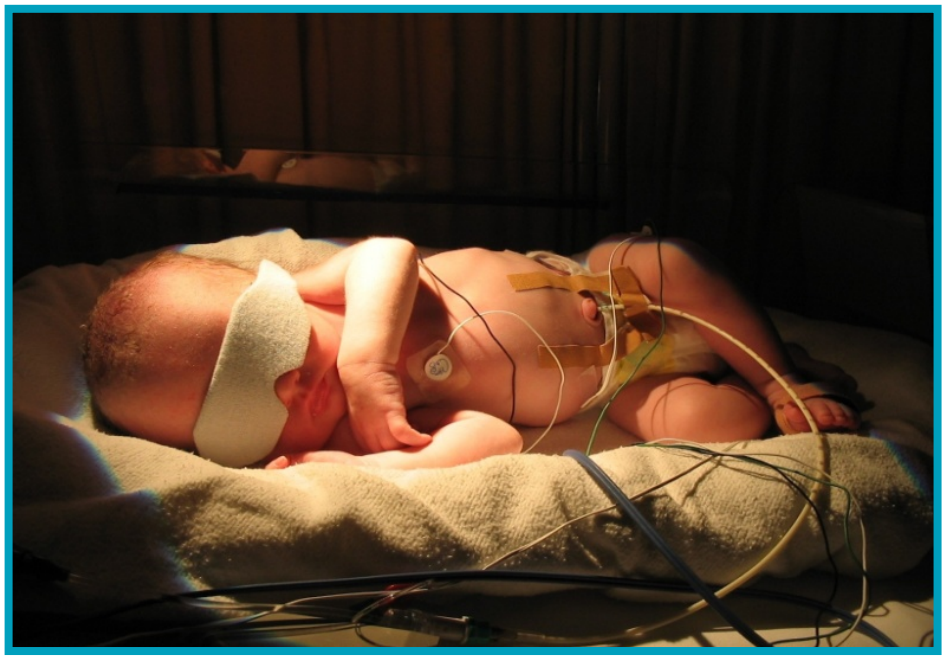
Leids Universitair Medisch Centrum

Postnatal management and outcome in neonates with Rhesus hemolytic disease



Enrico Lopriore, Head of Neonatal Intensive Care Unit
LEIDEN UNIVERSITY MEDICAL CENTER, THE NETHERLANDS

Outline

1. Rhesus disease in The Netherlands:
   - organization and outcome

2. Neonatal management

Early phase - ***1st wk***

hyperbilirubinemia

Late phase - ***2nd wk - 3 months***

Hyporegenerative anemia

3. Long-term neurodevelopmental outcome after IUT
   - LOTUS study


Iceland
Finland
Sweden
Norway
Russia
Estonia
Latvia
Den-
mark
Lithuania
Kazakhstan
Ireland
United
Kingdom
Belarus
Nether-
lands
Poland
Belgium
Germany
Ukraine
Luxembourg
Czech Republic
Slovakia
Mol-
dova
France
Switzer-
land
Liecht
Austria
Hungary
Romania
Georgia
Azerbaijan
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nia
Croatia
Armenia
Monaco
Bosnia and
Herzego-
vina
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San
Marino
Bulgaria
Andorra
Monte-
negro
Iran
Portugal
Italy
Spain
Mace-
donia
Vatican City
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Turkey
Greece
Syria
Iraq
Cyprus
Leba-
non
Morocco
Algeria
Tunisia
Malta
Israel
Jordan
Saudi Arabia

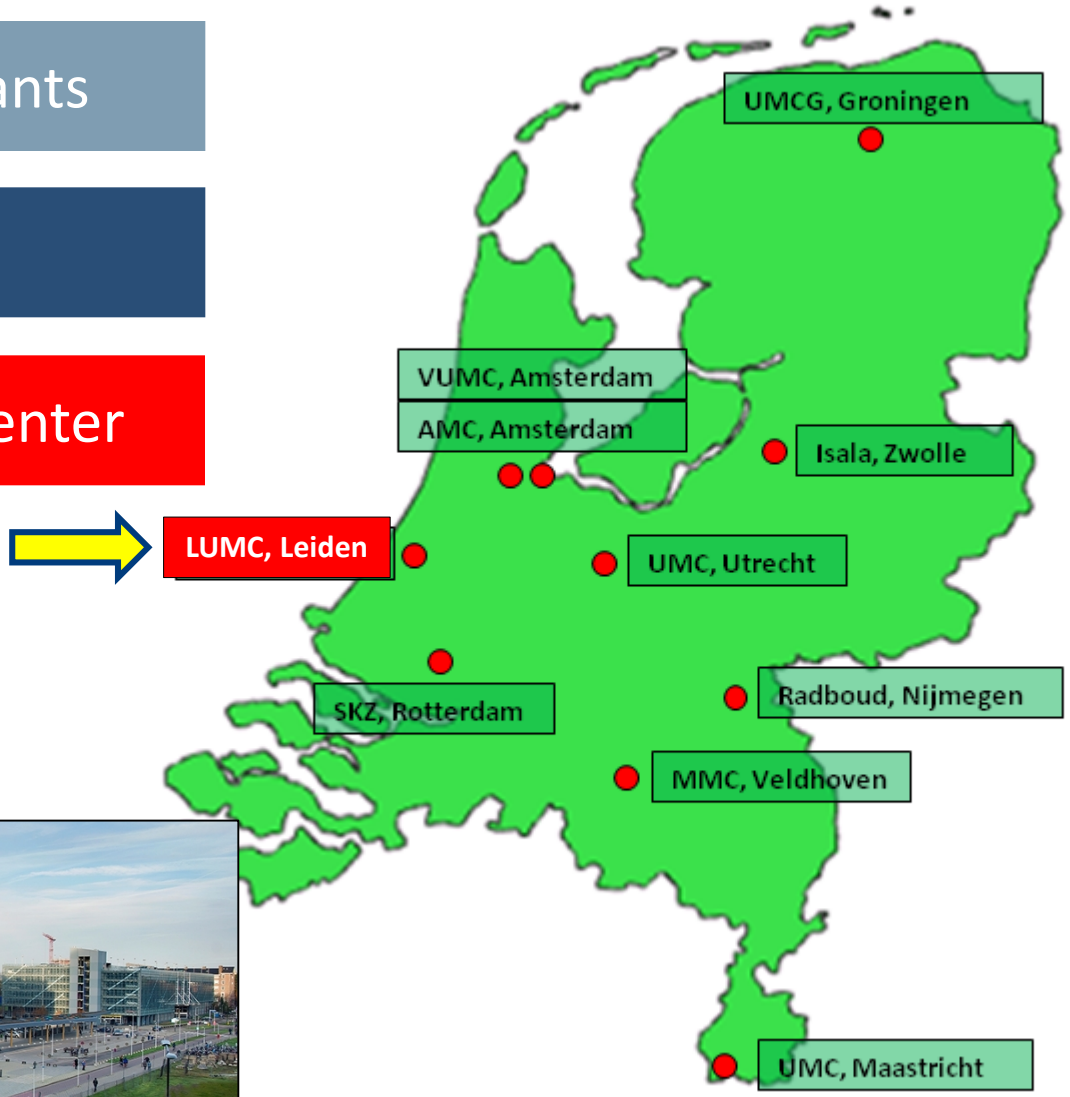
The Netherlands:

