Exchange transfusions and top-up transfusions in neonates with Kell haemolytic disease compared to Rh D haemolytic disease. Vox Sang 2011; 100:312-6.
12. De Boer IP, Zeestraten EC, Lopriore E, Van Kamp IL, Kanhai HH, Walther FJ: Pediatric outcome in Rhesus hemolytic disease treated with and without intrauterine transfusion. Am J Obstet Gynecol 2008; 198:54e1-4.
13. Smits-Wintjens VE, Walther FJ, Rath ME, Lindenburg IT, te Pas AB, Kramer CM et al: Intravenous immunoglobulin in neonates with rhesus hemolytic disease: a randomized controlled trial. Pediatrics 2011; 127:680-6.
14. Rath ME, Smits-Wintjens VE, Oepkes D, van Zwet EW, Van Kamp IL, Brand A et al: Thrombocytopenia at birth in neonates with red cell alloimmune haemolytic disease. Vox Sang 2012; 102(3):228-33.
15. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114:297-316.
16. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L et al: Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978; 187:1-7.
17. Volpe JJ: Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In: Volpe JJ, editor. Neurology of the newborn. Philadelphia: Saunders; 2001. p. 428-93.

18. Smits-Wintjens VE, Steggerda SJ, Oepkes D, Van Kamp IL, Kramer CM, Walther FJ et al: Bacillus cereus cerebral abscesses in a term neonate with rhesus hemolytic disease treated with exchange transfusion. J Pediatr Inf Dis 2010; 5:277-80.
19. Maisels MJ, Watchko JF: Treatment of jaundice in low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2003; 88:F459-F463.
20. Inglis GD, Davies MW: Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters. Cochrane Database Syst Rev 2005;CD005251.
21. Fergusson D, Hebert PC, Barrington KJ, Shapiro SH: Effectiveness of WBC reduction in neonates: what is the evidence of benefit? Transfusion 2002; 42:159-65.
22. Xanthou M, Nicolopoulos D, Gizas A, Matsaniotis N: The response of leukocytes in the peripheral blood during and following exchange transfusion in the newborn. Pediatrics 1973; 51:570-4.
23. Rath ME, Smits-Wintjens VE, Walther FJ, Lopriore E: Hematological morbidity and management in neonates with hemolytic disease due to red cell alloimmunization. Early Hum Dev 2011; 87:583-8.
24. Blanco E, Johnston DL: Neutropenia in infants with hemolytic disease of the newborn. Pediatr Blood Cancer 2011; doi:10.1002/pbc.23233.
25. Williams S, Chan AK: Neonatal portal vein thrombosis: diagnosis and management. Semin Fetal Neonatal Med 2011; 16:329-39.
26. Samsom JF, Groenendijk MG, van der Lei J, Okken A: Exchange transfusion in the neonate, a comparison between citrate-, heparinized- and reconstituted whole blood. Eur J Haematol 1991; 47:153-4.
27. Saade GR, Moise KJ, Jr., Copel JA, Belfort MA, Carpenter RJ, Jr: Fetal platelet counts correlate with the severity of the anemia in red-cell alloimmunization. Obstet Gynecol 1993; 82:987-91.
28. Van den Akker ES, de Haan TR, Lopriore E, Brand A, Kanhai HH, Oepkes D: Severe fetal thrombocytopenia in Rhesus D alloimmunized pregnancies. Am J Obstet Gynecol 2008; 199:387-4.
29. Maisels MJ, Li TK, Piechocki JT, Werthman MW: The effect of exchange transfusion on serum ionized calcium. Pediatrics 1974; 53:683-6.
30. Doyle PE, Eidelman AI, Lee K, Daum C, Gartner LM: Exchange transfusion and hypernatremia: possible role in intracranial hemorrhage in very-low-birth-weight infants. J Pediatr 1978; 92:848-9.
31. Steele AM, Brown DL, Lipsitz PJ: Relationship of exchange transfusion to hypernatremia. J Pediatr 1979; 94:168-9.
32. Smits-Wintjens VEHJ, Walther FJ, Lopriore E: Rhesus hemolytic disease of the newborn: postnatal management, associated morbidity and long-term outcome. Semin Fetal Neonatal Med 2008; 13:265-71.