Le Immunoglobuline nella Profilassi e Terapia della Sepsi Neonatale

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Neonatal sepsis

Epidemiology

- 0.5-1% live births
- 50% NICU admissions
- 20-40% mortality rate

Neurodevelopmental and Growth Impairment Among Extremely Low-Birth-Weight Infants With Neonatal Infection

Barbara J. Stoll; Nellie I. Hansen; Ira Adams-Chapman; et al.  

- Infants who had at least 1 sepsis episode had an increased rate of:
  - Cerebral palsy
  - Low mental development index (Bayley scale)
  - Low psychomotor development index
  - Vision impairment
  - Impaired head growth
Sepsis is defined as the systemic inflammatory response to infection.
The immaturity of the immune response plays a pivotal role in susceptibility to infections and relates inversely to gestational age.

From 12th week of gestation begins the active placental transfer of maternal IgG with the achievement in term newborn of IgG levels equal or even higher than the adult subject, while preterm infant presents a significant hypogammaglobulinemia that exposes them to a greater risk of infection.

At birth, most of Ig are maternal IgG, whose concentration decreases rapidly.

Only at the third month of life Ig production slowly begins and at about 4-6 years IgG levels are comparable to adults.

Non-antibiotic (adjuvant) therapy

- Pentoxifylline
- G-CSF, GM-CSF
- White cell transfusions
- Immunoglobulins
Immunoglobulins: rationale for use

- Bind cell surface receptors
- Provide opsonic activity
- Activate complement fixation
- Promote antibody dependent cytotoxicity
- Improve neutrophil chemiluminescence
- Improve phagocytosis
- Promote release of stored neutrophils
Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants.

Ohlsson A, Lacy JB. Cochrane Database Syst Rev. 2013

- 5000 preterm and/or LBW infants
- significant reduction in sepsis was noted (RR: 0.85, 95% CI: 0.74 to 0.98)
- no differences in mortality from all causes, mortality from infection; in incidence of NEC, BPD or IVH or in length of hospital stay.
- no major adverse effects of IVIG were reported in any of these studies.

CONCLUSION

The decision to use prophylactic IVIG will depend on the costs and the values assigned to the clinical outcomes. There is no justification for conducting additional RCTs to test the efficacy of previously studied IVIG preparations in reducing nosocomial infections in preterm and/or LBW infants.
Immunoglobulins for treatment of neonatal sepsis
The state of the art in 2010
Neonatal sepsis

Figure 1. Forest plot of comparison: IVIG vs placebo or no intervention for suspected infection, outcome: 1.1 Mortality from any cause.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>treatment</th>
<th>Events</th>
<th>Total</th>
<th>control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed 2006</td>
<td></td>
<td>4</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td></td>
<td>21.2%</td>
<td>0.40 [0.14, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Christensen 1991</td>
<td></td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td></td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Erdem 1993</td>
<td></td>
<td>6</td>
<td>20</td>
<td>9</td>
<td>24</td>
<td></td>
<td>17.3%</td>
<td>0.80 [0.34, 1.86]</td>
<td></td>
</tr>
<tr>
<td>Haque 1988</td>
<td></td>
<td>1</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td></td>
<td>12.7%</td>
<td>0.17 [0.02, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Samatha 1997</td>
<td></td>
<td>5</td>
<td>30</td>
<td>8</td>
<td>30</td>
<td></td>
<td>17.0%</td>
<td>0.63 [0.23, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Shenoi 1999</td>
<td></td>
<td>7</td>
<td>25</td>
<td>7</td>
<td>25</td>
<td></td>
<td>14.8%</td>
<td>1.00 [0.41, 2.43]</td>
<td></td>
</tr>
<tr>
<td>Sidiropoulos 1981</td>
<td></td>
<td>4</td>
<td>41</td>
<td>8</td>
<td>41</td>
<td></td>
<td>17.0%</td>
<td>0.50 [0.16, 1.53]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td>187</td>
<td></td>
<td>191</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.58 [0.38, 0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td>27</td>
<td></td>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.97, df = 5 (P = 0.55); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.53 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Citation: Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub3.
The state of the art in 2010
Neonatal sepsis

Figure 2. Forest plot of comparison: 2 IVIG vs placebo or no intervention for proven infection, outcome: 2.1 Mortality from any cause.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>treatment</th>
<th>control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Chen 1996</td>
<td>2</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Erdem 1993</td>
<td>5</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Haque 1988</td>
<td>1</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Mancilla-R 1992</td>
<td>2</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Samatha 1997</td>
<td>0</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Sidiropoulos 1981</td>
<td>2</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Weisman 1992</td>
<td>2</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>129</td>
<td>133</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 14

Heterogeneity: Chi² = 3.53, df = 6 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.04 (P = 0.04)

Citation: Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub3.
... and then something happened...