Centralization of tertiary care

16.8 M inhabitants

10 NICUs

1 fetal therapy center



Complications of IUT: lessons learned after 1678 procedures. *Zwiers C. et al UOG 2017*

N=589 fetuses/1678 procedures
Overall survival: 93.4%

Outcome	1988-2000 (n=255/741)	2001-2014 (n=334/937)	OR (95% CI)	P value
Survival, no. (%)	226 (88.6)	324 (97.0)	4.16 (2.0-8.7)	<0.001
Procedure-related complications, no.	32	12		
Per fetus, no (%)	25 (9.8)	11 (3.3)	0.31 (0.2-0.7)	0.001
Per procedure, no (%)	25 (3.4)	11 (1.2)	0.34 (0.2-0.7)	0.003
Procedure-related losses, no.	12	6		
Per fetus, %	4.7	1.8	0.37 (0.1-1.0)	0.053
Per procedure, %	1.6	0.6	0.39 (0.1-1.0)	0.059

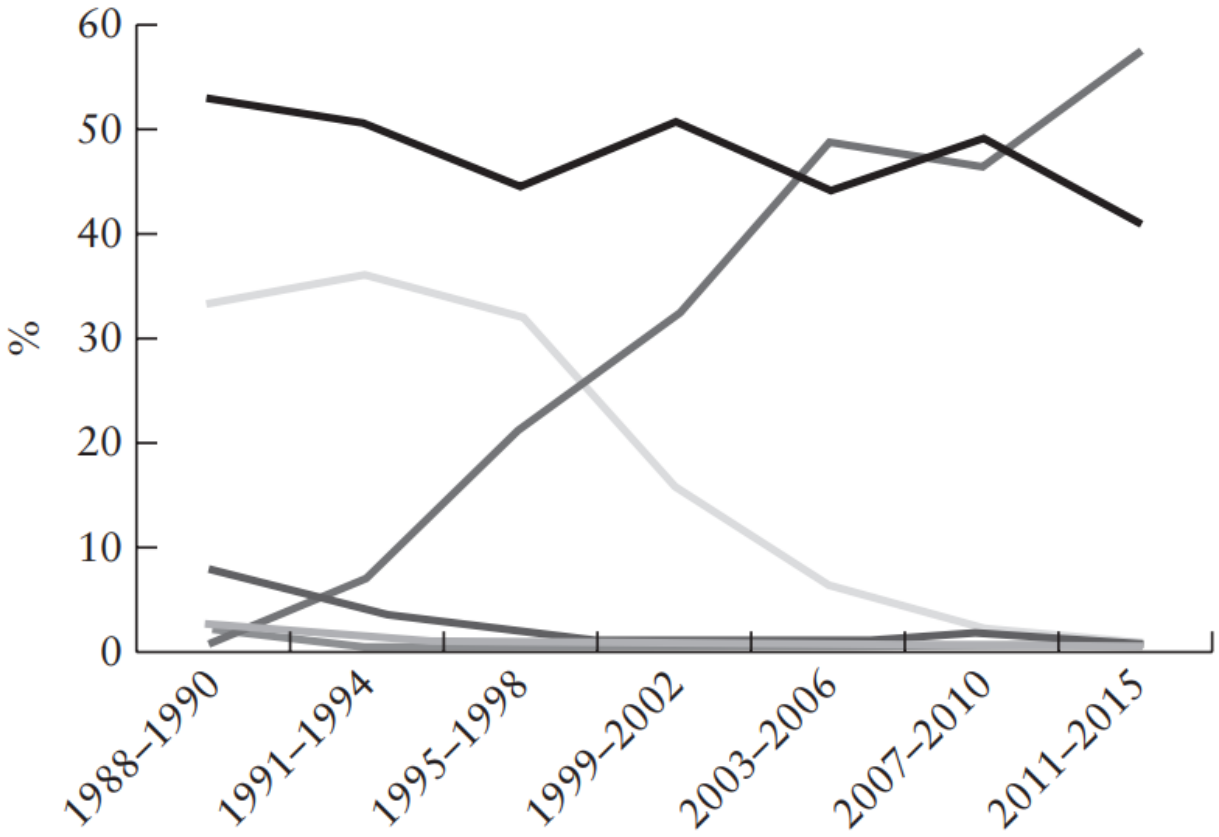
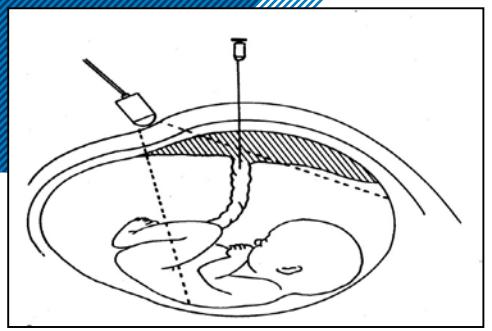
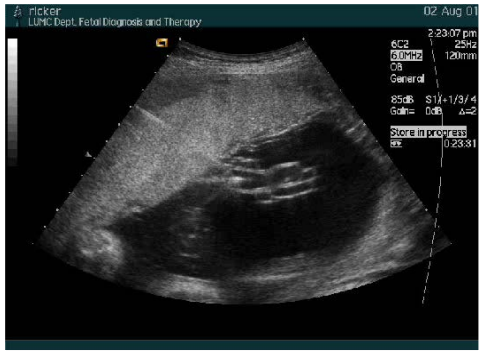
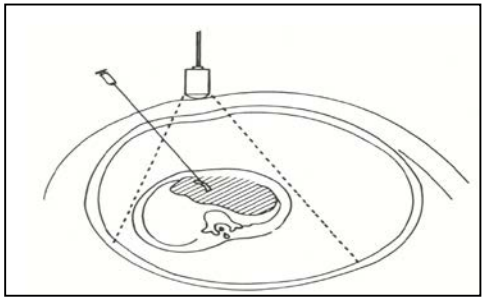
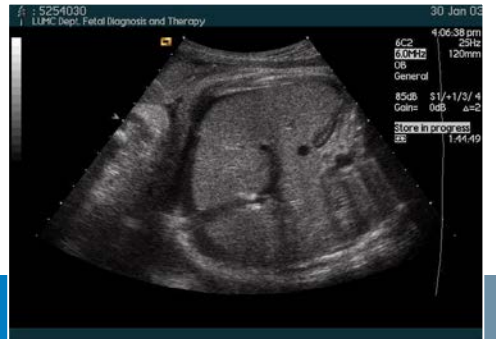


Figure 1 Trends in procedure access sites for intrauterine intravascular blood transfusion between January 1988 and January 2015. ——, liver (plus intraperitoneal); ——, placental cord insertion; ——, transamniotic venous; ——, arterial (cord insertion or transamniotic); ——, intraperitoneal; ——, unknown vessel, heart, chorionic vein.

