Sepsis in the ICU: IVIG-therapy

Anna Norrby-Teglund
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Intravenous Polyspecific Immunoglobulin (IVIG)

- IgG from pooled plasma from >10,000 healthy blood donors
- Used in several acute inflammatory & autoimmune disorders

Mechanistic actions in infections:

- **Bacterial opsonization**
- **Toxin neutralization**
- **Immunoregulation**

**No IVIG**

**IVIG**

**SAg**

**SAg + IVIG**

- FcR-interactions
  - Expression of FcγRIIB
  - Pro-inflammatory cytokines
  - Anti-inflammatory cytokines
  - Anti-cytokine autoantibodies
  - Soluble immune components
Alejandria et al 2013 Cochrane review on IVIG in bacterial sepsis or septic shock

All RCT (IVIG vs placebo) in sepsis, severe sepsis, septic shock: 43 studies out of 88 potentially eligible

Subgroup analysis of polyclonal IVIG in adults: significant reduction in mortality

In total: 17 trials, n = 1958  RR 0.77; 95% CI 0.68 - 0.87
Standard IVIG: 10 trials, n= 1430  RR 0.81; 95% CI 0.70 - 0.93
IgM-enriched: 7 trials,  n = 528   RR 0.66; 95% CI 0.51 - 0.85

When studies with high risk of bias were excluded only 5 trials remained and significance was lost. *The totality of the evidence is still insufficient to support a robust conclusion of benefit.*

Need for more studies in targeted patient groups
IVIG-therapy in Streptococcal Toxic Shock Syndrome (STSS)

IVIG therapy in superantigen-mediated STSS:
- Observational cohort study (Kaul R, et al. 1999 Clin Inf Dis)
- Multicenter placebo-controlled trial (Darenberg J, et al. 2003 CID)
- Observational study (Linnér et al. Clin Infect Dis 2014)

All prospectively identified cases

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Survival d. 30 Cases</th>
<th>Survival d. 30 Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaul, CID 1999 cases 21; controls 32</td>
<td>67</td>
<td>34</td>
<td>0.02</td>
</tr>
<tr>
<td>Darenberg, 2003 cases 10; controls 11</td>
<td>90</td>
<td>64</td>
<td>0.2</td>
</tr>
<tr>
<td>Linnér, CID 2014 cases 23; 44 controls</td>
<td>87</td>
<td>50</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Clinical Efficacy of Polyspecific Intravenous Immunoglobulin Therapy in Patients With Streptococcal Toxic Shock Syndrome: A Comparative Observational Study

Anna Linnér, Jessica Darenberg, Jan Sjölin, Birgitta Henriques-Normark, and Anna Norrby-Teglund

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simple logistic regression</th>
<th></th>
<th>Multiple logistic regression</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>SAPS</td>
<td>1.05 (1.0-1.1)</td>
<td>0.007</td>
<td>1.1 (1.0-1.1)</td>
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<tr>
<td>Clindamycin</td>
<td>7.5 (2.0-27.3)</td>
<td>0.002</td>
<td>8.6 (1.8-40.4)</td>
</tr>
<tr>
<td>IVIG</td>
<td>6.7 (1.7-25.7)</td>
<td>0.006</td>
<td>5.6 (1.2-26.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4.4 (1.4-13.9)</td>
<td>0.012</td>
<td>-</td>
</tr>
</tbody>
</table>
Inclusion of studies with STSS cases prospectively identified using the consensus criteria, and with available data on clindamycin use.

Primary endpoint: Death at 30 days in the subgroup of patients with STSS who received clindamycin.

Mortality 33.7% vs 15.7%  
RR 0.46; CI 0.26–0.83; P = 0.01
IVIG-therapy in Sepsis: Yes or No?

IVIG in sepsis: Still insufficient evidence and many questions to resolve:
- IVIG versus IgM-enriched
- Dosage
- Timing
- Targeted patient groups: microbial aetiology, host immune status

IVIG in STSS: Yes - sufficient evidence to recommend use

- Low evidence level
- Lack of large RCT

Strong observational data based on prospectively identified cases

Strong mechanistic data
INSTINCT: RCT of IVIG in Necrotizing Soft Tissue Infections (NSTI)

Trial conducted at Copenhagen University Hospital, Rigshospitalet

**Study drugs:** 25 g IVIG/day for 3 days
Placebo (0.9% Saline)

**Inclusion criteria:**
Confirmed NSTI admitted to ICU. All infectious causes.

**Exclusion criteria:**
Patients who had received >one dose of IVIG before randomization had NSTI for >48 h
known hypersensitivity to IVIG or hyperprolinemia women who were pregnant or breast-feeding

**I⁰ endpoint:**
Physical component summary (SF36)
INSTINCT study: 1º endpoint

<table>
<thead>
<tr>
<th>Microbe</th>
<th>IVIG</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. A Strep</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>8%</td>
<td>19%</td>
</tr>
</tbody>
</table>
Alejandria et al 2013 Cochrane review on IVIG in bacterial sepsis or septic shock

Neonatal sepsis:
Standard polyclonal IVIG does not reduce mortality.

