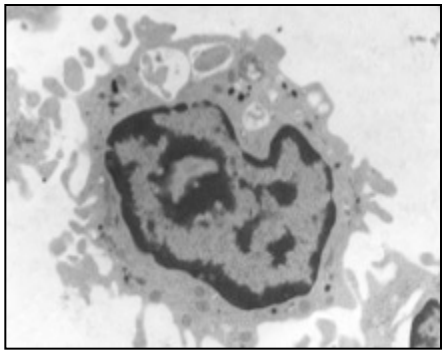


Effects of trauma and early resuscitation on inmmune function and outcomes

Mark W. Hall, MD
Chief, Critical Care Medicine
Director, Immune Surveillance Laboratory
Nationwide Children's Hospital, Columbus, OH

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

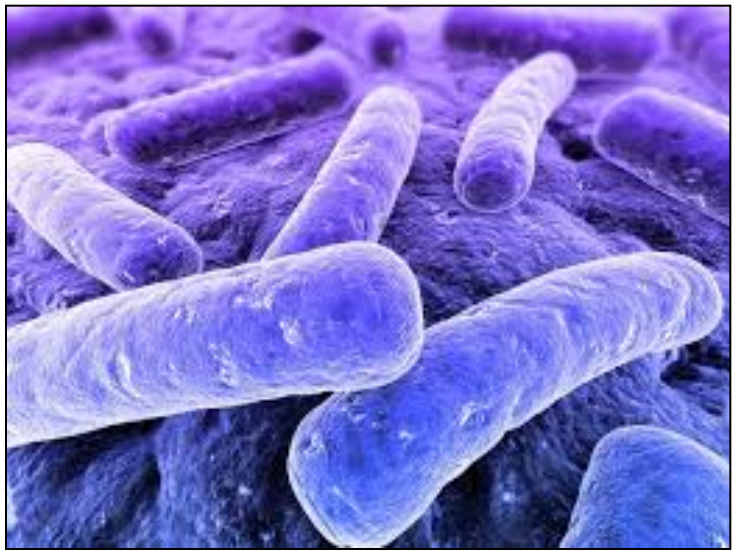
THE OHIO STATE UNIVERSITY

Disclosures

- No financial disclosures.
- I will be discussing off-label use of GM-CSF as an immunomodulator.

Trauma survivors need an immune system.

- Contamination
  - Perforated viscus
  - Grossly contaminated wounds
  - Foreign bodies
  - Non-sterile resuscitation conditions
  - Donkey shit…..
- Prevention of secondary infection
- Wound healing and tissue remodeling



≥ 20% incidence?

Trauma-related Infections in Battlefield Casualties From Iraq

(*Ann Surg* 2007;245: 803–811)

Kyle Petersen, DO, Mark S. Riddle, MD, MPH, TM,† Janine R. Danko, MD, MPH,* David L. Blazes, MD, MPH,‡ Richard Hayden, MS, Mt(ASCP)SBB,§ Sybil A. Tasker, MD,* and James R. Dunne, MD‖*

- 211 patients evacuated to the USNS Comfort during a three month period in 2003.
- 56 (27%) developed post-injury infection
- Infections:
  - Wound 84%
  - Bloodstream 38%
  - Acinetobacter, E. Coli, Pseudomonas most common bacteria

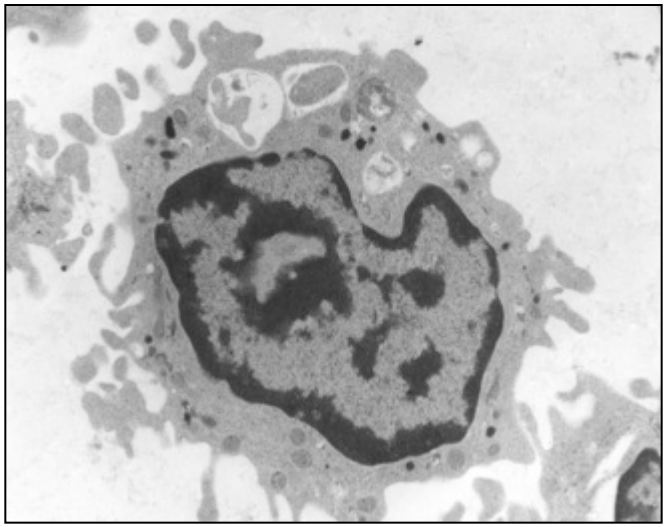
Infections Complicating the Care of Combat Casualties During Operations Iraqi Freedom and Enduring Freedom

(*J Trauma.* 2011;71: S62–S73)

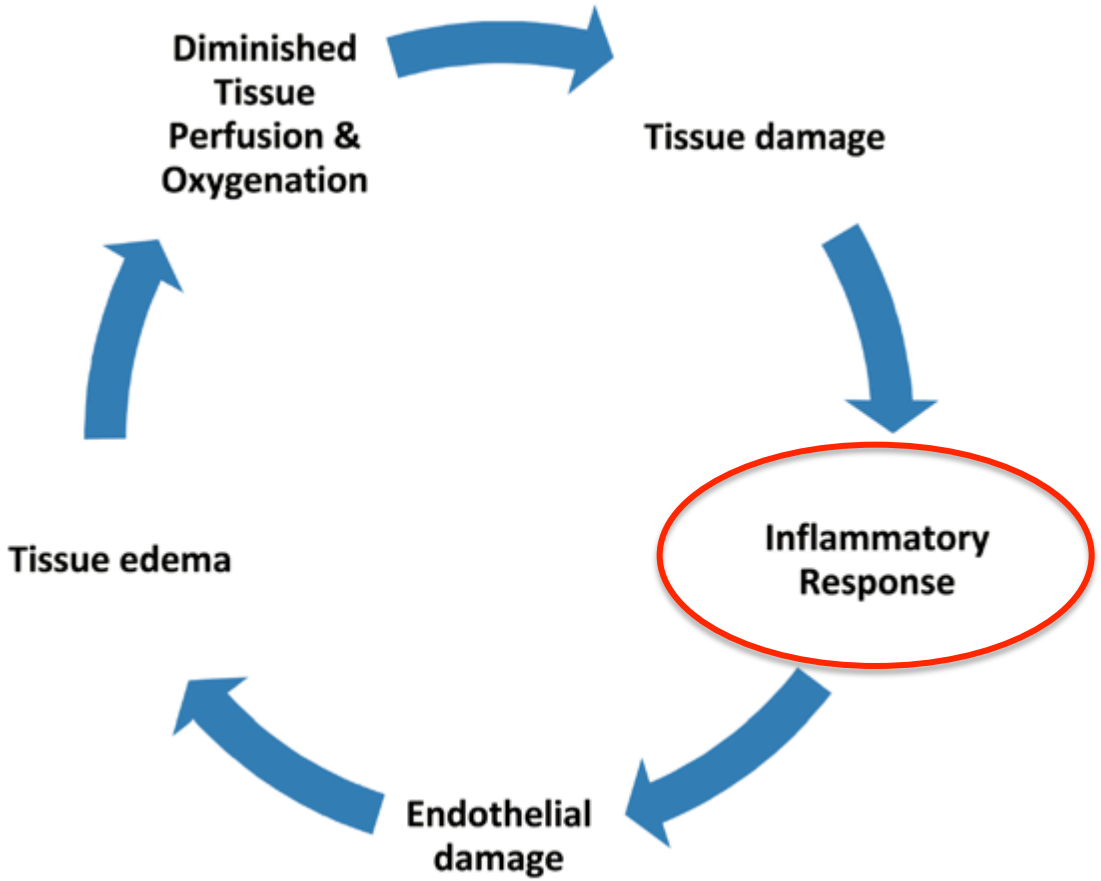
Clinton K. Murray, MD, Kenneth Wilkins, PhD, Nancy C. Molter, PhD, Fang Li, MS, Lily Yu, MS, Mary Ann Spott, MPH, MBA, Brian Eastridge, MD, Lorne H. Blackbourne, MD, and Duane R. Hospenthal, MD, PhD

- ICD-9 based query of the Joint Theater Trauma Registry
  - Records for combat injuries from 3/2003 – 4/2009
  - 16,742 injuries reviewed
- Infection was documented in 921 patients (~6%).
- Higher ISS and head injury were risk factors.
- Likely underestimates the true incidence of infection due to problems inherent in the administrative database.