Treatment of Neonatal Sepsis with Intravenous Immune Globulin

The INIS Collaborative Group*
Randomized, placebo controlled, multicentre, international trial

1454 UK
1043 Australia
480 Argentina
355 New Zealand
181 Continental Europe
BACKGROUND
Neonatal sepsis is a major cause of death and complications despite antibiotic treatment. Effective adjunctive treatments are needed. Newborn infants are relatively deficient in endogenous immunoglobulin. Meta-analyses of trials of intravenous immune globulin for suspected or proven neonatal sepsis suggest a reduced rate of death from any cause, but the trials have been small and have varied in quality.

METHODS
At 113 hospitals in nine countries, we enrolled 3493 infants receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years.

RESULTS
There was no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or nonmajor disability or of adverse events.

CONCLUSIONS
Therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis. (Funded by the United Kingdom Medical Research Council and others; INIS Current Controlled Trials number, ISRCTN94984750.)
Intravenous immunoglobulin for suspected or proven infection in neonates (Review)

Ohlsson A, Lacy JB

Figure I. Forest plot of comparison: IVIG versus placebo or no intervention for suspected infection, outcome: I.1 Mortality from any cause.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed 2006</td>
<td>4</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>4.5%</td>
<td>0.40 [0.14, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Christensen 1991</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erdem 1993</td>
<td>6</td>
<td>20</td>
<td>9</td>
<td>24</td>
<td>3.6%</td>
<td>0.80 [0.34, 1.86]</td>
<td></td>
</tr>
<tr>
<td>Hacue 1988</td>
<td>1</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>2.7%</td>
<td>0.17 [0.02, 1.30]</td>
<td></td>
</tr>
<tr>
<td>INIS 2011</td>
<td>185</td>
<td>1030</td>
<td>176</td>
<td>1017</td>
<td>79.0%</td>
<td>1.04 [0.86, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Samantha 1997</td>
<td>5</td>
<td>30</td>
<td>8</td>
<td>30</td>
<td>3.6%</td>
<td>0.63 [0.23, 1.89]</td>
<td></td>
</tr>
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<td>4</td>
<td>41</td>
<td>8</td>
<td>41</td>
<td>3.6%</td>
<td>0.50 [0.16, 1.53]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>1217</td>
<td>1208</td>
<td>100.0%</td>
<td></td>
<td>0.94 [0.80, 1.12]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 212 224

Heterogeneity: Chi² = 8.39, df = 6 (P = 0.21); I² = 28%

Test for overall effect: Z = 0.69 (P = 0.49)

Citation: Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub4.
Immunoglobulins and sepsis

Intravenous immunoglobulin for suspected or proven infection in neonates (Review)
UPDATE 2013 The Cochrane Collaboration.

Authors’ conclusions
In previous reviews, we encouraged researchers to undertake well-designed trials to confirm or refute the effectiveness of IVIG in reducing adverse outcomes in neonates with suspected infection. Such a trial has been undertaken. Results of the INIS trial, which enrolled 3493 infants, carry a heavy weight in the current update of this review, and the undisputed results show no reduction in death or major disability at 2 years of age.

Routine administration of IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended
Immunoglobulins for neonatal sepsis: has the final word been said?
A word of concern about the INIS study

Is the primary outcome where it should be?

- Average day at randomization = 8
- Average day at discharge = 64
- Investigate death or sequelae = day 810

Exogenous IgG persist in the bloodstream for 2 weeks

Suspected or proven sepsis

**A few questions about the INIS study**

Percentage of patients who had 2 or more sepsis episodes:

- 28% sIVIG group
- 29.9% Placebo group

- How many times were they allowed to use sIVIG?

  *Just once* ......
More concerns about the INIS study

• How soon after the diagnosis were the sIVIG infused? *(Unable to find the information)*

• Why different preparations of IgG in different locations?

