Modulating the host response in septic shock: Apheresis and IVIG

Canadian Critical Care Forum, 2019
November 12, 2019

Ryan Zarychanski MD MSc FRCPC
Divisions of Critical Care & Hematology/Medical Oncology
Manitoba, Canada
Disclosures

None
Objectives

1. Discuss the rationale for the use of IVIG and apheresis in septic shock
2. Outline the evidence to support the use of IVIG and apheresis in sepsis
3. Present progress on research programs related to IVIG and apheresis in critically ill patients with septic shock
Background

- Sepsis accounts for 15% of ICU admissions
- 2\textsuperscript{nd} most frequent cause of death in ICU
- Mortality 25-45%
- Global impact
- Incidence increasing

Angus et al. 2001; Brun-Buisson et al. 2008
Background

• Current Evidence-Based Therapies
  - Antimicrobials
  - Source-control
  - Supportive Care

• Novel Therapeutics under investigation
  - Heparin
  - Cellular immunotherapy
  - Optimal fluid strategies
  - Vitamin C
  - Intravenous Immune Globulin
  - Apheresis / Plasma exchange
Intravenous immunoglobulin (IVIG)
IVIG: Potential mechanisms of action in sepsis

- Microbial toxin neutralization
- Complement mediation
- Fc-mediated immune modulation
- Cytokine neutralization
- Suppression of pro-inflammatory monocytes
- T cell regulation
IVIG in necrotizing soft tissue infections
(mainly toxin producing staph and strep)

• ‘Routine’ in many parts of the world despite the absence of high quality data
  – Retrospective studies and case reports
  – Only RCT was stopped prematurely (n=14 patients)
Effectiveness of Clindamycin and Intravenous Immunoglobulin, and Risk of Disease in Contacts, in Invasive Group A Streptococcal Infections

Jonathan R. Carapetis, Peter Jacoby, Kylie Carville, Seong-Jin Joel Ang, Nigel Curtis, and Ross Andrews

• Observational cohort study from 2002-2004
• Baseline imbalances; single geographic region in Australia
• Addition of clindamycin and IVIG associated with best survival
Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial

Martin B. Madsen¹, Peter B. Hjortrup¹, Marco B. Hansen², Theis Lange³, Anna Norrby-Teglund⁵, Ole Hyldegaard² and Anders Perner¹*

• 100 patients randomized to 25 g IVIG daily x 3 days or placebo
• All required surgical exploration and ICU admission
• No difference in physical function at 180 days
• No difference in mortality

Perner A et al. ICM. 2017
What about IVIG in undifferentiated sepsis?
IVIG in sepsis: Evidence from published trials

Meta-analysis: Intravenous Immunoglobulin in Critically Ill Adult Patients with Sepsis
Alexis F. Turgeon, MD, MSc; Brian Hutton, MSc; Dean A. Fergusson, MHA, PhD; Lauralyn McIntyre, MD, MSc; Alan A. Tinmouth, MD, MSc; D. William Cameron, MD; and Paul C. Hébert, MD, MSc

Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock (Review)
Alejandria MM, Lansang MAD, Dans LF, Mantaring III JB
• 20 RCTs (n=2,671 patients)
• IVIG associated with lower risk of death
  – **RR 0.74**, 95% CI 0.62 to 0.89, p=0.001
• Dose of ≥1 g/kg and a duration of therapy longer than 2 days were associated with increased survival benefit
Evaluation of the Effect of Intravenous Immunoglobulin Dosing on Mortality in Patients with Sepsis: A Network Meta-analysis

Yi Yang, Master¹,*; Xian Yu, PhD¹,*; Fan Zhang, PhD²; and Yifan Xia, MD³

- 13 RCTs (n=1,041 patients)
- Results were similar to the meta-analysis of Turgeon (2007)
  - RR 0.61, 95%CI 0.41 to 0.92, p=0.02

Yang Y, Clinical therapeutics. 2019 in press
IgM enriched IgG (IVIgGM)

• More closely resembles plasma Ig
• Enhanced LPS opsonizing ability
• Increased ability to neutralize streptococcal superantigen

• Uncertain if net clinical benefits of IVIgGM are superior to IVIgG
The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis

Jie Cui, Xuxia Wei, Haijin Lv, Yuntao Li, Ping Li, Zhen Chen and Genglong Liu

• 19 included studies (15 RCTs; 4 observational studies)
• n=1,530 patients
• IVIgGM reduced mortality risk in septic patients
  – RR 0.60; 95%CI 0.52 to 0.69,
What do the guidelines say about IVIG in sepsis?

