Immune function and immunomodulation in sepsis: Finding shelter from the storm

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Disclosures

• I have no conflict of interest to disclose.
• I will be discussing the off-label use of immunomodulators including anakinra and GM-CSF.
Objectives

• Review the immunobiology of the inflammatory response in sepsis.
• Identify potential opportunities for the use of specific immunomodulators to reduce the pro-inflammatory response.
• Identify a strategy for targeted stimulation of immune function in sepsis.
• Identify some unintentional modulators of immune function in sepsis.
The Cast of Characters – Innate immunity

- Includes PMNs, monocytes, macrophages, dendritic cells, NK cells
- First line of cellular defense
- Recognize broad classes of pathogens/molecules via cell-surface receptors (e.g. TLRs, FcR)
- Phagocytosis, intracellular killing, antigen presentation, cytokine production
The Cast of Characters – Adaptive immunity

- Include T and B lymphocytes
- Typically require antigen presentation
- Perpetuate and modulate the immune response
- Response is highly antigen-specific, memory
- Cytokines and chemokines (helper T cells), cellular killing (cytotoxic T cells), Antibody (B cells)
Pro-inflammatory

- TNFα
- IL-1β
- IL-6
- IL-8
- IL-17
- IFNγ
- IL-2

Anti-inflammatory

- IL-10
- TGFβ
- IL-11
- sTNF receptor
- IL-1ra

LPS
PG
MDP
HMGB-1
DNA
We should work to remove these mediators from our critically ill patients, right?

Yeah….but therapies targeting reduction of pro-inflammatory mediators have consistently failed to improve sepsis outcomes...

- Anti-LPS
- IL-1ra
- Anti-TNFα*
- Anti-bradykinin
- Anti-PAF
- Methylprednisolone/dexamethasone
META-ANALYSIS

Anti-TNF-α therapy for patients with sepsis: a systematic meta-analysis

Int J Clin Pract, April 2014,

S. Lv,1,2,* M. Han,2,* R. Yi,3 S. Kwon,4 C. Dai,1 R. Wang1

Trend toward benefit in subjects with plasma IL-6 > 1000 pg/ml.
**Important exceptions – rhIL-1ra**

<table>
<thead>
<tr>
<th>HLH (22)</th>
<th>Sepsis/SIRS/MODS</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular Diagnosis:</strong>&lt;br&gt;Present</td>
<td><strong>Molecular Diagnosis:</strong>&lt;br&gt;Absent</td>
<td><strong>Molecular Diagnosis:</strong>&lt;br&gt;Absent</td>
</tr>
<tr>
<td><strong>Five of the following 8 criteria:</strong>&lt;br&gt;Fever</td>
<td><strong>Fever</strong></td>
<td><strong>Fever</strong>&lt;br&gt;Visceromegaly +/-</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td><strong>Visceromegaly +/-</strong></td>
<td><strong>Visceromegaly +/-</strong></td>
</tr>
<tr>
<td>Cytopenia of 2 of 3 lineage:&lt;br&gt;Hgb &lt;9 g/L; platelets, 100 × 10⁹&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cytopenia of 2 of 3 lineage:&lt;br&gt;Hgb &lt;9 g/L; platelets, 100 × 10⁹; Neutrophils &lt;1 × 10⁹&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Cytopenia of 2 of 3 lineage:&lt;br&gt;Neutrophils &lt;1 × 10⁹ (23–25)</td>
</tr>
<tr>
<td>Hypertryglyceridemia (Fasting triglycerides ≤265 mg/dL) or Hyperfibrinogenemia &lt;1.5 g/L</td>
<td>Hypertryglyceridemia (Fasting triglycerides ≤265 mg/dL) (33–37) or Hyperfibrinogenemia &lt;1.5 g/L (33–37)</td>
<td>Hyperfibrinogenemia &lt;1.5 g/L (23–25)</td>
</tr>
<tr>
<td>Hemophagocytosis in bone marrow, spleen or lymph nodes</td>
<td>Hemophagocytosis in bone marrow, spleen or lymph nodes (38–41)</td>
<td>Hemophagocytosis in bone marrow, spleen or lymph nodes (23–25)</td>
</tr>
<tr>
<td>Ferritin ≥500 µg/L</td>
<td>Ferritin ≥500 µg/L (42–45)</td>
<td>Ferritin ≥500 µg/L (23–25)</td>
</tr>
<tr>
<td>Low or absent NK cell activity (according to local laboratory reference)</td>
<td>Low or absent NK cell activity (according to local laboratory reference) (55, 56, 58, 59)</td>
<td>Low or absent NK cell activity (according to local laboratory reference) (23–25, 57)</td>
</tr>
<tr>
<td>Soluble CD25 (soluble IL-2 receptor) &gt;2400 U/mL</td>
<td>Soluble CD25 (soluble IL-2 receptor) &gt;2400 U/mL (50, 52, 54)</td>
<td>Soluble CD25 (soluble IL-2 receptor) &gt;2400 U/mL (23–25, 49)</td>
</tr>
</tbody>
</table>