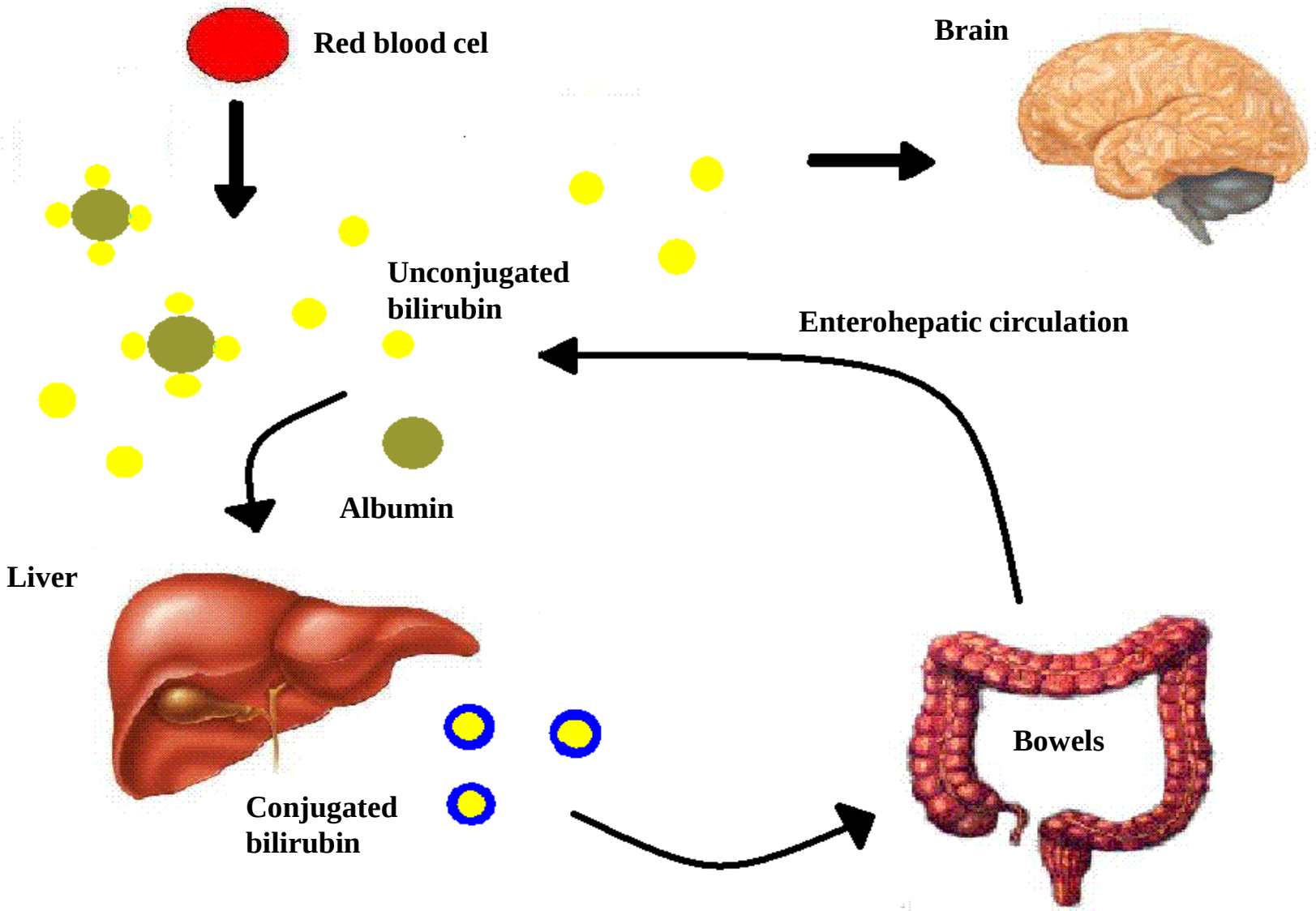






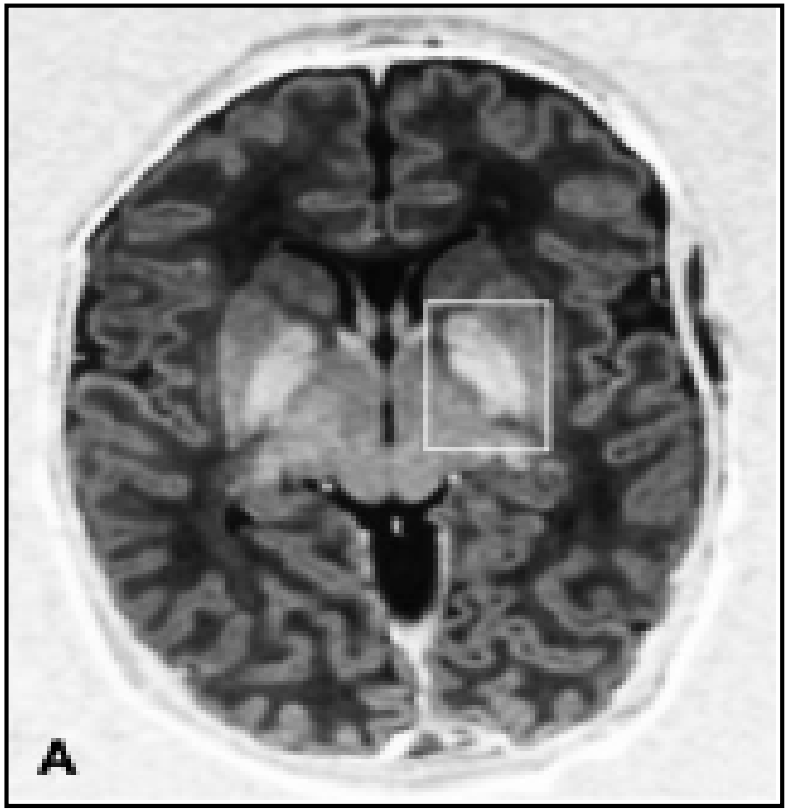


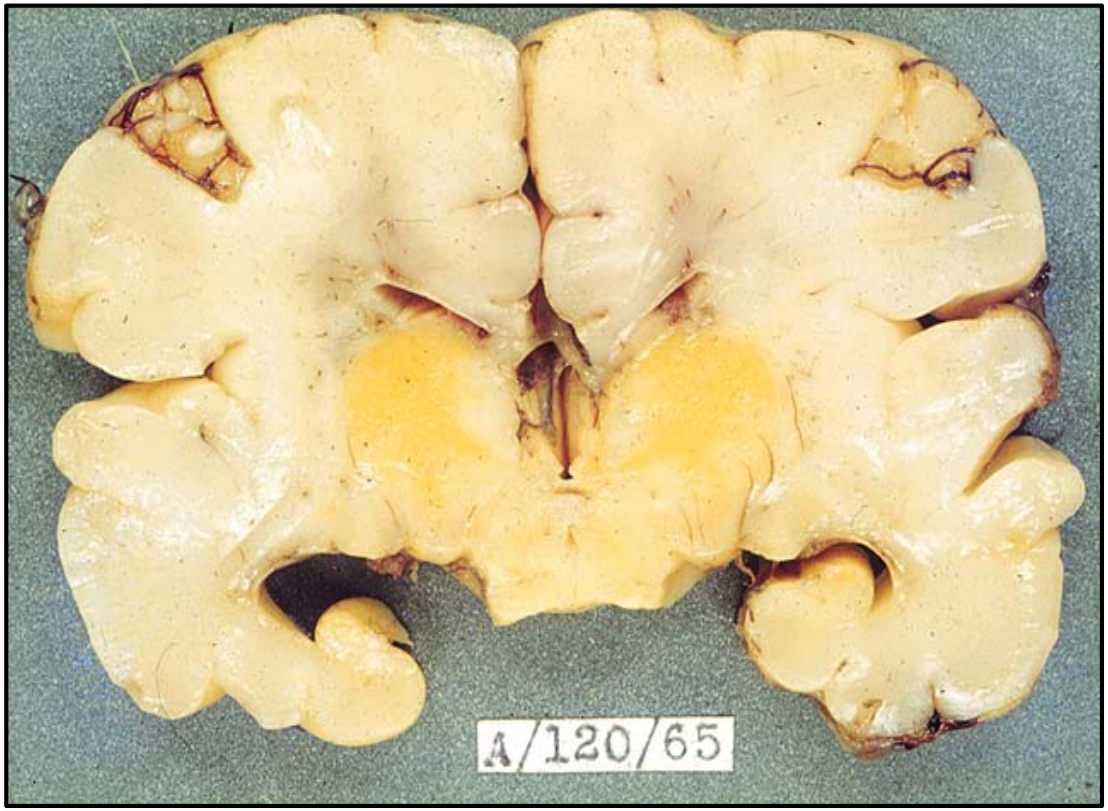
Neonatal management



Main aim: Prevent kernicterus!

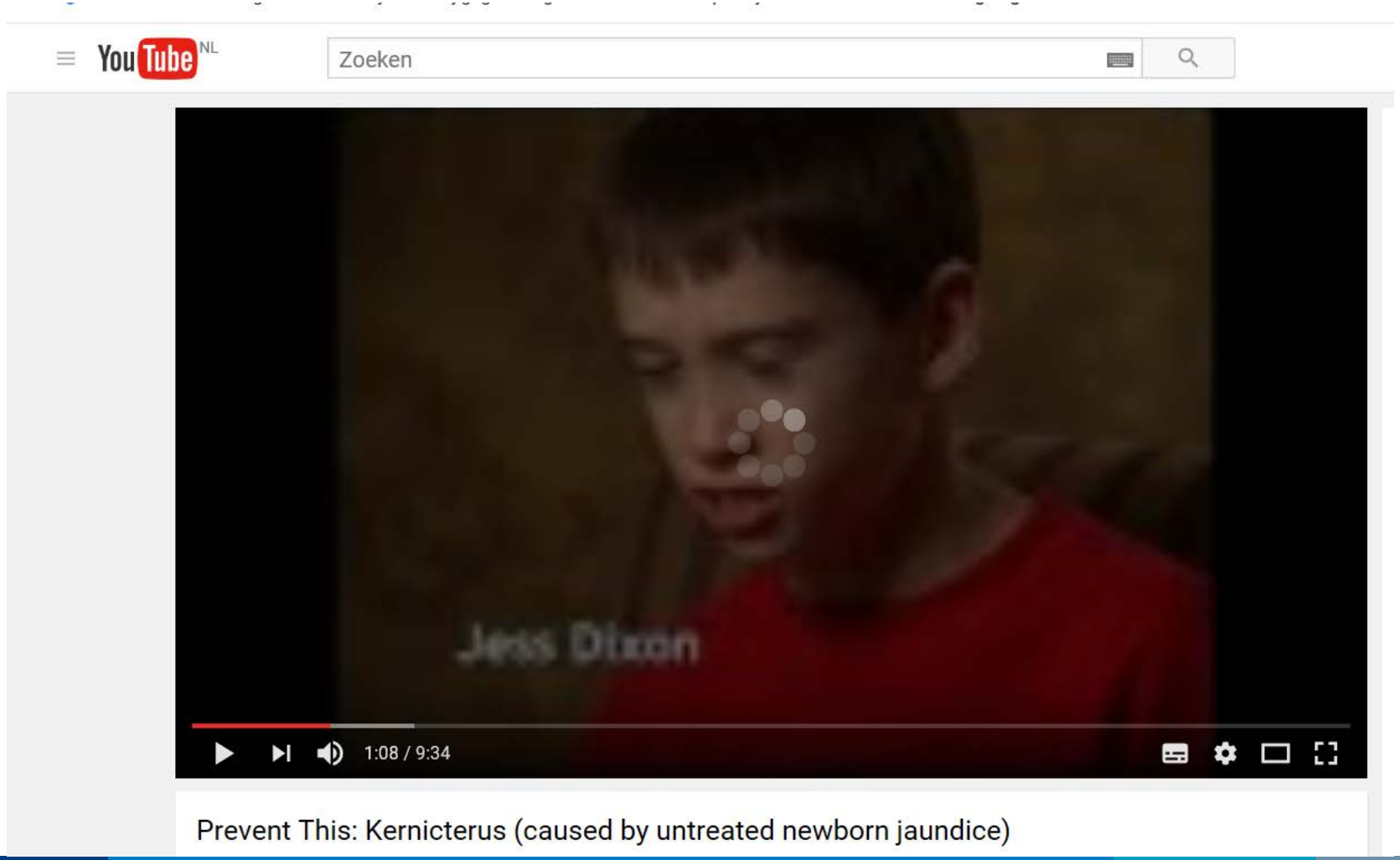
Bilirubin=neurotoxic, causes encefalopathy