**Surviving Sepsis Campaign:** International Guidelines for Management of Sepsis and Septic Shock: 2016

• Does **not** recommend the use of IVIG for the treatment of septic shock

(*weak recommendation based on low evidence quality*)
Knowledge gaps – What we don’t know

• Current practice/utilization patterns
• Barriers to clinical use
• Contemporary estimates of efficacy at relevant time points
  – (e.g. 60 or 90 day mortality)
• Safety
• Cost-effectiveness
InVIGIS

IntraVenous Immune Globulin In Septic Shock

- National Survey
  - Utility
  - Barriers/facilitators
  - Willingness to study

- Utilization
  - Determinants

- Modeled Economic Evaluation
  - Cost-utility

- Population Cohort
  - Long-term sepsis-mortality
  - Health-care utilization

- Integrated Economic Evaluation

- Pilot RCT

- Phase 3 International Multicentre RCT
National Survey

1. Establish reported utilization patterns of IVIG in septic shock

2. Identify facilitators/barriers to use of IVIG in septic shock

3. Understand what has limited uptake of previous research of IVIG in septic shock

4. Determine willingness of colleagues to participate in a future clinical trial
Study design and sample frame

**Survey Design**
Multi-modal, self-administered cross sectional survey

**Sample Frame**
Academic Critical Care & Infectious Disease specialist physicians in Canada
Response rate: 55% (364/661)

 podróżents

Infectious Diseases
34%
n = 123

Critical Care
66%
N = 241
BASE SPECIALTY

Internal Medicine 70%

Anesthesiology 11%

Emergency Medicine 5%

Surgery 9%

Other 5%
PREVIOUS USE OF IVIG IN SEPTIC SHOCK (ANY ETIOLOGY)

Yes
91%
n = 333

No
9%
N = 31
IVIG Utilization, by Etiology of Septic Shock

- **Necrotizing fasciitis**: 86%
- **Bacterial, toxin-mediated septic shock**: 52%
- **Undifferentiated septic shock**: 5%

<table>
<thead>
<tr>
<th>Indication for IVIG</th>
<th>Undifferentiated septic shock</th>
<th>Bacterial, toxin-mediated septic shock</th>
<th>Necrotizing fasciitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>189</td>
<td>312</td>
<td></td>
</tr>
</tbody>
</table>
Barriers to the use of IVIG

- Insufficient evidence: 91%
- Cost: 61%
- Supply: 28%
- Risk of toxicity or adverse reaction: 23%
- Consultation with other services: 17%
- Lack of familiarity with IVIG by other team members: 15%
- Informed consent for blood products: 12%
- Paperwork: 12%
- Delays from ordering to administration: 10%

<table>
<thead>
<tr>
<th>Delays from ordering to administration</th>
<th>Paperwork</th>
<th>Informed consent for blood products</th>
<th>Lack of familiarity with IVIG by other team members</th>
<th>Consultation with other services</th>
<th>Risk of toxicity or adverse reaction</th>
<th>Supply</th>
<th>Cost</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barriers</td>
<td>36</td>
<td>42</td>
<td>43</td>
<td>55</td>
<td>60</td>
<td>85</td>
<td>103</td>
<td>222</td>
</tr>
</tbody>
</table>
IVIG definitely reduces mortality

IVIG may reduce mortality

Uncertain whether IVIG reduces mortality

IVIG may not reduce mortality

IVIG definitely does not reduce mortality
Are future trials of IVIG in septic shock warranted?
Patient Population of Interest for a Clinical Trial of IVIG in Septic Shock

<table>
<thead>
<tr>
<th>Indication for IVIG</th>
<th>Undifferentiated septic shock</th>
<th>Bacterial, toxin-mediated septic shock</th>
<th>Necrotizing fasciitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>197</td>
<td>274</td>
<td>264</td>
</tr>
</tbody>
</table>

- Necrotizing fasciitis: 73%
- Bacterial, toxin-mediated septic shock: 75%
- Undifferentiated septic shock: 54%
Retrospective Cohort study of IVIG use

Objective:
1. To describe the clinical utilization patterns of IVIG

2. To characterize the patient populations receiving IVIG

3. To identify determinants of IVIG use
Cohort with septic shock

• 270,084 patients with septic shock
  
  – Data from the Premier Perspectives database (2008-2013)
  
  – IVIG: 685 (0.3%)
  – No IVIG: 267,818
  
  – Median dose : 1 g/kg (IQR 0.5-1.8 g/kg) over 1 day
Cohort with septic shock

- Patients who received IVIG were more likely to:
  - Be Caucasian
  - Have private health insurance
  - Be diagnosed with necrotizing fasciitis or toxic shock syndrome
  - Have more organ dysfunction at baseline
  - Be immunocompromised
InVIGIS