• Enrolment to complete data acquisition approx **11 years**
Has “anything” changed during the study period?

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2011</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>11.5%</td>
<td>10 %</td>
<td>-8.4</td>
</tr>
<tr>
<td>Death or morbidity</td>
<td>54 %</td>
<td>44.9 %</td>
<td>-9.1</td>
</tr>
<tr>
<td>Any late infection</td>
<td>22.3 %</td>
<td>13.9 %</td>
<td>-8.4</td>
</tr>
</tbody>
</table>
More questions about the INIS study....

Preparations of standard IgG were used in INIS.

LETTER

Passive immunotherapy of sepsis with intravenous immune globulin: not all IVIg preparations are created equal

Tchavdar Vassilev* and Michael Bauer

Compared to sIVIG, **IgM enriched** IVIG have:
- better binding to bacterial antigens and toxins
- more efficient complement activation
- better opsonization

Norby-Teglund et al Clin Infect Dis 2000; 31: 1175
Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis

A recent prospective study showed that the combined presence of low levels of IgG1, IgM and IgA in plasma is associated with reduced survival in adult patients with severe sepsis or septic shock (OR 5.27, 95% CI 1.41-19.69; \( P = 0.013 \))

IgM - IVIG
The state of the art in 2013

Figure 5. Forest plot of comparison: 4 IgM-enriched IVIG for suspected infection at trial entry, outcome: 4.1 Mortality from any cause during initial hospitalisation.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IgM enriched IVIG</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M.H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdem 1993</td>
<td>6  20</td>
<td>9  24</td>
<td>36.9%</td>
<td>0.80 [0.34, 1.86]</td>
</tr>
<tr>
<td>Haque 1988</td>
<td>1  30</td>
<td>6  30</td>
<td>27.0%</td>
<td>0.17 [0.02, 1.30]</td>
</tr>
<tr>
<td>Samuel 1997</td>
<td>5  30</td>
<td>8  30</td>
<td>36.1%</td>
<td>0.63 [0.23, 1.69]</td>
</tr>
</tbody>
</table>

Total (95% CI) 80 84 100.0% 0.57 [0.31, 1.04]

Total events 12 23

Heterogeneity: Chi² = 2.04, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 1.83 (P = 0.07)

Citation: Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub4.
Are IgM-enriched immunoglobulins an effective adjuvant in septic VLBW infants?

Letizia Capasso¹*, Angela Carla Borrelli¹, Claudia Parrella¹, Silvia Lama¹, Teresa Ferrara¹, Clara Coppola¹, Maria Rosaria Catania², Vita Dora Iula² and Francesco Raimondi¹

Abstract

**Aim:** To investigate the effectiveness of IgM-enriched immunoglobulins (IgM-eIVIG) in reducing short-term mortality of neonates with proven late-onset sepsis.

**Methods:** All VLBW infants from January 2008 to December 2012 with positive blood culture beyond 72 hours of life were enrolled in a retrospective cohort study. Newborns born after June 2010 were treated with IgM-eIVIG, 250 mg/kg/day iv for three days in addition to standard antibiotic regimen and compared to an historical cohort

- Monocentric, retrospective study
- Culture proven, late-onset sepsis in VLBW babies
The Pyramid of Evidence Based Medicine

- Systematic Reviews
- Randomized Control Trials
- Cohort Studies
- Case-Control Studies
- Case Series, Case Reports
- Editorials, Expert Opinions

The bottom – up approach
Are IgM-enriched immunoglobulins an effective adjuvant in septic VLBW infants?

Letizia Capasso¹*, Angela Carla Borrelli¹, Claudia Parrella¹, Silvia Lama¹, Teresa Ferrara¹, Clara Coppola¹, Maria Rosaria Catania², Vita Dora Iula² and Francesco Raimondi¹

<table>
<thead>
<tr>
<th>Table 1 Main characteristics of the whole study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM-eIVIG</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
</tr>
<tr>
<td>Snap II score</td>
</tr>
<tr>
<td>Cesarean section</td>
</tr>
<tr>
<td>Prenatal steroids</td>
</tr>
<tr>
<td>CRP positive</td>
</tr>
</tbody>
</table>
Cases:
Antibiotics
+ IgM-IVIG*