*Castillo, PCCM, 2009*
Important exceptions

- Post hoc analysis of a 1997 anakinra trial in septic adults
  - An MAS-like sepsis phenotype may exist…
  - PHENOMS study (Carcillo, PI) is underway (stay tuned!)
  - Anakinra may resurface in sepsis RCTs in selected patients

hepatobiliary dysfunction (HBD) and DIC – surrogate markers for MAS
Important exceptions – anti-IL-6

- Anti-IL-6 therapy – tocilizumab (rhIL-6 receptor blocker)
- Approved for treatment of JIA
- Has been used for the treatment of MAS/HLH, cytokine storm.

Teachey, Blood, 2013
Immunotherapy to reduce the systemic inflammatory response in critical illness will likely need to be:

- Highly specific
- Done in carefully selected subjects
- Short acting or reversible
- Studied……..again
Pro-inflammatory

TNFα
IL-1β
IL-6 (?)
IL-8
IL-17
IFNγ
IL-2

Anti-inflammatory

IL-10
TGFβ
IL-11
sTNF receptor
IL-1ra

LPS
PG
MDP
HMGB-1
DNA
SIRS: ↑ Plasma IL-6, IL-8 levels
- Fever
- Capillary leak
- Organ dysfunction

CARS: ↑ Plasma IL-10 levels
- ↓ Monocyte HLA-DR expression
- ↓ Ex vivo LPS-induced TNFα production capacity
- ↓ Lymphocyte cytokine production capacity
- ↑ Lymphocyte apoptosis

Uncomplicated course
Complicated course

Time

Pro-inflammatory response
Anti-inflammatory response
1. Phagocytosis
2. Intracellular killing
3. Antigen presentation (HLA-DR)
4. Extracellular TNFα production
1. ↓Phagocytosis

2. ↓Intracellular killing

3. ↓Antigen presentation
   (HLA-DR < 30% or < 8,000 mol/cell)

Suppressed monocyte

4. ↓Extracellular TNFα production
   (ex vivo LPS-induced TNFα production capacity)
Immunoparalysis (ex vivo LPS-induced TNFα production capacity < 200 pg/ml) in critically ill children with MODS:

Table 1 Relative risks for development of nosocomial infection and death, analyzed for all subjects and by transplant status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Immunoparalysis</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes/No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>17/24, 10/46</td>
<td>3.3</td>
<td>1.8–6.0a</td>
</tr>
<tr>
<td>Death</td>
<td>12/24, 4/46</td>
<td>5.8</td>
<td>2.1–16b</td>
</tr>
<tr>
<td>Transplant patients only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>9/12, 3/13</td>
<td>3.3</td>
<td>1.1–9.2b</td>
</tr>
<tr>
<td>Death</td>
<td>8/12, 3/13</td>
<td>2.9</td>
<td>1.0–8.4c</td>
</tr>
<tr>
<td>Nontransplant patients only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>8/12, 7/33</td>
<td>3.1</td>
<td>1.5–6.8d</td>
</tr>
<tr>
<td>Death</td>
<td>4/12, 1/33</td>
<td>11</td>
<td>1.4–89e</td>
</tr>
</tbody>
</table>
- Critically ill children who died (n = 8) had lower *ex vivo* LPS-induced TNFα production capacity than did children who survived (n = 44).
76 Critically injured children underwent prospective, longitudinal innate immune function testing.
Does innate immune suppression represent a target for immunomodulation?
Incubation with plasma from patients with immunoparalysis resulted in internalization of HLA-DR molecules in healthy monocytes. The addition of anti-IL10 neutralizing antibody partially resorted monocyte HLA-DR expression.
GM-CSF

- Granulocyte-macrophage colony stimulating factor
  - FDA approved for adults and children in 1991 for the reconstitution of bone marrow after BMT and/or chemo for certain leukemias.
  - Side effect profile very favorable.
  - Known to increase immune cell numbers but also will increase function of existing cells.
  - FDA-approved dose is 250 µg/m²...potentially for weeks
Effect of Granulocyte-Monocyte Colony-Stimulating Factor Therapy on Leukocyte Function and Clearance of Serious Infection in Nonneutropenic Patients