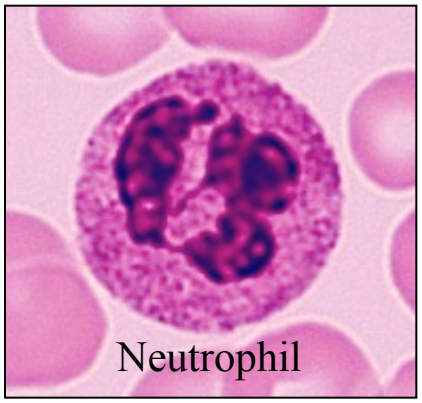
Is the immune system to blame?

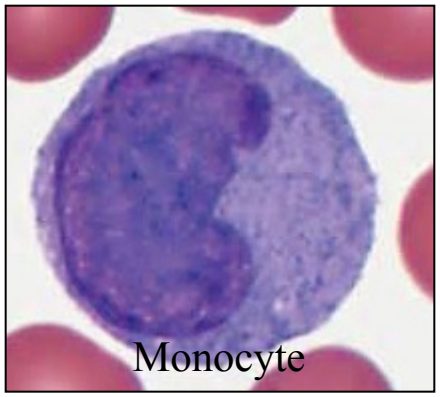


Trauma and inflammation



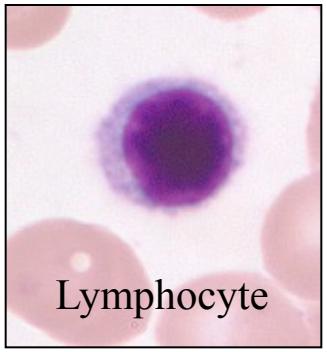
The Cast of Characters – Innate immunity


Neutrophil


Monocyte

- Includes PMNs, monocytes, macrophages, dendritic cells, NK cells
- First line of cellular defense
- Recognize broad classes of pathogens/molecules via cell-surface receptors (*eg* TLRs, FcR)
  - Pathogen-associated molecular patterns (e.g. LPS)
  - Damage-associated molecular patterns (e.g. HMGB1, mtDNA)
- 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)

Cytokines

Pro-inflammatory

TNFα

IL-1β

IL-6

IL-8

IL-17

IFNγ

IL-2

Anti-inflammatory

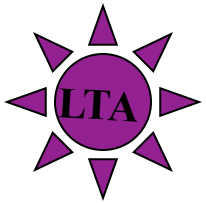
IL-10

TGFβ

IL-11

sTNF receptor

IL-1ra



Cytokines

- Concurrently high systemic levels of *anti-inflammatory* mediators have also been associated with adverse outcomes:
  - IL-10 (pediatric) *Doughty, 1996*
  - IL-10 (adult) *Kellum, 2007*
  - IL-10 (pediatric) *Hall, 2007*
  - IL-10, IL-1ra (pediatric) *Hall 2013*

???

Anti-inflammatory

IL-10

TGFβ

IL-11

sTNF receptor

IL-1ra

IL-4

Cytokines

Pro-inflammatory

TNFα

IL-1β

IL-6

IL-8

IL-17

IFNγ

IL-2

Anti-inflammatory

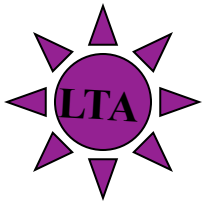
IL-10

TGFβ

IL-11

sTNF receptor

IL-1ra

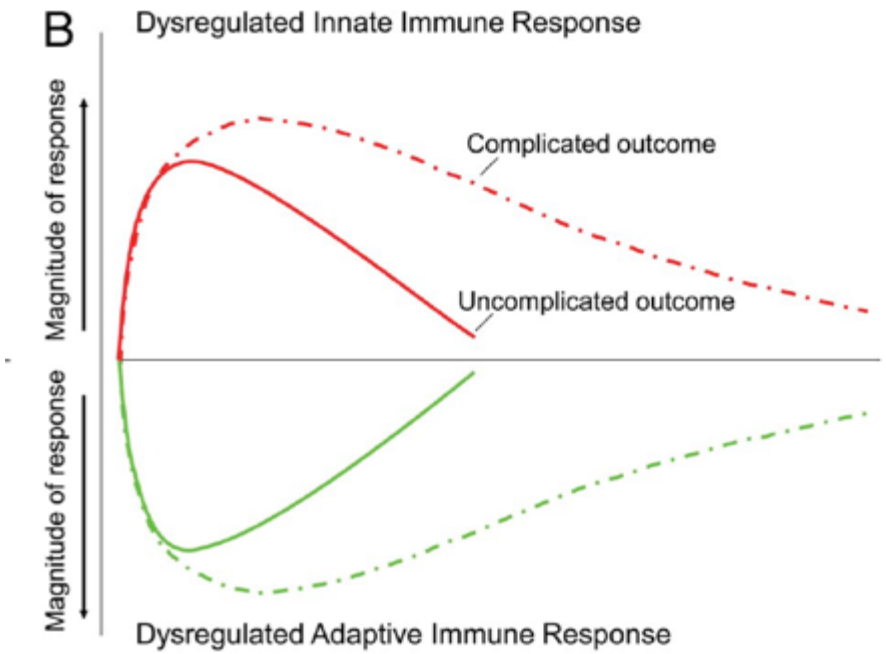


JEM
Published November 21, 2011

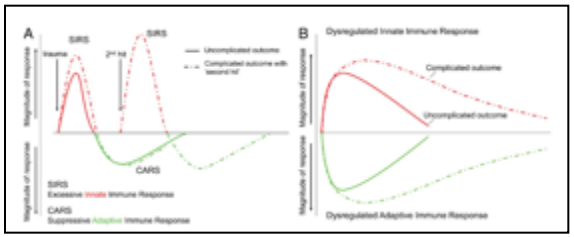
A genomic storm in critically injured humans

Wenzhong Xiao,[1,4] Michael N. Mindrinos,[4] Junhee Seok,[4]

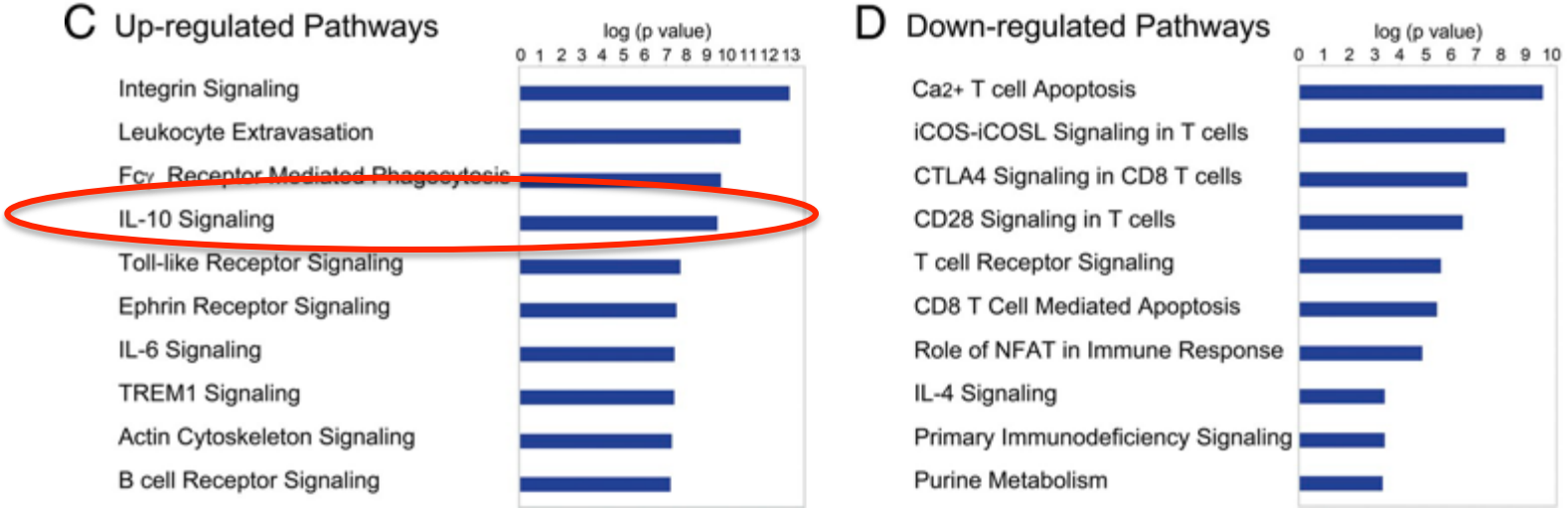
- Serial genomic (mRNA) evaluation of PRBC from 167 adult trauma patients with shock.