Adult sepsis:
Polyclonal IVIG reduced mortality, but this benefit was not seen in trials with low risk of bias.

IgM enriched IVIG:
The totality of the evidence is still insufficient to support a robust conclusion of benefit. The reduction in deaths observed with polyclonal IgM-enriched preparations as add-on therapy for sepsis needs to be confirmed in large studies that use high quality methods.

Factors accounted for: age, bias, poly- or monoclonal. Sufficient?
INSTINCT study: 2º endpoint

![Graph showing survival rates for IVIG group and Placebo group over days since randomisation. The graph includes a Log-rank test p-value of 0.53. Numbers at risk: IVIG group: 50 at 42 and 38 days, Placebo group: 50 at 40 and 36 days.]

Madsen et al Int Care Med 2017
Intravenous Immunoglobulin and Mortality in Pneumonia Patients With Septic Shock: An Observational Nationwide Study

Takashi Tagami,1,2 Hiroki Matsui,1 Kiyohide Fushimi,3 and Hideo Yasunaga1

8734 Eligible mechanically ventilated pneumonia patients with septic shock

470 Excluded
258–IVIG received more than 5g/day for 3 days
212–started receiving IVIG on Day 6 or later

No difference in 28 days mortality: 36.7% vs 36.0% in IVIG vs controls

Dose: 5g/day for 3 days

1045 Propensity-matched IVIG group
1045 Propensity-matched Controlled group
Comparative observational study of IVIG in STSS patients

STSS cases identified in a prospective nation-wide surveillance 2002-04 (Darenberg et al Clin Infect Dis 2007)

746 iGAS patients identified

654 completed questionnaire

Second questionnaire: Clinical Treatment

75 STSS cases

67 STSS cases: 23 IVIG & 44 non-IVIG

8 excluded: incomplete data or not fulfilling STSS criteria

IVIG cases: 0.5 g/kg 65% >1 dose

Linnér et al Clin Infect Dis 2014
129 patients were screened for eligibility

29 were excluded
- 17 did not have NSTI
- 5 were not admitted to the ICU
- 4 had active treatment withdrawn on admission
- 2 had received >1 dose of IVIG
- 1 was diagnosed >48 h before screening
- 1 due to lack of research capacity
- 1 had previous allergic reaction to IVIG

100 patients randomised

50 assigned to the IVIG group
- 4 discontinued the trial protocol
  - 1 discontinued on the request of surrogates
  - 3 discontinued due to a SAR
- In 8 patients SF-36 scores were not obtained
- 42 (84%) included in the analysis of the primary outcome
- 50 (100%) included in the analyses of the secondary outcomes

50 assigned to the placebo group
- 7 discontinued the trial protocol
  - 3 discontinued on the request of surrogates
  - 4 discontinued due to a SAR
- In 5 patients SF-36 scores were not obtained
- 45 (90%) included in the analysis of the primary outcome
- 50 (100%) included in the analyses of the secondary outcomes
IVIG in children


- Multicenter, retrospective cohort study of children with STSS

Inclusion criteria:

ICD-9 codes for TSS + ICD-9 for Streptococcus or a billing charge for iv penicillin

192 patients: IVIG group, n=84: mortality 4.5%
Non-IVIG group, n=108: mortality 4.5%

The question of IVIG in children with STSS remains unresolved as

- Underpowered
- The definition criteria of STSS were not used
  (low mortality; 21% not admitted to ICU)
- The IVIG group had significantly higher:
  ICU admission (86% versus 74%)
  #arterial blood gas measurements (6 versus 1)
  corticosteroid receipt (54% versus 30%)
  vasoactive infusion (82% versus 54)
  etc.
Acknowledgement

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Don E Low
Allison McGeer
Rupert Kaul
Improvement in organ function post-IVIG

SOFA score pre-treatment

Changes in SOFA score during treatment

IVIG Placebo

Before treatment

Treatment days

p=NS  p=0.019  p=0.043

Promising but low evidence level. Need more studies!

Darenberg et al 2003 Clin Infect Dis
Carapetis et al Clin Infect Dis 2014

Effectiveness of Clindamycin and Intravenous Immunoglobulin, and Risk of Disease in Contacts, in Invasive Group A Streptococcal Infections

Active surveillance of invasive group A streptococcal infections 2002-2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinda, n=53</th>
<th>Non-Clinda, n=31</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 (4-88)</td>
<td>70 (3-96)</td>
<td>.0088</td>
</tr>
<tr>
<td>STSS</td>
<td>37/53 (70)</td>
<td>12/31 (39)</td>
<td>.005</td>
</tr>
<tr>
<td>NF</td>
<td>28/51 (55%)</td>
<td>1/28 (4%)</td>
<td>.0001</td>
</tr>
<tr>
<td>IVIG</td>
<td>14/52</td>
<td>0/31</td>
<td>.001</td>
</tr>
<tr>
<td>Mortality d30</td>
<td>8/53 (15%)</td>
<td>12/31 (39)</td>
<td>.014</td>
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