Kernicterus: late symptoms

https://www.youtube.com/watch?v=7G-V6zQ_u8A



Management

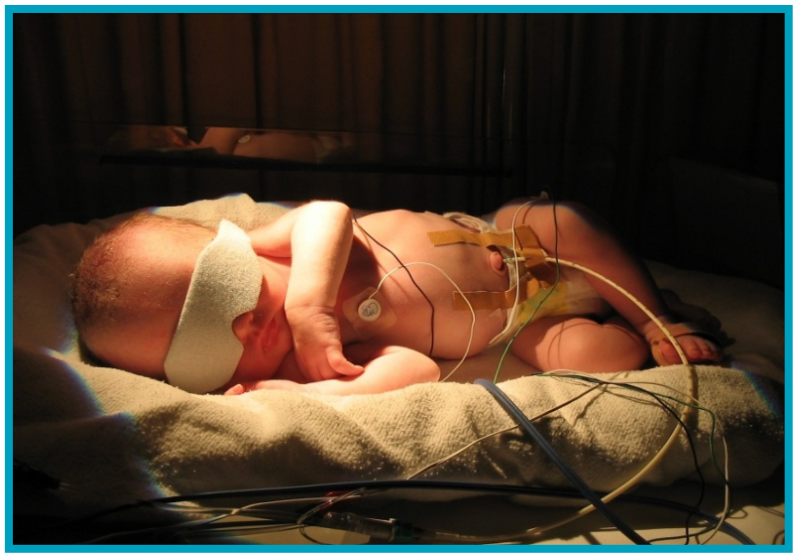
hyperbilirubinemia

Early phase (1st week)

Intensive phototherapy

Exchange transfusions

IVIG?



