Postnatal management and outcome in neonates with Rhesus hemolytic disease

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

2. Neonatal management
   Early phase - 1st wk
   Late phase - 2nd wk - 3 months

   hyperbilirubinemia
   Hyporegenerative anemia

3. Long-term neurodevelopmental outcome after IUT
   - LOTUS study
The Netherlands:
Centralization of tertiary care

- 16.8 M inhabitants
- 10 NICUs
- 1 fetal therapy center

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

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

- Red blood cell
- Unconjugated bilirubin
- Albumin
- Conjugated bilirubin
- Brain
- Enterohepatic circulation
- Bowels

Liver
Main aim: Prevent kernicterus!

Bilirubin = neurotoxic, causes encephalopathy
Kernicterus: late symptoms

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

Prevent This: Kernicterus (caused by untreated newborn jaundice)
Management

Early phase (1\textsuperscript{st} week)
Intensive phototherapy
Exchange transfusions
IVIG?

Late phase (2\textsuperscript{d} 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

Mortality: 0.3%
Morbidity: 6-24%

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

Exception:
Kell-immunization

Neonatal morbidity after exchange transfusion for red cell alloimmune hemolytic disease.
Smits-Wintjens et al. Neonatology. 2013
Rhesus haemolytic disease of the newborn: Postnatal management, associated morbidity and long-term outcome.
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?


Association ≠ causation
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**

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

### IVIg in isoimmune haemolytic disease of newborn: an updated systematic review and meta-analysis.


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IVIg Events</th>
<th>IVIg Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 High risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpay 1999</td>
<td>2</td>
<td>13</td>
<td>5</td>
<td>10</td>
<td>15.5%</td>
<td>0.31 [0.07, 1.27]</td>
</tr>
<tr>
<td>Dagoglu 1995</td>
<td>4</td>
<td>22</td>
<td>15</td>
<td>19</td>
<td>37.1%</td>
<td>0.23 [0.09, 0.58]</td>
</tr>
<tr>
<td>Elafy 2011</td>
<td>2</td>
<td>40</td>
<td>11</td>
<td>50</td>
<td>14.8%</td>
<td>0.23 [0.05, 0.97]</td>
</tr>
<tr>
<td>Nasseri 2006</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>15.2%</td>
<td>0.23 [0.05, 0.95]</td>
</tr>
<tr>
<td>Pishva 2000</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>18</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Rubo 1992</td>
<td>2</td>
<td>16</td>
<td>11</td>
<td>16</td>
<td>17.4%</td>
<td>0.18 [0.05, 0.69]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td>0.23 [0.13, 0.40]</td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 4 (P = 0.99); I² = 0%
| Test for overall effect: Z = 5.16 (P < 0.000001) |

| **1.1.2 Low risk of bias** |
| Garcia 2004       | 7           | 11         | 6              | 7             | 63.4%  | 0.74 [0.43, 1.27]              |
| Santos 2013       | 6           | 46         | 7              | 46            | 18.1%  | 0.86 [0.31, 2.36]              |
| Smiths 2011       | 7           | 41         | 6              | 39            | 18.5%  | 1.11 [0.41, 3.01]              |
| **Subtotal (95% CI)** |
| Total events      | 20          | 19         |                |               |        | 0.82 [0.53, 1.26]              |
| Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
| Test for overall effect: Z = 0.90 (P = 0.37) |

Test for subgroup differences: Chi² = 12.50, df = 1 (P = 0.0004), I² = 92.0%
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**
Late fase (2\textsuperscript{nd} week – 3 months)

Top-up blood transfusions (1\textsuperscript{st} 3 months)

- 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

EPO?
Time for a trial!

Rhesus haemolytic disease of the newborn: Postnatal management, associated morbidity and long-term outcome.

Yves Brossard Paris 2018
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

Darbepoetin 10u/kg 1x/wk
Associated neonatal morbidity

Cholestasis

- Incidence: 15%

- Cause?
  - high ferritine
  - Iron deposition liver


Trombocytopenia

- Incidence: 26%

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

## Long-term outcome after IUT

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

1988-2008
n=451

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

Lost-to-follow-up
n=51

Included
n=291

n=342
2-17 yr

n=62
17-22 yr

n=404

Yves Brossard Paris 2018
<table>
<thead>
<tr>
<th>Condition</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy (CP)</td>
<td>2.3% (6)</td>
</tr>
<tr>
<td>Severe developmental delay</td>
<td>3.2% (9)</td>
</tr>
<tr>
<td>Bilateral deafness</td>
<td>1.0% (3)</td>
</tr>
<tr>
<td>Neurodevelopmental impairment</td>
<td>4.8% (14)</td>
</tr>
</tbody>
</table>

Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the newborn
## Risk factors analysis

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

- Optimize intensive phototherapy
- Try to avoid exchange transfusion
- Beware of cholestasis, iron overload, trombocytopenia
- Long-term outcome after IUT is good!
Future perspectives - 4 keypoints

- Reduce hyperbilirubinemia and ET
  antenatal steroids? Phenobarbital?

- Reduce Top-up transfusions
  EPO? Lower transfusion thresholds?

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

- 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)