Innate signaling



- Longitudinal transcriptome measurement suggested:
  - Persistent *up-regulation* of pro- and anti-inflammatory innate immune gene expression
  - Persistent *down-regulation* of adaptive immune gene expression



Xiao, JEM, 2011

Trauma and inflammation

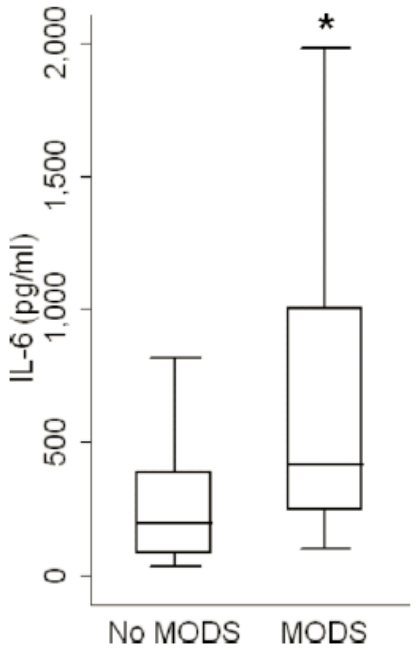


Table 1

Independent Predictors for the Development of MODS with development cohort

Clinical Parameter	Odds Ratio for Development of MODS* (95% CI)
Sex, male	9.19 (2.07–40.85)
ISS	1.02 (1.01–1.05)
Blood transfusion > 6 u/12 h	1.68 (1.10–3.26)
IL-6 ≥ 350 pg/ml	3.87 (1.13–11.19)

Compared to patients without that characteristic.

- Early inflammation predicts post-traumatic MODS. (n=79)

  Cuschieri et al, Shock, 2011

Inflammatory Mediators (0–24 Hr Postinjury)	Hypotensive Patients	Normotensive Patients	Fold Change	*p*
IL-6	3,696	1,368	2.7	< 0.001
Monocyte chemotactic protein-1	5,255	1,976	2.6	< 0.001
IL-7	525	216	2.4	0.01
IL-8	646	279	2.3	< 0.001
IL-10	204	100	2	0.003
Interferon-γ	126	68	1.9	0.003
Macrophage inflammatory protein-1α	285	148	1.9	0.007
IL-17	293	162	1.8	0.02
No_2^-/No_3^-	159	121	1.3	0.03

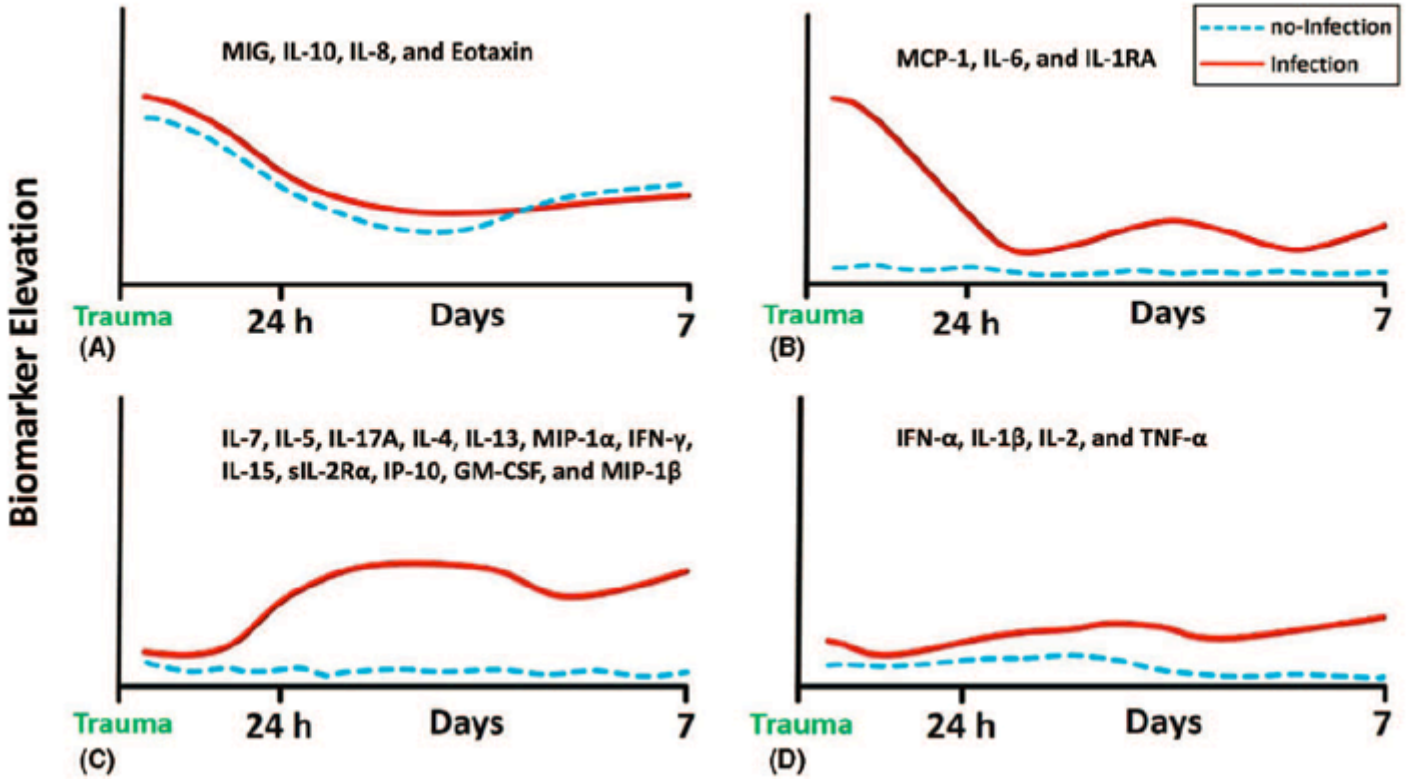
IL = interleukin.

- Pre-hospital hypotension was associated with marked elevations in pro- and anti-inflammatory mediators.
- Patients with pre-hospital hypotension had more organ failure and longer ICU stays.