Late anemia

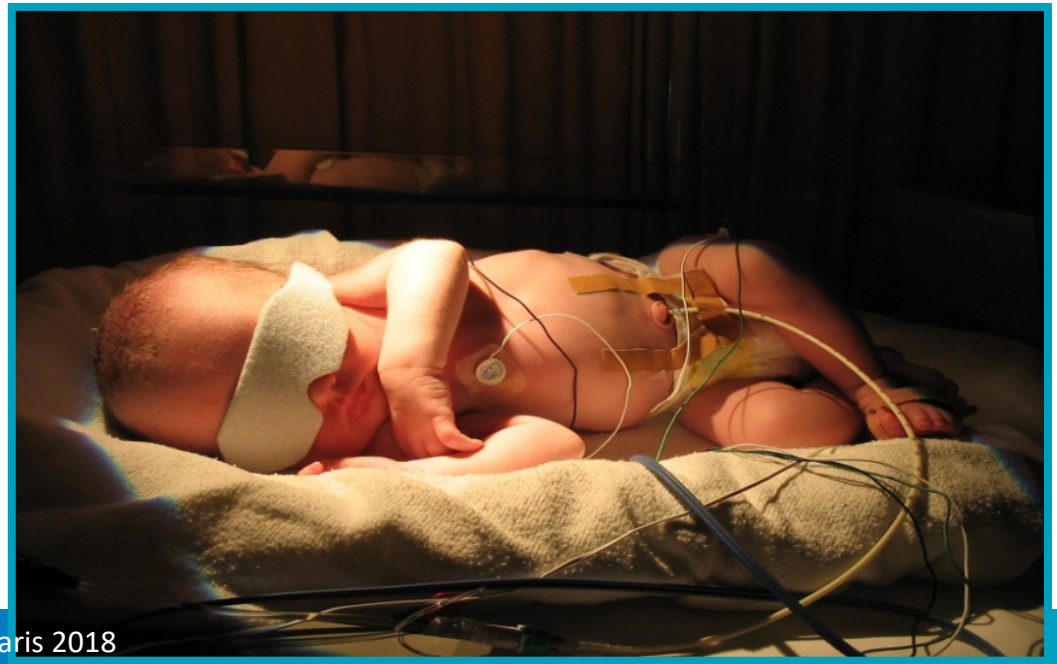
Late phase (2d week – 3 months)

Top-up transfusions

EPO?

Intensive phototherapy (PT)

1. Admit to NICU within 15 min after birth
2. Start intensive PT directly
3. Intensive PT = 3 to 4 lamps (no diaper!), short distance
4. Bili check every 2-3 hours
5. No breastfeeding in first 2-3 days



Exchange transfusion (ET)

160 ml/kg

time: 90-150 min

Exception:
Kell-immunization

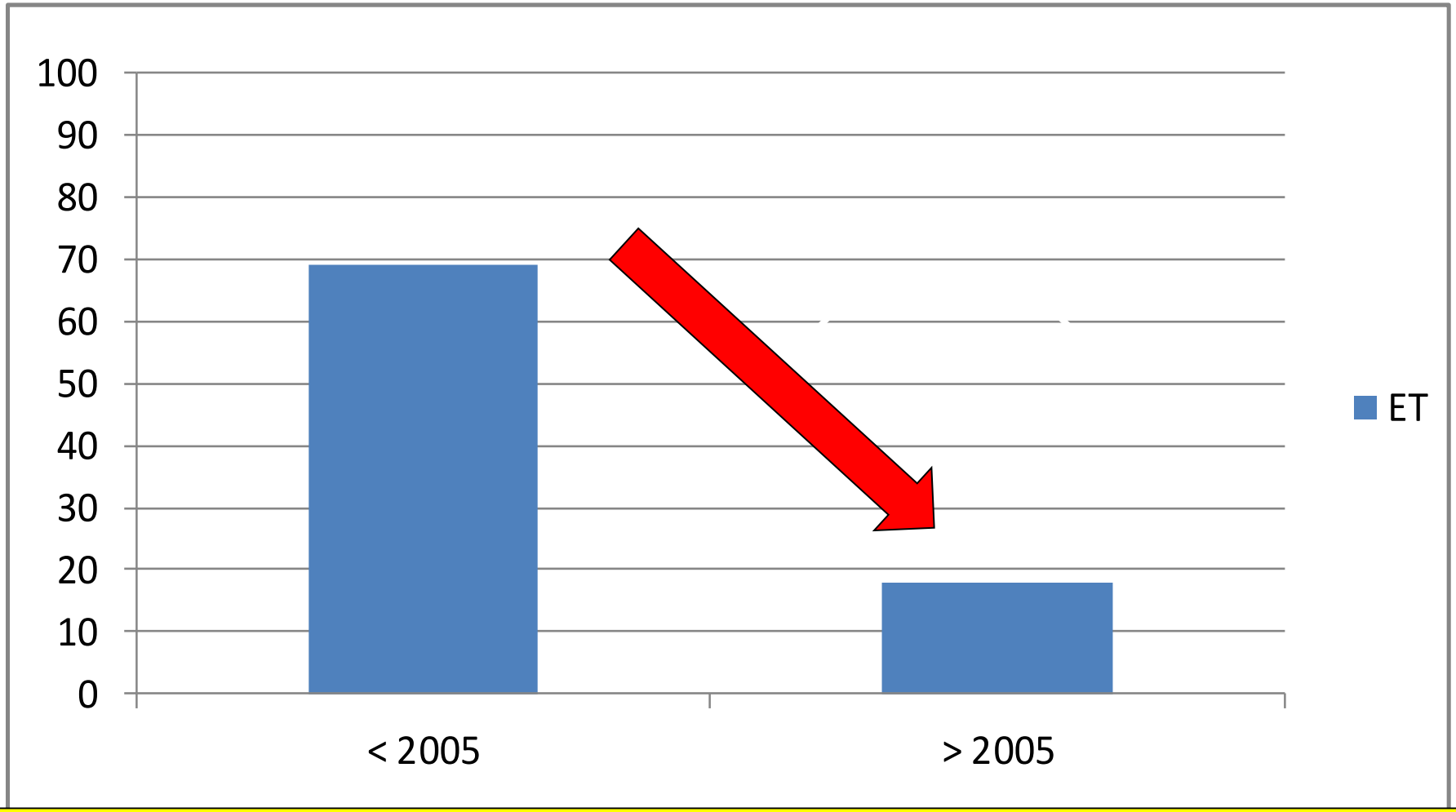
Mortality: 0.3%

Morbidity: 6-24%

- Sepsis, NEC, catheter-related complications, thrombocytopenia, hypocalciemia

Neonatal morbidity after exchange transfusion for red cell alloimmune hemolytic disease.
Smits-Wintjens et al. **Neonatology.** 2013

Exchange transfusion, LUMC



Rhesus haemolytic disease of the newborn: Postnatal management, associated morbidity and long-term outcome.
Smits-Wintjens et al. **Semin Fetal Neonatal Med. 2008**