Alan J. Rosenbloom, Peter K. Linden, Adrienne Dorrance, Nicole Penkosky, Mark H. Cohen-Melamed and Michael R. Pinsky

*Chest* 2005; 127: 2139-2150

- Faster resolution of infection in GM-CSF group.

\[ n = 15 \quad n = 18 \]
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression
A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

Christian Meisel1*, Joerg C. Schefold2*, Rene Pschowski2, Tycho Baumann1, Katrin Hetzger1, Jan Gregor3, Steffen Weber-Carstens4, Dietrich Hasper2, Didier Keh4, Heidrun Zuckermann3, Petra Reinke2,5, and Hans-Dieter Volk1,5


GM-CSF group:
↓ Time on vent
↓ APACHE-II score

n = 19 subjects per group
There were no nosocomial infections in the GM-CSF treated group. All patients in the standard therapy group developed secondary infection.
We’ve been talking about this for years.....why has this not gained traction?
Flow cytometry – Pitfalls

• HLA-DR: “% +”

• Meaningfulness of results depends on:
  o How you choose (and titrate) your antibodies
  o How you set your cytometer (voltage, compensation)
  o How you determine positive and negative
HLA-DR Quantification

Quantibrite® beads (Becton Dickinson)

Döcke, *Clinical Chemistry*, 2005
*Ex vivo* LPS-induced TNFα production capacity

- LPS stimulation procedures must be standardized in order to compare results
  - Type/strain of bacteria
  - LPS purification method
  - Dose
  - Blood volume used
  - Incubation conditions/time
Immune Surveillance Laboratory

- We ship immune testing kits to centers across North America.
- We provide GLP analysis of cytokines and cell surface markers.
  - But these are all “Research Use Only” tests in the U.S. …….
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs targeting innate immune suppression</strong></td>
<td></td>
<td></td>
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<tr>
<td>INF-γ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polk, 1992</td>
<td>RCT</td>
<td>Severely injured adults</td>
<td>193</td>
<td>↑ mHLA-DR expression in treated group.</td>
</tr>
<tr>
<td>Dries, 1994</td>
<td>RCT</td>
<td>Severely injured adults</td>
<td>416</td>
<td>↓ Incidence of infection-related mortality in treated group</td>
</tr>
<tr>
<td>Dacke, 1997</td>
<td>Non-randomized, interventional</td>
<td>Septic adults with low mHLA-DR expression</td>
<td>9</td>
<td>↑ mHLA-DR expression and TNF-α production capacity after treatment</td>
</tr>
<tr>
<td>Wasserman, 1998</td>
<td>RCT</td>
<td>Adults with severe burn injury</td>
<td>216</td>
<td>No differences in infection-related mortality</td>
</tr>
<tr>
<td>Nakos, 2002</td>
<td>RCT (Inhaled IFN-γ)</td>
<td>Severely injured adults</td>
<td>52</td>
<td>↑ alveolar macrophage HLA-DR expression and lower rates of ventilator pneumonia in treated group</td>
</tr>
<tr>
<td>Delsing, 2014</td>
<td>Non-randomized, interventional</td>
<td>Adults with severe invasive fungal sepsis</td>
<td>8</td>
<td>Increased mHLA-DR expression and enhanced anti-fungal pro-inflammatory cytokine production</td>
</tr>
<tr>
<td><strong>GM-CSF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilgin, 2001</td>
<td>RCT</td>
<td>Septic neonates with neutropenia</td>
<td>60</td>
<td>↓ mortality in treatment group</td>
</tr>
<tr>
<td>Drossou-Agakidou, 2002</td>
<td>RCT</td>
<td>Septic neonates</td>
<td>56</td>
<td>↑ mHLA-DR in GM-CSF treated group compared to G-CSF or placebo</td>
</tr>
<tr>
<td>Pressnell, 2002</td>
<td>RCT</td>
<td>Septic adults with pulmonary dysfunction</td>
<td>18</td>
<td>↑ neutrophil function and improved oxygenation in treated group</td>
</tr>
<tr>
<td>Nierhaus, 2003</td>
<td>Non-randomized, interventional</td>
<td>Septic adults with low mHLA-DR expression</td>
<td>9</td>
<td>↑ mHLA-DR expression and TNF-α production capacity after treatment</td>
</tr>
<tr>
<td>Rosenbloom, 2005</td>
<td>RCT</td>
<td>Septic adults</td>
<td>33</td>
<td>↑ mHLA-DR expression and faster resolution of infection in treated group</td>
</tr>
<tr>
<td>Orozco, 2006</td>
<td>RCT</td>
<td>Adults with abdominal sepsis</td>
<td>58</td>
<td>↓ hospital stay and ↓ infectious complications in treated group</td>
</tr>
<tr>
<td>Meisel, 2009</td>
<td>RCT</td>
<td>Septic adults with low mHLA-DR</td>
<td>38</td>
<td>↑ mHLA-DR expression and ↓ durations of mechanical ventilation and ICU stay in treated group</td>
</tr>
<tr>
<td>Hall, 2011</td>
<td>RCT</td>
<td>Children with MODS and low TNFα production capacity</td>
<td>14</td>
<td>Enhanced TNF-α production capacity and lower incidence of nosocomial infection in treated group</td>
</tr>
<tr>
<td>Paine, 2012</td>
<td>RCT</td>
<td>Adults with ALI/ARDS</td>
<td>132</td>
<td>No difference in ventilator-free days</td>
</tr>
</tbody>
</table>
GM-CSF for Immunomodulation Following Trauma (GIFT) Study  (NCT01495637)
GIFT Study