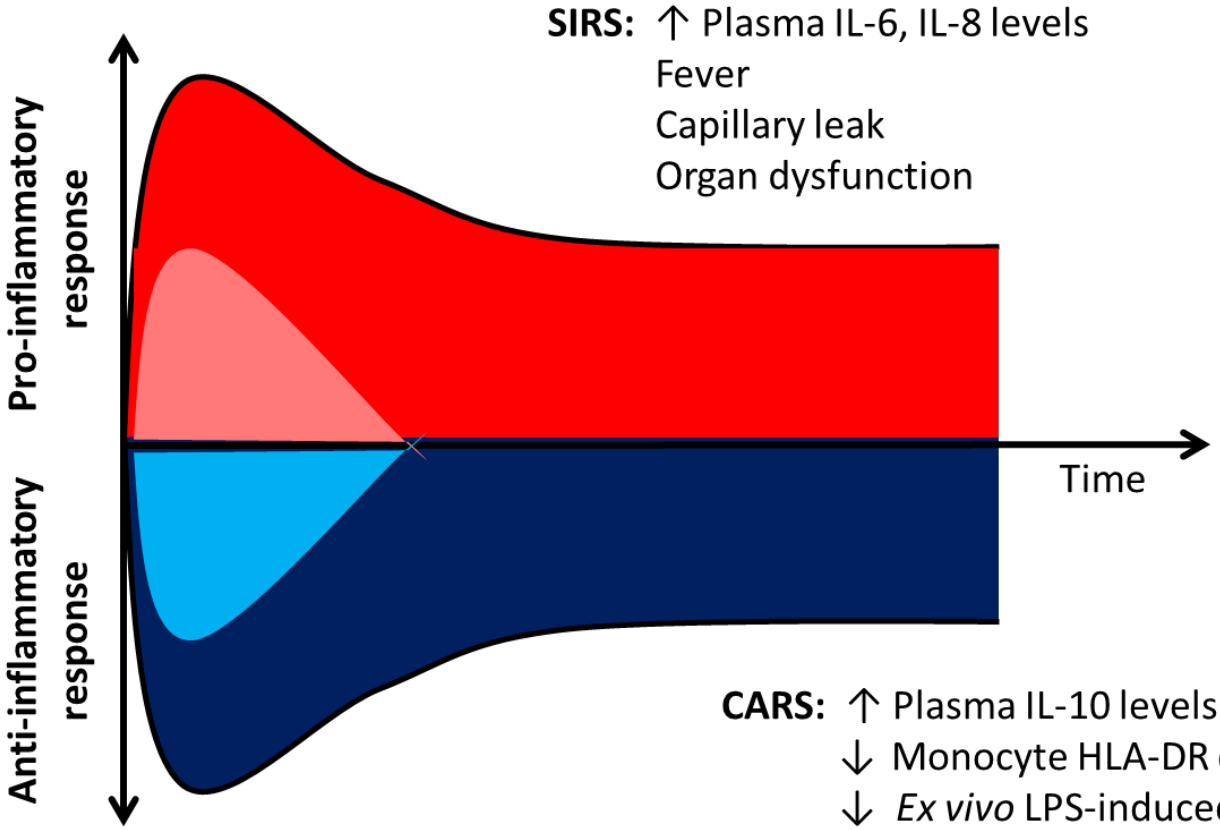
Temporal Patterns of Circulating Inflammation Biomarker Networks Differentiate Susceptibility to Nosocomial Infection Following Blunt Trauma in Humans

(*Ann Surg* 2016;263:191–198)

Rami A. Namas, MD,† Yoram Vodovotz, PhD,*†‡ Khalid Almahmoud, MD,* Othman Abdul-Malak, MD,* Akram Zaaqoq, MD,§ Rajaie Namas, MD,*¶ Qi Mi, PhD,|| Derek Barclay, BS,* Brian Zuckerbraun, MD,* Andrew B. Peitzman, MD,* Jason Sperry, MD, MPH,* and Timothy R. Billiar, MD*†*




What about *function*?