IntraVenous Immune Globulin In Septic Shock

National Survey
- Utility
- Barriers/facilitators
- Willingness to study

Utilization
- Determinants

Cohort Study
- Mortality

Modeled Economic Evaluation
- Cost-utility

Population Cohort
- Long-term sepsis-mortality
- Health-care utilization

Integrated Economic Evaluation

Pilot RCT

Phase 3 International Multicentre RCT
Apheresis / Therapeutic Plasma Exchange (TPE)

Separation of blood components

Removal of the desired product

Returning the remainder back to the patient
Indications for apheresis/TPE in critical care

ASFA Category I indications

• TTP (thrombotic thrombocytopenic purpura) (1A)
• Sickle Cell Disease – Acute Stroke (1C)
• Myasthenia Gravis (1B)
• Guillian Barré (1A)
• Alveolar hemorrhage [ANCA or anti-GBM] (1C)
• Babesiosis (1C)
Indications for apheresis/TPE in critical care

ASFA Category II indications

• Sickle Cell Disease - Chest crises (2A)
• Catastrophic antiphospholipid antibody syndrome (2C)
• Acute disseminated encephalomyelitis (2C)
Indications for apheresis/TPE in critical care

ASFA Category III considerations

• Sepsis
• Drug overdose
• Fulminant Wilson’s disease
Biologic rationale

- Removal of harmful bacterial toxins
- Removal of inflammatory cytokines
- Removal of activated coagulation factors
- Replacement of deficient blood components – natural anticoagulants, ADAMTS13
- Restoration of homeostasis
Apheresis/TPE in sepsis?

• **Animal models of sepsis and septic shock** (Natanson C. *Transfusion*. 1993)
  • No clear survival benefit of plasmapheresis
  • Possible increase in mortality?

• **Observational data**
  • Results range widely:
    • 25% decrease in mortality (Gardlund B. *Scand J Infect Dis* 1993)
    • 4-fold increase survival (Stegmayr BG. *Blood Purif* 1996)
    • 4-5% increase in survival (Schmidt J. *Intensive Care Med* 2000)
  • Limited by small sample size and lack of comparator
Apheresis/TPE in sepsis?

The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis

Emily Rimmer\textsuperscript{1,2}, Brett L Houston\textsuperscript{3}, Anand Kumar\textsuperscript{1}, Ahmed M Abou-Setta\textsuperscript{4}, Carol Friesen\textsuperscript{5}, John C Marshall\textsuperscript{6}, Gail Rock\textsuperscript{7}, Alexis F Turgeon\textsuperscript{8}, Deborah J Cook\textsuperscript{9,10}, Donald S Houston\textsuperscript{1,2} and Ryan Zarychanski\textsuperscript{1,2,4*}
Apheresis/TPE in sepsis?

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Plasmapheresis Events Total</th>
<th>Usual Care Events Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.3.1 Children only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>0</td>
<td>5</td>
<td>4.6%</td>
<td>0.11 [0.01, 1.64]</td>
</tr>
<tr>
<td>Reeves 1999 children only</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>3.90 [0.31, 2.63]</td>
</tr>
<tr>
<td>Long 2013</td>
<td>10</td>
<td>25</td>
<td>3</td>
<td>2.60 [0.84, 6.33]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>13</td>
<td>35</td>
<td>44.2%</td>
<td>0.96 [0.28, 3.38]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>13</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.69; Chi² = 4.95, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 0.06 (P = 0.95)

| **1.3.2 Adults**           |                            |                         |        |                              |
| Busund 2002                | 18                         | 54                      | 28     | 52 37.1%                      |
| Reeves 1999 adult only    | 3                          | 9                       | 6      | 13 18.7%                      |
| **Subtotal (95% CI)**      | 63                         | 65                      | 55.8%  | 0.63 [0.42, 0.96]            |
| **Total events**           | 21                         | 34                      |        |                              |

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Total (95% CI) 98 96 100.0% 0.83 [0.45, 1.52]
Total events 34 44
Heterogeneity: Tau² = 0.21; Chi² = 7.45, df = 4 (P = 0.11); I² = 46%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%
Apheresis/TPE in sepsis?

• Data are weak, at risk of bias, and substantially unclear

• No recommendation can be made at this time:
  • Small numbers
  • Uncertain standards of care among the included studies
  • Widely desperate methods and ‘doses’ of plasma exchange
  • Lack of safety data
TAMOF (Thrombocytopenia associated multiorgan failure)

• ~30% of septic shock
• 90% have evidence of VWF-mediated micro-thrombosis
• Mean ADAMTS13 levels are reduced (40% activity)
• Increased ULWVF observed in 50% of cases

• Hypothesis: TPE may especially improve outcomes in TAMOF by reducing micro-thrombosis

Nguyen TC. Crit Care Clin. 2015
New studies since our systematic review?

Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers

Hannah Knaup¹,†, Klaus Stahl²†, Bernhard M. W. Schmidt¹, Temitayo O. Idowu¹, Markus Busch², Olaf Wiesner³, Tobias Welte³, Hermann Haller¹, Jan T. Kielstein⁴, Marius M. Hoepfer³ and Sascha David¹*
Early TPE in septic shock...

• Non randomized, single center, open-label pilot study
• 20 patients with early septic shock requiring high doses of norepinephrine (NE; > 0.4 μg/kg/min)
• ONE plasma exchange volume
• Exchanged with frozen plasma

• Primary Outcome: Safety and feasibility

Pilot clinical trial of plasma exchange in sepsis/DIC

<table>
<thead>
<tr>
<th>N = 20 patients</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>35%</td>
</tr>
<tr>
<td>APACHE II</td>
<td>41</td>
</tr>
<tr>
<td>ADAMTS 13 (%)</td>
<td>44%</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>95%</td>
</tr>
<tr>
<td>Organ failures</td>
<td>LOTS</td>
</tr>
</tbody>
</table>

Changes in vasopressor requirements

Early TPE in septic shock...

- No change in humoral markers of inflammation
- Reductions in all cytokines measures
- Reductions in vascular permeability factors

- Plan of the investigative team is to conducted a randomized trial
What about Hemofiltration?

• Polymyxin B endotoxin absorption – no difference in mortality
  – Euphrates Trial. JAMA 2018

• Cytokine absorption – Early days. Clinical trials are needed
  – Cytosorb™
  – oXiris™ (endotoxin/cytokines/dialysis)
PLEXIS pilot study
Plasma exchange in sepsis shock
PLEXIS: pilot RCT of TPE in septic shock

Trial inclusion criteria and intervention details
• 72 patients with septic shock + 1 other organ failure
• 1 volume TPE for up to 5 days; FFP as replacement fluid

• Primary outcome measure: Feasibility
• Secondary outcomes:
  Mortality
  Change in organ function
  Duration of vasopressors
PLEXIS Inclusion

1. ≥ 18 years of age

2. Refractory hypotension (within the previous 36 hours)
   - SBP < 90 mm Hg OR
   - SBP decrease > 30 mmHg below baseline OR
   - MAP < 65 mm Hg
   **AND**
   - Received adequate fluid resuscitation
PLEXIS Inclusion

3. ONE OTHER ORGAN DYSFUNCTION:
   a) **Creatinine** \( \geq 1.5 \times \) the known baseline creatinine, or \( \geq 26.5 \mu\text{mol/L} \) (0.3 mg/dL) increase within 48 hours (without ESRD) or <0.5 mL/kg of urine output for 6-12 hours according to the KDIGO definition of AKI
   b) Need for invasive **ventilation** or a P/F ratio <250
   c) **Platelets** \( < 100 \times 10^9/\text{L} \) [<1.0 lakhs \((10^5)/\mu\text{L}\)], or a drop of 50 \( \times 10^9/\text{L} \) [0.5 lakhs \((10^5)/\mu\text{L}\)] in the 3 days prior to enrollment
   d) Arterial pH < 7.30 or base deficit > 5 mmol/L in association with a **lactate** \( \geq 4.0 \text{ mmol/L} \)
Conclusions: IVIG and apheresis in sepsis

• Sepsis and septic shock represent a significant burden of illness

• IVIG and plasma exchange may be important adjunctive modalities that may improve outcomes in sepsis

• Prior to adoption as routine care, adequately powered randomized trials are required to confirm efficacy, safety, and cost-effectiveness
InVIGIS team

**Adult**
Ryan Zarychanski
Murdoch Leeies
Alexis Turgeon
Sylvain Lother
Hayley Gershengorn
Emmanuel Charbonney
Allan Garland
Dean Fergusson

**Pediatric**
John Embil
Bojan Paunovic
John Marshall
Rob Fowler
Bill Cameron
Juthaporn Cowan
Srinivas Murthy
Eric Jacobsohn

Marisa Tucci
Jacques Lacroix
PLEXIS team

Ryan Zarychanski
Emily Rimmer
Gail Rock
Donald Houston
Alexis Turgeon
Allan Garland
Alison Fox-Robichaud

John Marshall
John Wilkins
Brett Houston
Bojan Paunovic
Eric Jacobsohn
Donnie Arnold
Ted Warkentin
Thank you

Ryan Zarychanski MD MSc FRCPC
rzarychanski@cancercare.mb.ca