• The study:
  o An open-label, multi-center dose finding study of GM-CSF for the reversal of trauma-induced immune suppression in critically injured children.
  o Immune function is tested on post-trauma days 1, 2, and/or 3.
  o Only children with severe immune suppression receive GM-CSF.
  o GM-CSF is given for 3 days at 1/8, 1/4, or 1/2 of the FDA-approved dose.

  We give GM-CSF at a *fraction* of the FDA-approved dose for a *fraction* of the time.
GIFT Study

- Goals: Improve immune function, reduce nosocomial sepsis risk
- Establish lowest dose of GM-CSF that can safely and effectively improve immune function in this setting.
Ongoing/recent GM-CSF trials

• UK: 100 vs 250 µg/m²/day of SQ GM-CSF or placebo for 4 or 7 days in adults with severe sepsis/septic shock and decreased neutrophil function. Target n=70
  o Primary outcome: Neutrophil phagocytosis
  o Secondary outcomes: Inflammation, HLA-DR, SOFA, mortality

• France: 125 µg/m²/day of SQ GM-CSF or placebo for 5 days in adults with severe sepsis/septic shock and low monocyte HLA-DR expression. Target n=488
  o Primary outcome: Nosocomial infection by Day 28 or d/c
  o Secondary outcomes: organ failure, mortality
SIRS: ↑ Plasma IL-6, IL-8 levels
- Fever
- Capillary leak
- Organ dysfunction

CARS: ↑ Plasma IL-10 levels
- ↓ Monocyte HLA-DR expression
- ↓ Ex vivo LPS-induced TNFα production capacity

Uncomplicated course
- ↓ Lymphocyte cytokine production capacity
- ↑ Lymphocyte apoptosis

Complicated course
Sepsis-Induced Apoptosis Causes Progressive Profound Depletion of B and CD4⁺ T Lymphocytes in Humans

Richard S. Hotchkiss, Kevin W. Tinsley, Paul E. Swanson, Robert E. Schmieg, Jr., Jia Ji Hui, Katherine C. Chang, Dale F. Osborne, Bradley D. Freeman, J. Perren Cobb, Timothy G. Buchman, and Irene E. Karl


Nationwide Children's Hospital
When your child needs a hospital, everything matters.

The Ohio State University
• Prolonged lymphopenia
  o ALC < 1000 for a week
  o Associated with secondary infection:
    OR 5.5 (95% CI 1.7-17)
  o Associated with death:
    OR 6.8 (95% CI 1.3-34)
Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Jonathan S. Boomer, PhD

A Immunohistochemical staining for HLA-DR

B Immunohistochemical staining for CD4

CD4 T cells

CD8 T cells

Control patient

Patient with sepsis

Control patient

Patient with sepsis
Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Jonathan S. Boomer, PhD

JAMA, December 21, 2011
Early adaptive immune suppression in children with septic shock: a prospective observational study

Critical Care 2014, 18:R145

Jennifer A Muszynski, Ryan Nofziger, Kristin Greathouse, Lisa Steele, Lisa Hanson-Huber, Jyotsna Nateri and Mark W Hall

- 22 children with septic shock sampled within 48 hours of shock onset and again at Day 7 (if still in ICU).
- Evaluated for new or persistent infection (still culture-positive at initial infection site at Day 7).
Regulatory T cells ($T_{reg}$)

- Ultra immunosuppressive CD4+ T cells
- “Naturally occurring”
  - CD25+, CD127lo
  - Not activated $T_H1$, $T_H2$
  - Express FOXP3 transcription factor
  - IL-10, TGFβ, direct inhibition
- Appear to be resistant to the wave of apoptosis that affects other T cells in sepsis.
  - Monneret, 2003; Venet, 2004
- …but not in children?
  - Muszynski, 2014
Is the lymphocyte a target for immunostimulatory therapy?
• Negative co-stimulatory receptor (lymphocyte) and ligand (APC) expression are higher in sepsis non-survivors.
Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients

Caroline Guignant¹, Alain Lepape², Xin Huang³, Hakim Kherouf³, Laure Denis⁴, Françoise Poitevin¹, Christophe Malcus¹, Aurélie Chéron⁵, Bernard Allaouchiche⁵, François Gueyffier⁶, Alfred Ayala³, Guillaume Monneret¹* and Fabienne Venet¹*
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollias, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Szollosi, M.D.