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

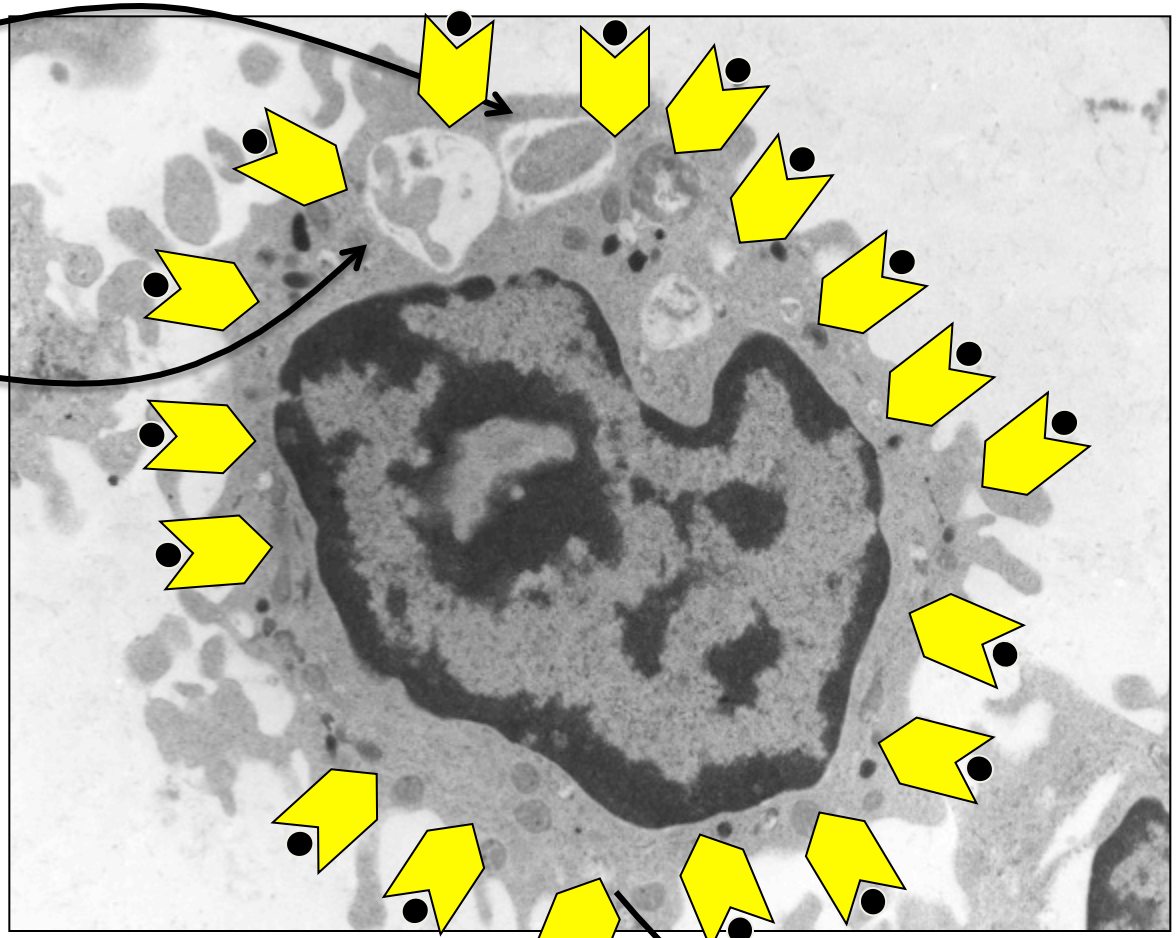
Complicated course

1. **Phagocytosis**

2. **Intracellular killing**

3. **Antigen presentation (HLA-DR)**

Healthy monocyte



TNFα

TNFα

TNFα

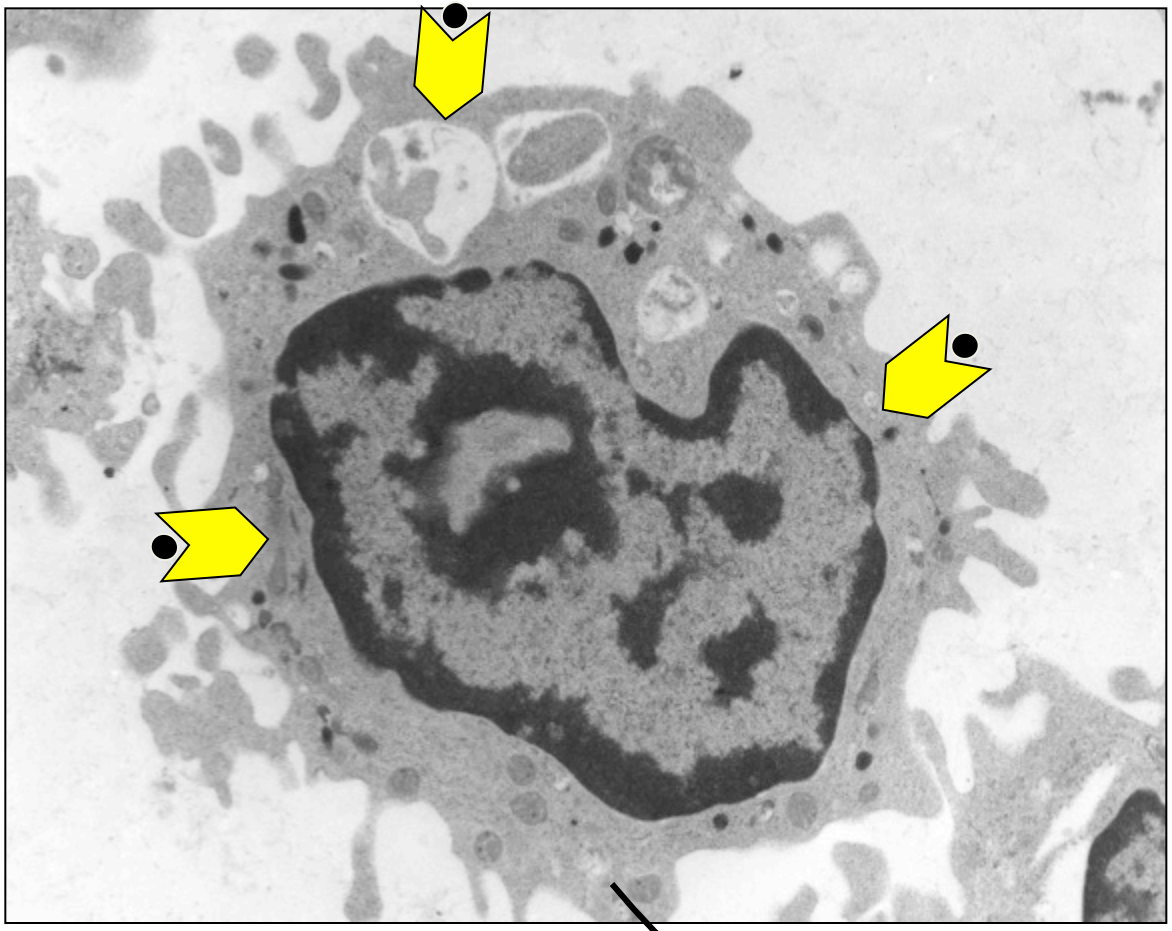
4. **Extracellular TNFα production**

1. ↓Phagocytosis

2. ↓Intracellular killing

3. ↓Antigen presentation
(HLA-DR < 30%)

Immunoparalyzed monocyte



4. ↓Extracellular TNFα production

TNFα

TNFα

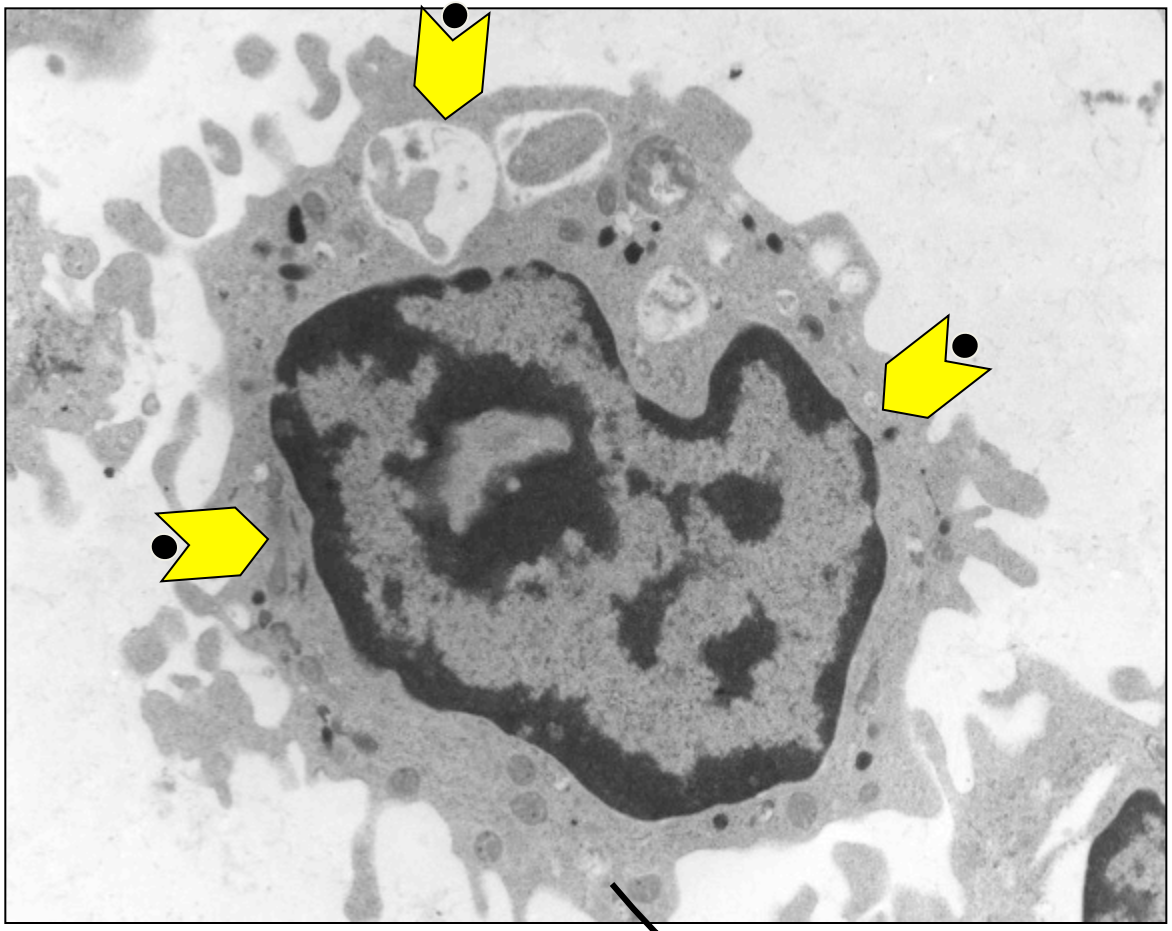
TNFα

1. ↓Phagocytosis

2. ↓Intracellular killing

3. ↓Antigen presentation

Immunoparalyzed monocyte



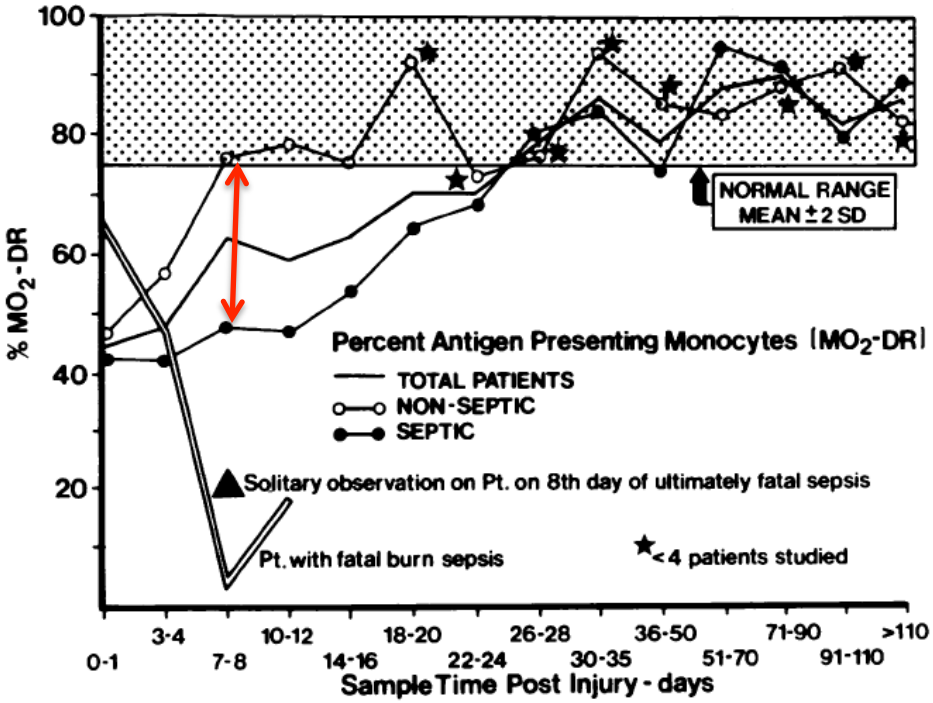
4. ↓Extracellular TNFα production
(*ex vivo* LPS-induced TNFα production capacity)

A Systematic Study of Host Defense Processes in Badly Injured Patients

Ann. Surg. • September 1986

HIRAM C. POLK, JR., M.D.
CHRISTOPHER D. GEORGE, F.R.C.S.*
SAMUEL R. WELLHAUSEN, PH.D.
KAREN COST, PH.D.
PATTIE R. DAVIDSON, R.N.
MICHAEL P. REGAN, M.D.
ANTHONY P. BORZOTTA, M.D.†

- The trauma community was among the first to recognize this.
- 20 patient cohort of critically injured (Mean ISS = 36) presumably immunocompetent adults.



Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after major trauma

Cheron *et al. Critical Care* 2010, **14**:R208

Aurélie Cheron[1], Bernard Floccard[1], Bernard Allaouchiche[1], Caroline Guignant[2], Françoise Poitevin[2], Christophe Malcus[2], Jullien Crozon[1], Alexandre Faure[1], Christian Guillaume[1], Guillaume Marcotte[1], Alexandre Vulliez[1], Olivier Monneuse[3], Guillaume Monneret[2*]

- 105 acutely critically injured adults
  - Median ISS: 39
- 35% incidence of post-traumatic sepsis

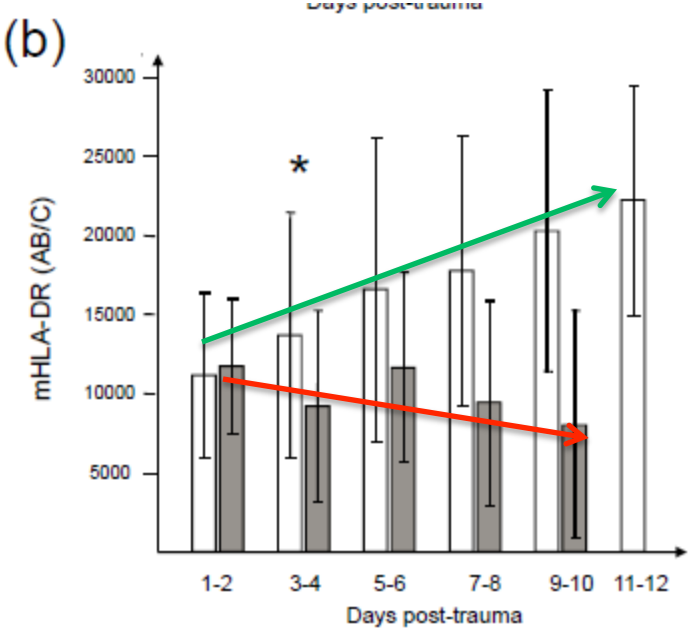


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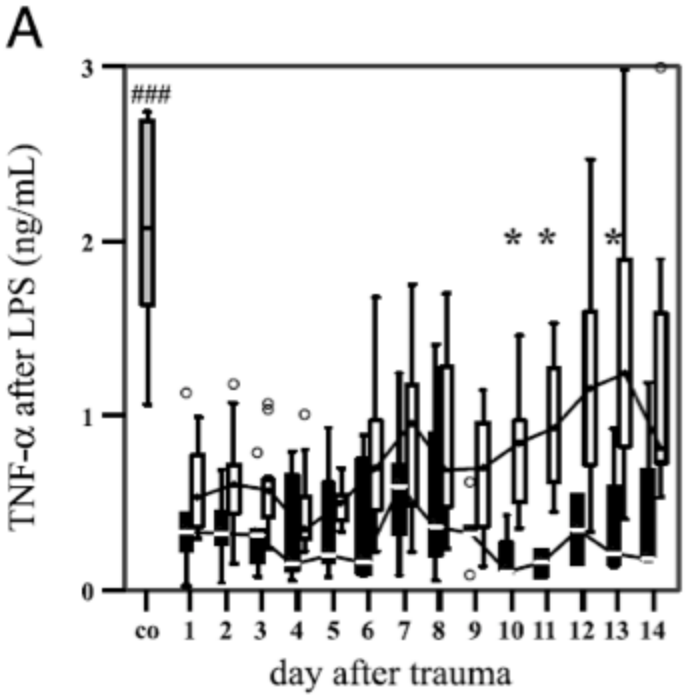
Table 2 Univariate and multivariate logistic regression analysis used to differentiate septic and non-septic patients

		Univariate (*n* = 105)			Multivariate (*n* = 77)		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Sex male	Positive	1.62	0.63-4.13	0.3129			
Severe brain injury	Positive	3.28	1.42-7.56	0.005	2.87	0.95-8.72	0.06
Severe thoracic injury	Positive	0.57	0.23-1.37	0.21			
ISS	≥40	2.19	0.95-5.06	0.066	2.84	0.88-9.16	0.08
SAPS II	≥37	3.17	1.38-7.32	0.007	2.01	0.67-6.08	0.21
D3 and 4/D1 and 2 mHLA-DR	≤1.2	4.81	1.45-16	0.009	5.41	1.42-20.52	0.013
Massive transfusion	Positive	1.5	0.63-3.57	0.35			

LIPOPOLYSACCHARIDE-INDUCED TUMOR NECROSIS FACTOR α PRODUCTION AND NOT MONOCYTE HUMAN LEUKOCYTE ANTIGEN–DR EXPRESSION IS CORRELATED WITH SURVIVAL IN SEPTIC TRAUMA PATIENTS

SHOCK, Vol. 25, No. 2, pp. 129–134, 2006

Martin Ploder,*# Linda Pelinka,† Claudia Schmuckenschlager,* Barbara Wessner,* Hendrik Jan Ankersmit,* Walter Fuerst,† Heinz Redl,† Erich Roth,* and Andreas Spittler*