Intravenous immunoglobulins (IVIg)

Cochrane 2002: No evidence for routine IVIg: “further trials needed”

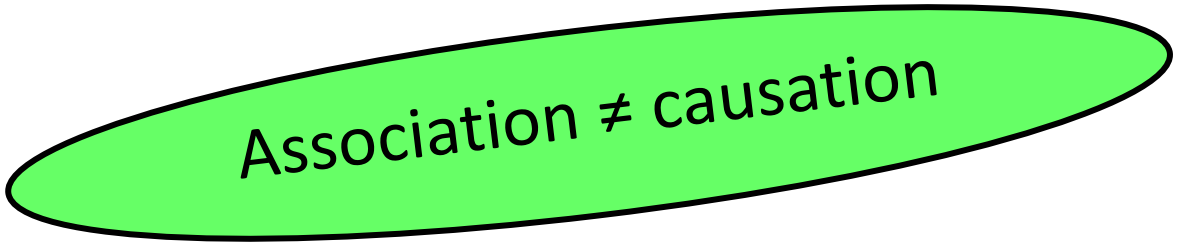
AAP – guideline 2004: IVIg 0.5-1 g/kg if phototherapy fails

Does it really work? Side effects?

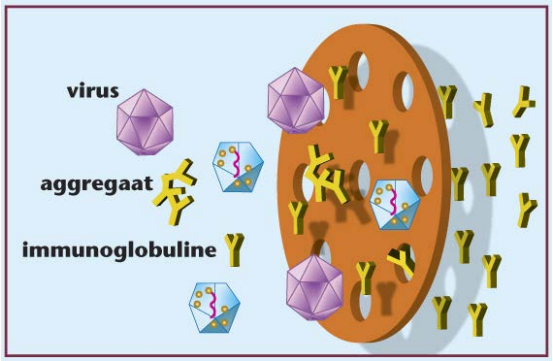
Necrotizing enterocolitis following the use of **intravenous immunoglobulin** for haemolytic disease of the newborn.
Navarro M, Negre S, Matoses ML, Golombek SG, Vento M. Acta Paediatr. 2009 Jul;98(7):1214-7.

Necrotizing enterocolitis in a term neonate following **intravenous immunoglobulin** therapy.
Krishnan L, Pathare A.Indian J Pediatr. 2011 Jun;78(6):743-4

Necrotizing enterocolitis in a newborn following **intravenous immunoglobulin** treatment for haemolytic disease.
Kara S, Ulu-ozkan H, Yilmaz Y, Arikan FI, Dilmen U, Bilge YD. J Coll Phys Surg Pak. 2013 Aug;23(8):598-600



IVIg RCT *Smits-Wintjens et al*, Pediatrics 2011



Eligible
n=121

Exclusion
- **no RhD or c: n=16**
- **No consent: n=19**

Inclusion
n=80

IUT
n=53

No IUT
n=27

IVIG (0.75 g/kg)
n=27

Placebo (glu 5%)
n=26

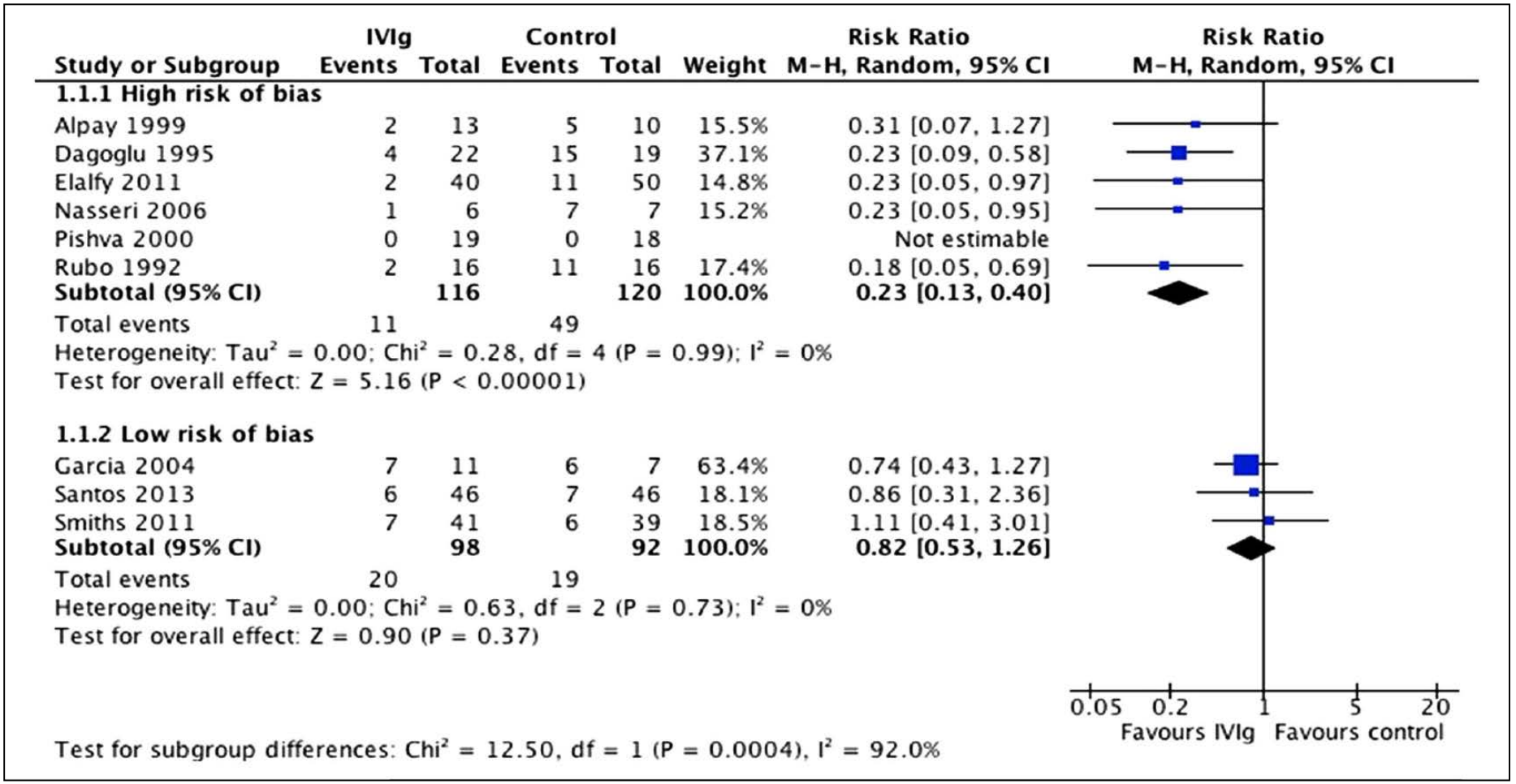
IVIG (0.75 g/kg)
n=14

Placebo (glu 5%)
n=13

IVIg RCT *Smits-Wintjens et al*, Pediatrics 2011

	IVIG-group n=41	Placebo-group n=39	P-value
Neonates treated with ET	7/41 (17%)	6/39 (15%)	1.00
Number of Ets/neonate	0.2 ± 0.5	0.2 ± 0.5	0.90
Phototherapy (days)	4.7 ± 1.8	5.1 ± 2.1	0.34
Admission LUMC (days)	7 ± 4	7 ± 3	0.37
Top-up transfusions/neonate	34/41 (83%)	34/39 (87%)	0.76
Number of top-ups/neonate	2.2 ± 1.6	2.2 ± 1.5	0.93

Metanalysis IVIg



IVIg in isoimmune haemolytic disease of newborn: an updated systematic review and meta-analysis.
Louis et al. **Arch Dis Child Fetal Neonatal Ed**. 2014

Alternatives to reduce hyperbilirubinemia?