Controls:
Antibiotics

*IgM – IVIG 250 mg /kg/ day i.v for 3 days started together with antibiotics as soon as sepsis was suspected (within 24 h)
HOW QUICK you are to respond

*Time is a critical matter!*

Relationship between the timing of administration of IgM and IgA enriched immunoglobulins in patients with severe sepsis and septic shock and the outcome: A retrospective analysis


Abstract

**Purpose:** Because the use of IgM and IgA enriched polyclonal intravenous immunoglobulins (elg) is a standard of care in critically ill patients admitted to our intensive care unit (ICU) with the diagnosis of severe sepsis or septic shock, we investigated if the delay from the onset of severe sepsis and septic shock and their administration could influence the outcome.

**Materials and Methods:** The medical records of all patients with severe sepsis or septic shock admitted to our ICU from July 2004 through October 2009 and treated with elg (Pentaglobin®; Biotest, Dreieich, Germany) were retrospectively examined.

**Results:** A total of 129 adult patients with severe sepsis or septic shock were considered eligible. Thirty-two percent of patients died during the ICU stay. Survivors were given elg significantly earlier than nonsurvivors (23 vs 63 hours, $P < .05$). The delay in the administration of elg and the Simplified Acute Physiology Score II were the only variables that entered stepwise a propensity score-adjusted logistic model. The delay in the administration of elg was a significant predictor of the odds of dying during the ICU stay (odds ratio for 1 hour of delay, 1.007; $P < .01$; 99% confidence interval from 1.001 to 1.010) and proved to be independent from the Simplified Acute Physiology Score II and other variables.
• **Primary outcome:** mortality within 7 or 21 days from treatment (short term mortality)

• **Secondary outcome:** mortality at discharge (total mortality); IVH; PVL; NEC; BPD

<table>
<thead>
<tr>
<th>Table 2 Primary and secondary outcomes of the whole study population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgM-eIVIG</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Short term mortality</td>
</tr>
<tr>
<td>Total mortality</td>
</tr>
<tr>
<td>IVH</td>
</tr>
<tr>
<td>PVL</td>
</tr>
<tr>
<td>NEC</td>
</tr>
<tr>
<td>BPD</td>
</tr>
</tbody>
</table>

*p < 0.05 (IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia).
Figure 1 Main pathogens isolated from blood cultures.
## Patients with Blood Culture Positive for Candida spp

<table>
<thead>
<tr>
<th></th>
<th>TREATED n=10</th>
<th>UNTREATED n=15</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td>28±3</td>
<td>28±3,9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Birth Weight (grams)</strong></td>
<td>1065±270</td>
<td>940±396</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Snap II Score</strong></td>
<td>12±10</td>
<td>11±6,2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Short term mortality</strong></td>
<td>1 (10%)</td>
<td>8 (53%)</td>
<td>0,04*</td>
</tr>
</tbody>
</table>

*OR: 0.1; IC 95° 0.01-0.97

Innate immunity is principal defense against Candida spp

Opsonization enhances killing of Candida by neutrophils and monocytes

Ab against Candida’s mannan antigen causes activation of complement
Are IgM-enriched immunoglobulins an effective adjuvant in septic VLBW infants?

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Conclusion

This hypothesis-generator study shows that IgM-eIVIG is an effective adjuvant therapy in VLBW infants with proven sepsis reducing short term mortality.

We believe that this analysis fulfilled its original purpose to set the ground for larger, randomized prospective trials. Given the considerable burden of morbidity and mortality imposed by neonatal sepsis, new research should urgently be addressed not only to validate our results but also to tailor the optimal scheme of treatment.
Summary

• Neonates especially preterm may represent a target population for IVIG supplementation to fight neonatal sepsis

• prophylactic IVIG in preterm doesn't affect mortality and principal outcomes

• INIS study tested standard IgG and demonstrated no efficacy in reducing death or morbidity at 2 years of age

• IgM - IVIG have higher antimicrobial activity than standard IgG

• IgM-IVIG showed reduction in short term mortality for VLBW infants with culture proven sepsis by G+, G- and Candida spp.
Conclusions

We do NOT think that the final word has been said, yet..

A large multicenter study is warranted to test:

- a clinically plausible primary endpoint

- one IVIg preparation with the best biological background like IgM enriched Ig
Grazie

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raimondi@unina.it

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Napoli