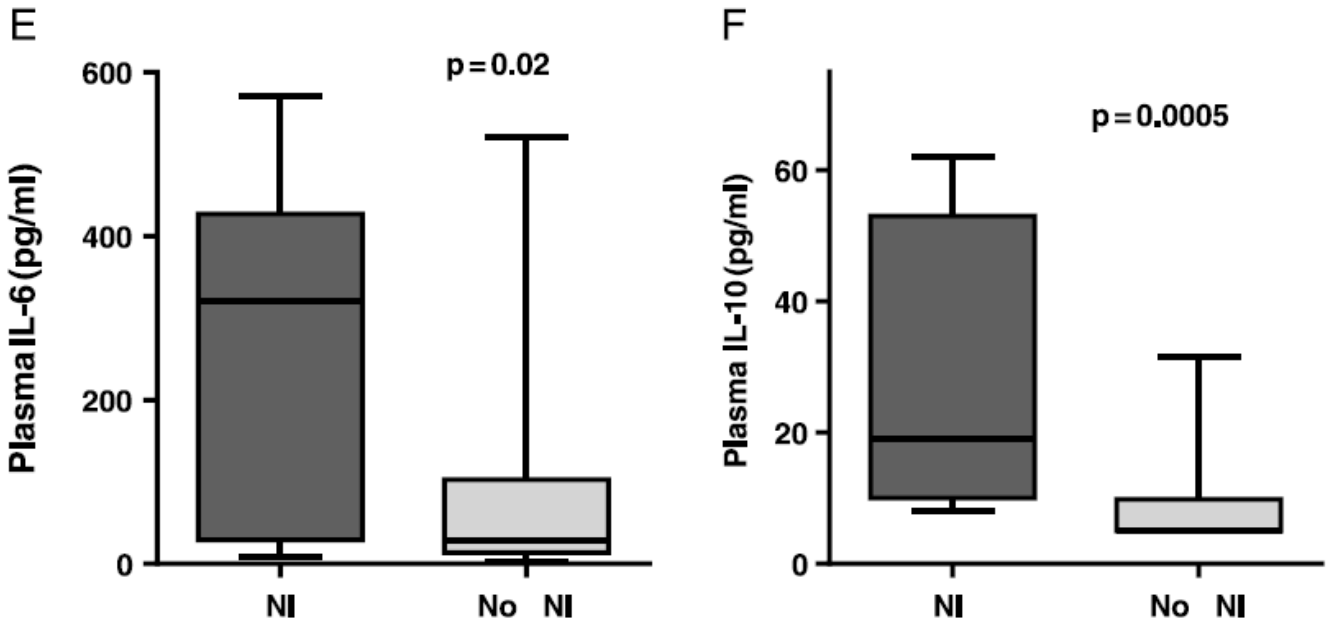
n=19, 6 deaths

SHOCK, Vol. 42, No. 4, pp. 313–321, 2014

INNATE IMMUNE FUNCTION PREDICTS THE DEVELOPMENT OF NOSOCOMIAL INFECTION IN CRITICALLY INJURED CHILDREN

Jennifer A. Muszynski,*† Ryan Nofziger,‡ Kristin Greathouse,† Jyotsna Nateri,† Lisa Hanson-Huber,† Lisa Steele,† Kathleen Nicol,§ Jonathan I. Groner,‖ Gail E. Besner,‖ Corey Raffel,¶ Susan Geyer,** Osama El-Assal,†† and Mark W. Hall*†

- 76 Critically injured children underwent prospective, longitudinal innate immune function testing. 16 (21%) developed nosocomial infection.



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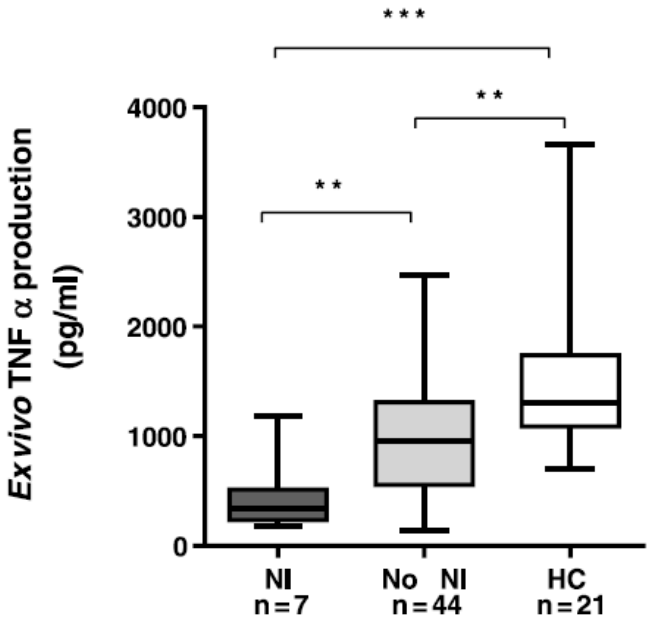

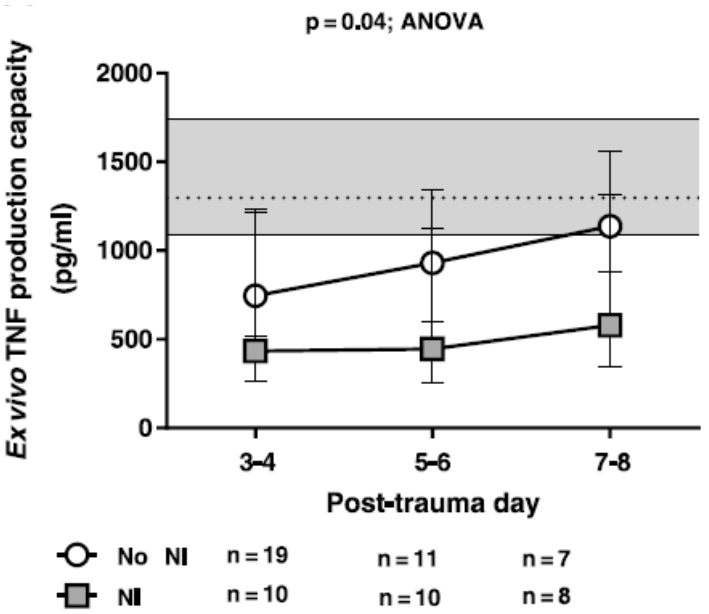

SHOCK, Vol. 42, No. 4, pp. 313–321, 2014

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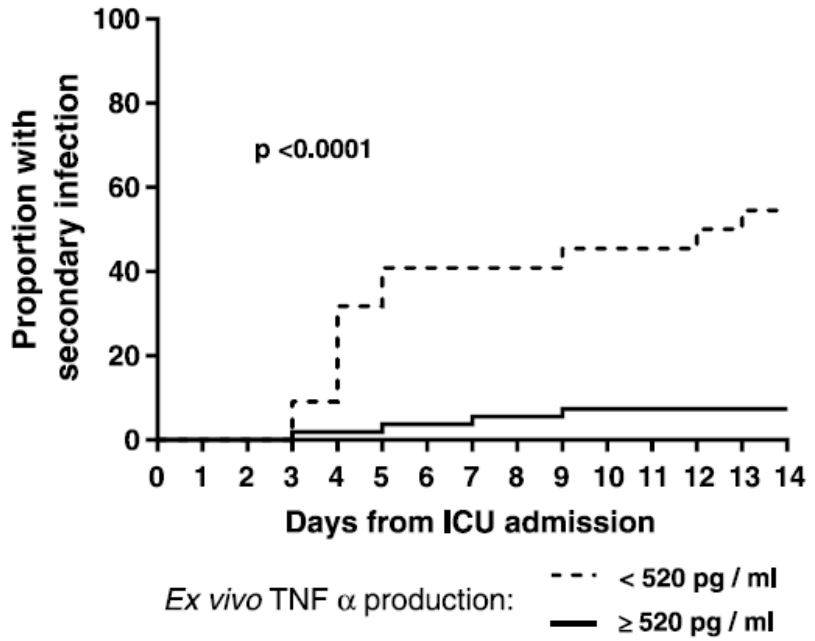
B



Infections occurred a median of 5 days after injury (range 3 – 13 days)

Does innate immune dysfunction represent a *modifiable* risk factor for adverse trauma outcomes?

GM-CSF

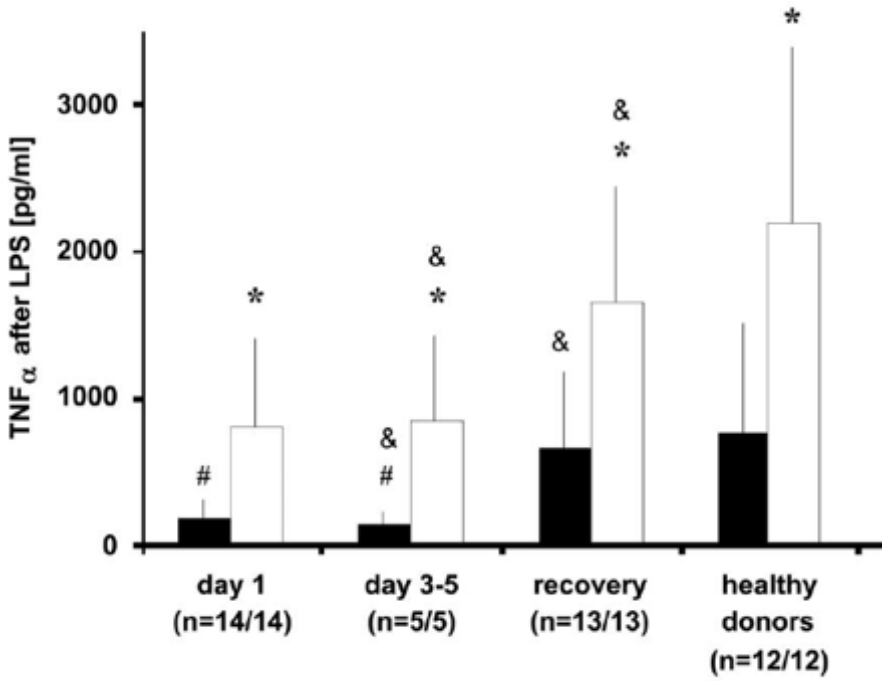
- Granulocyte-macrophage colony stimulating factor
  - FDA approved for adults and children in 1991 for the reconstitution of bone marrow after BMT and/or chemo for certain leukemias.
  - Side effect profile very favorable.
  - Given subcutaneously or IV
  - Known to increase immune cell numbers but also will increase function of existing cells.