Stay tuned…
Unintended Immunomodulation

Transfusion (likely suppressive)
Malnutrition (suppressive)
  Trace element deficiency (Zn, Se)
Hyperglycemia (likely pro-inflammatory)
Hypothermia (suppressive)
Medications.....
Which of these commonly used ICU medications are immunomodulators?

- Furosemide  
- Fentanyl  
- Midazolam  
- Methylprednisolone  
- Insulin  
- Dopamine  
- Epinephrine  
- Tacrolimus  
- Cyclosporine  
- Dexamethasone  
- Norepinephrine  
- Morphine  
- Lorazepam  
- Azithromycin  
- Meropenem  
- Dobutamine
Which of these commonly used ICU medications are immunomodulators?

- Furosemide
- Fentanyl
- Midazolam
- Methylprednisolone
- Insulin
- Dopamine
- Epinephrine
- Tacrolimus

- Cyclosporine
- Dexamethasone
- Norepinephrine
- Morphine
- Lorazepam
- Azithromycin
- Meropenem
- Dobutamine
# Unintended Immunomodulation

<table>
<thead>
<tr>
<th>Drug / Class of Drugs</th>
<th>Immune Effect</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td>Antibacterial agents</td>
<td>↑</td>
<td>Release of bacterial components at the time of cell death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Direct enhancement of intracellular killing (β-lactams)</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>Bone marrow suppression (β-lactams)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased pro-inflammatory cytokine production (macrolides)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>↓</td>
<td>Upregulation of the endogenous cortisol axis</td>
</tr>
<tr>
<td>Catecholamines*</td>
<td>↑</td>
<td>Stimulation of α-adrenergic receptors</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>Stimulation of β-adrenergic receptors</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↓</td>
<td>Inhibition of prolactin secretion</td>
</tr>
<tr>
<td>Furosemide</td>
<td>↓</td>
<td>Reduced production of pro-inflammatory cytokines by mononuclear cells</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>Indirect reduction in hyperglycemia-induced pro-inflammatory cytokine production</td>
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<tr>
<td></td>
<td></td>
<td>Direct inhibition of the NFκB pathway</td>
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<tr>
<td>Opiates</td>
<td>↓</td>
<td>Suppression of IFN production</td>
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<td></td>
<td></td>
<td>Induction of lymphocyte apoptosis</td>
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<tr>
<td></td>
<td></td>
<td>Induction of macrophage apoptosis</td>
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<tr>
<td></td>
<td></td>
<td>Induction of TGFβ</td>
</tr>
<tr>
<td>Theophylline/Aminophylline</td>
<td>↓</td>
<td>Promotion of PMN apoptosis via blockade of adenosine receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of T cell response</td>
</tr>
</tbody>
</table>
Current and beyond.....

Time- and patient-specific therapies that are:
- Innate-targeted
- Adaptive-targeted
- Both
Summary

• Hyperinflammation *and* critical illness-associated immune suppression occur, can co-exist, and are both associated with adverse outcomes in sepsis.

• An increasingly broad array of recombinant proteins/antibodies offers the potential for targeted anti-inflammatory effects.
  o Patient selection, timing, and half-life are likely to be key considerations.

• Immune suppression is common in the setting of critical illness and can be quantified in the laboratory, though standardization and FDA-approval of measurement techniques is a persistent hurdle.
Summary

• Reversal of critical illness-associated immune suppression represents another form of immunomodulation, particularly in the setting of prospective immune function testing.

• Unintended immunomodulation is common in the ICU and further underscores the need for immune function tests to move to the clinical laboratory.
Acknowledgements

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Jennifer Muszynski, MD
Josey Hensley, RN
Jill Popelka, RN
Janet Cihla, RN
Maggie Flowers, RN

Key Collaborators
Joseph A. Carcillo
Hans Dieter Volk
Mark D. Wewers
Adrienne G. Randolph
Timothy T. Cornell
Thomas P. Shanley
Questions?
Genetic risk factor???