1. Zinc
2. Albumin
3. Phenobarbital
4. Metalloporphyrins
5. Clofibrate
6. Prebiotic supplementation
7. Antenatal corticosteroids

We need RCTs!

Accelerate *lung* maturation

Accelerate *liver* maturation

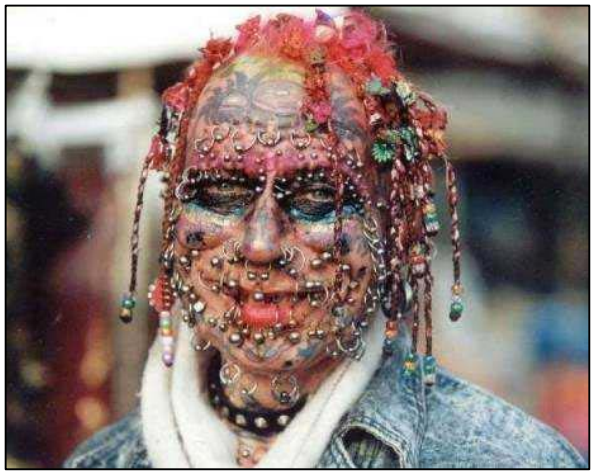
Neonatal management and outcome in alloimmune hemolytic disease
Ree I. et al. **Expert review of Hematology** 2017

Late fase (2nd week – 3 months)

Late anemia

Top-up blood transfusions (1st 3months)

- Hb + reticulocyte count:1x/week
- Folic acid 1 dd 50ugr, **NO IRON!**
- 60-85% at-least 1 top-up transfusion
- ± 5% 6 top-up transfusions



- **NO BONEMARROW ASPIRATION!**

Exchange transfusion, LUMC

Top-up transfusions

100
90
80
70
60
50
40
30
20
10
0

< 2005

> 2005

ET

EPO?
Time for a trial!

Rhesus haemolytic disease of the newborn: Postnatal management, associated morbidity and long-term outcome.
Smits-Wintjens et al. **Semin Fetal Neonatal Med. 2008**

EPO-4-Rhesus trial

Darbepoetin 10u/kg 1x/wk

Objective: to determine if treatment with EPO reduces the need for top-up transfusions in neonates

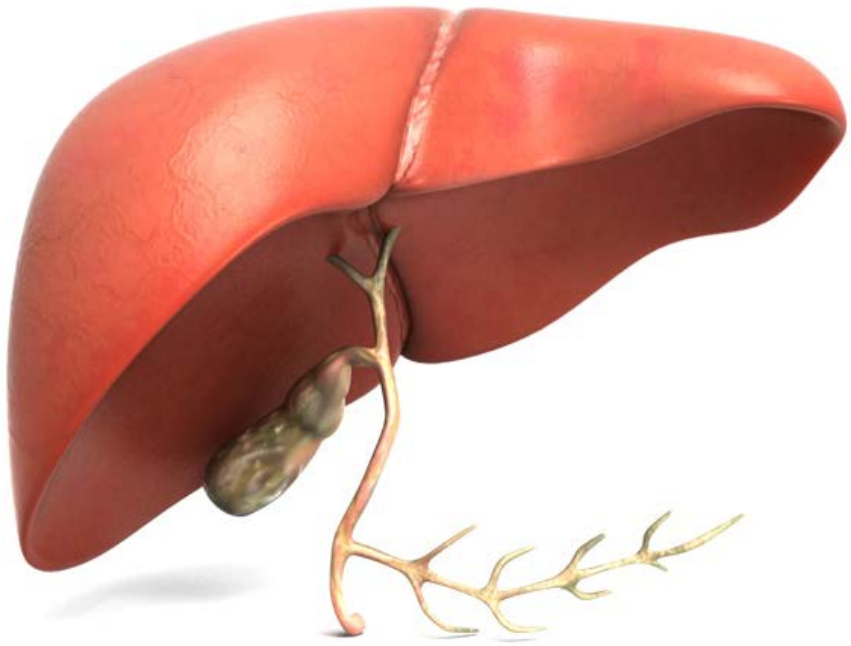
Design: Randomized controlled trial

Inclusion: neonates with HDFN ***treated with IUT***

Sample size: 22 neonates in each study arm to detect a 50% reduction in the median number of transfusions per neonate, from a median of 2 transfusions to 1 transfusion in EPO group

Associated neonatal morbidity

Cholestasis



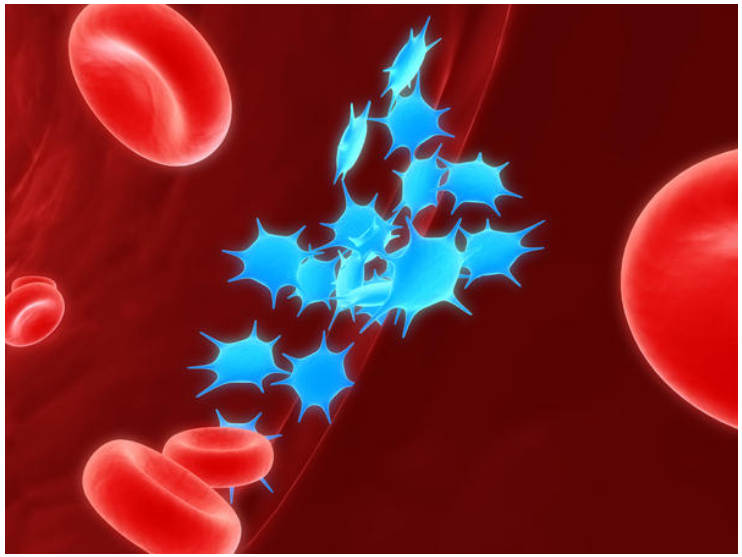
- Incidence: 15%
- Cause?
  - high ferritine
  - Iron deposition liver

Cholestasis in neonates with red cell alloimmune hemolytic disease. Smits-Wintjens et al. **Neonatology.** 2012

Iron status in infants with alloimmune haemolytic disease in the first 3 months of life. Rath et al. **Vox Sang.** 2013

Associated neonatal morbidity

Trombocytopenia



- Incidence: 26%

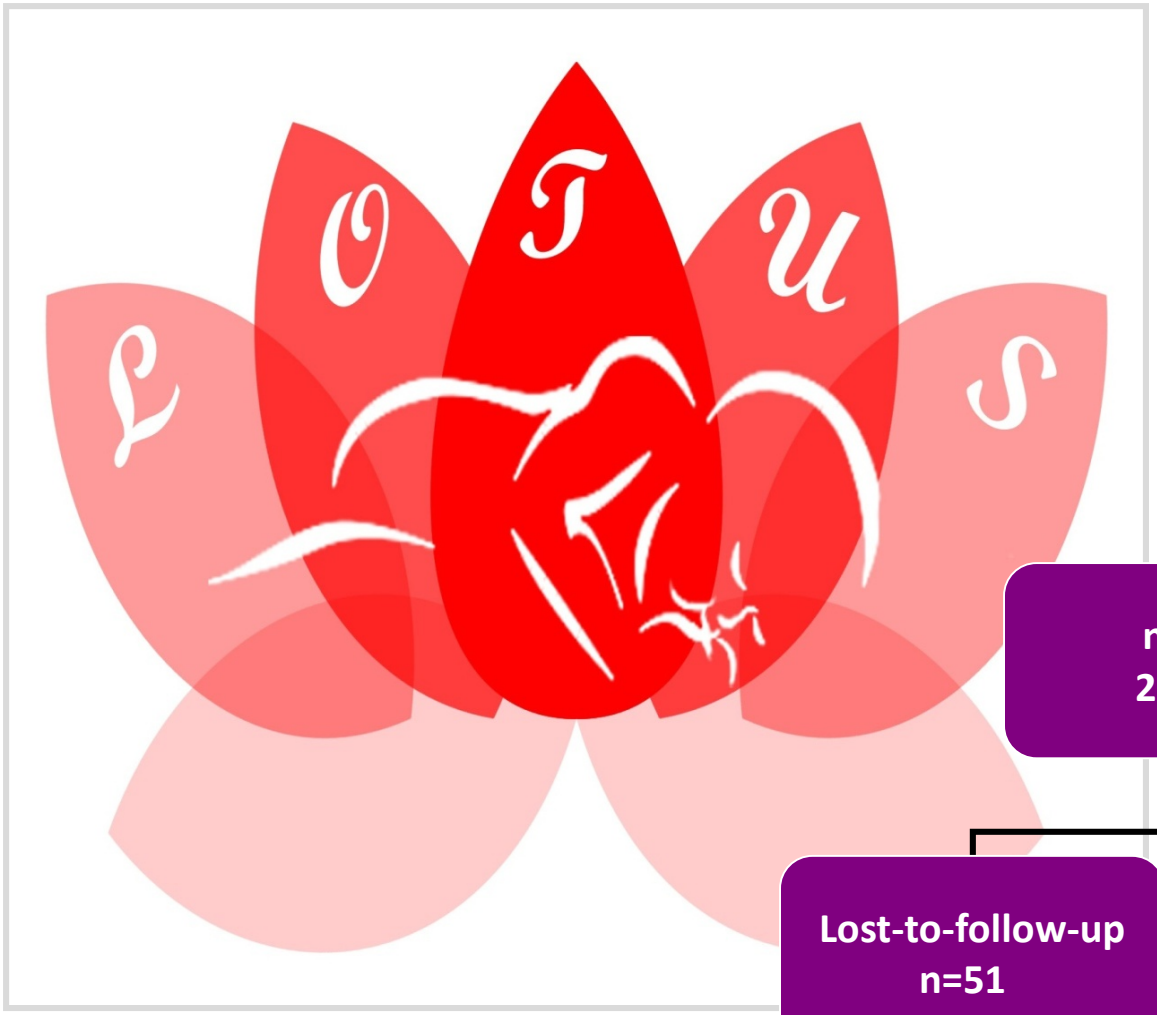
- Cause?
- ↓production
- ↑destruction due to Ab against megakaryocytes

Thrombocytopenia at birth in neonates with red cell alloimmune hemolytic disease. Rath et al, Vox Sang. 2012

Long-term outcome after IUT

Author, year	Outcome measure	Cerebral Palsy (CP)	Neurodevelopmental impairment (NDI)	Comments
Doyle, 1993	Bayley Scales	2.6% (1/38)	**7.9% (3/38)**	Controls not contemporaneous, transfusion group better SES
Stewart, 1994	Cattel Test	0% (0/8)	**0% (0/8)**	Insufficient information on patients and methods, insufficient power
Janssens, 1997	Denver Developmental Screening test	4.3% (3/69)	**10.1% (7/69)**	Age @ follow-up: 6 months to 6 years
Hudon, 1998	Gesell Schedules McCarthy Scales	4.5% (1/22)	n.a.	High lost to follow-up rate, no formal criteria NDI, insufficient power
Grab, 1999	School performance	0% (0/35)	n.a.	No developmental tests
Farrant, 2001	Questionnaire	3.3% (1/30)	n.a.	Insufficient information on methods, no developmental tests
Harper, 2006	Differential Ability Scale	6.3% (1/16)	**18.8% (3/16)**	Insufficient power
Weisz, 2009	Questionnaire	0% (0/40)	n.a.	No developmental tests

LOng-Term outcome after IUT Study



1988-2008
n=451

Death: n=44 (10%)
n=404

n=342
2-17 yr

n=62
17-22 yr

Lost-to-follow-up
n=51

Included
n=291

LOTUS study Lindenburg *et al*, AJOG 2012

	n = 291
Cerebral palsy (CP) - *% (n)*	2.3% (6)
Severe developmental delay - *% (n)*	3.2% (9)
Bilateral deafness - % *(n)*	1.0% (3)
Neurodevelopmetal impairment - % *(n)*	**4.8% (14)**

Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the newborn
Lindenburg et al. **Am J Obstet Gynecol**. 2012

Risk factors analysis

	NDI n = 14	No NDI n = 277	p-value	OR (95% CI)
Hydrops *n (%)*	9 (64%)	66 (24%)	0.002	5.8 (1.9 -17.8)
Hemoglobin at first IUT *(g/dl)*	4.2 ± 1.9	5.6 ± 2.4	0.032	1.3 per g/dl ↓ (1.0-1.7)
Number of IUTs	4 (1-5)	3 (1-6)	0.018	1.7 per IUT (1.1-2.5)
GA at birth <32wks	2 (14%)	4 (1%)	0.006	12.8 (2.1-79.5)
Perinatal asphyxia *n (%)*	1 (7%)	10 (4%)	0.51	2.0 (0.2-17.1)
Severe neonatal morbidity *n (%)*	6 (43%)	16 (6%)	< 0.001	13.1 (4.0 – 42.4)

Conclusions: *4 keypoints*

Optimize intensive phototherapy

Beware of cholestasis, iron overload, trombocytopenia

Try to avoid exchange transfusion

Long-term outcome after IUT is good!

Future perspectives - *4 keypoints*

Reduce hyperbilirubinemia and ET
antenatal steroids? Phenobarbital?

Reduce near-prematurity
From 35-37wks to > 38 wks?

Reduce Top-up transfusions
EPO? Lower transfusion thresholds?

Centralization of neonatal care
Optimal management, research

Research = teamwork

Thanks to co-workers at:

- Sanquin-research (I. Ree, M. de Haas)
- Dept. Obstetrics (I. van Kamp, D. Oepkes)
- Dept. Neonatology (V. Smits, J. van Klink)