Effect of granulocyte-macrophage colony-stimulating factor on the immune response of circulating monocytes after severe trauma

(Crit Care Med 2003; 31:2462–2469)

Sascha Flohé, MD; Sven Lendemans, MD; Christian Selbach; Christian Waydhas, MD; Marcus Ackermann, MD; F. Ulrich Schade, PhD; Ernst Kreuzfelder, PhD

- Critical injury-induced suppression of the immune response can be reversed *ex vivo* through pretreatment of the immune cells with GM-CSF prior to stimulation.

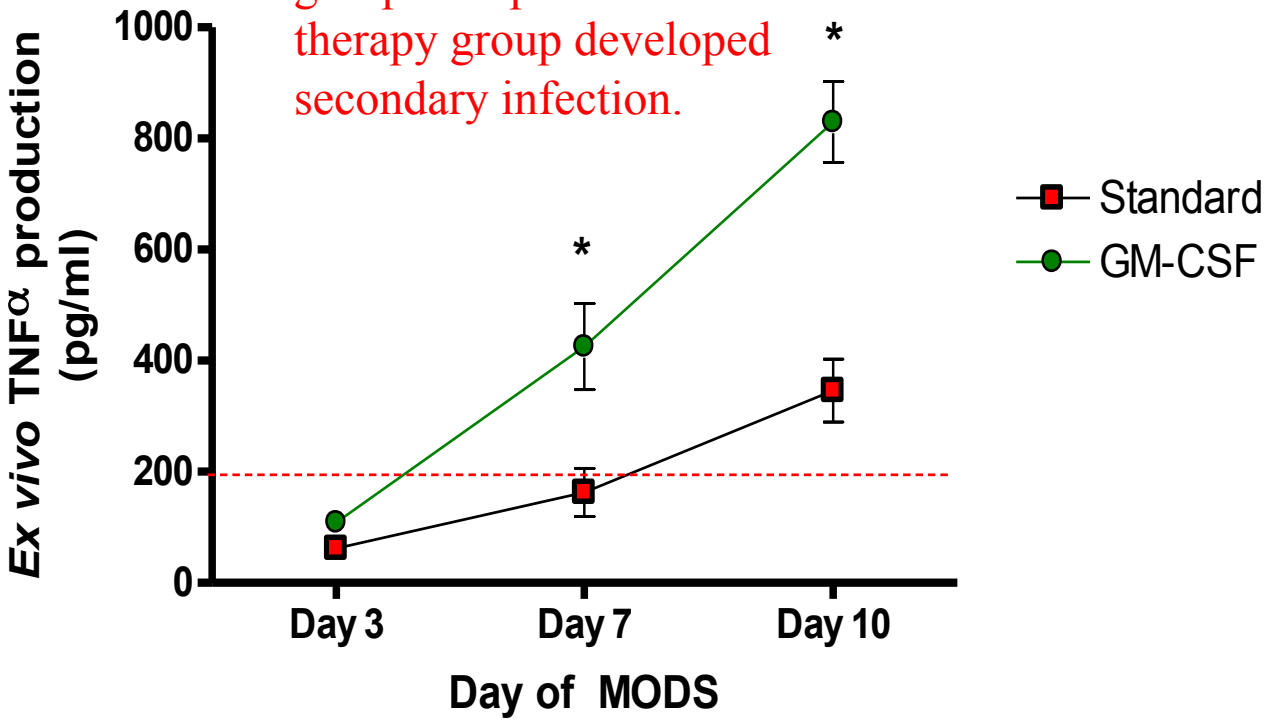


Mark W. Hall
Nina L. Knatz
Carol Vetterly
Steven Tomarello
Mark D. Wewers
Hans Dieter Volk
Joseph A. Carcillo

Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome

Intensive Care Med 2011

There were no nosocomial infections in the GM-CSF treated group. *All* patients in the standard therapy group developed secondary infection.



GM-CSF for Immunomodulation Following Trauma (GIFT) Study

National Institute of General Medical Sciences
One of the National Institutes of Health

CPCCRN NICHD Collaborative Pediatric Critical Care Research Network

R01GM094203 UG1HD083170

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

The Ohio State University

GIFT Study

- Multi-center clinical trial of GM-CSF for reversal of trauma-induced immune suppression in children.
- *Same day immune testing on post-trauma day 1, 2, and 3. Only subjects with low immune function will get drug.*
- Goals: Improve immune function, reduce infection risk
- Establish lowest dose of GM-CSF that can safely and effectively improve immune function in this setting.
- Later: Randomized controlled trial

Immune Surveillance Laboratory

- We produce, quality control, and ship immune testing kits to centers across North America.

GM-CSF

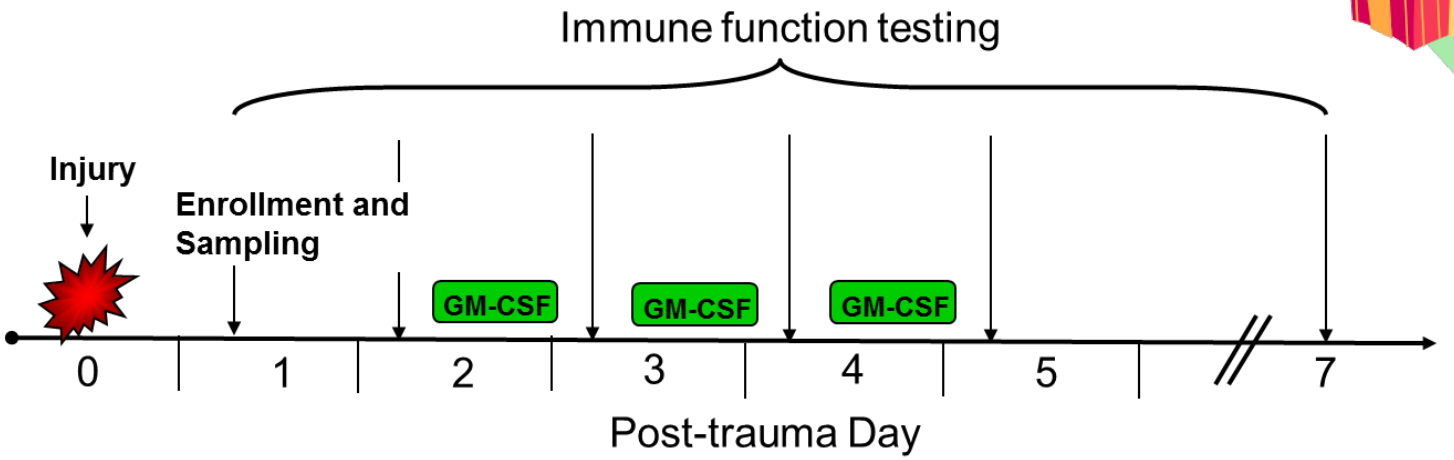
- What we don't know:
  - What dose of GM-CSF is sufficient to improve immune function over critical threshold?
    - Dose-finding for this purpose *has never been done.*
  - What are the influence of pubertal development and severe TBI (both of which could be expected to be important) on GM-CSF responsiveness?
    - This is completely unknown.

These data are necessary to inform the design of a subsequent RCT.

Study Design

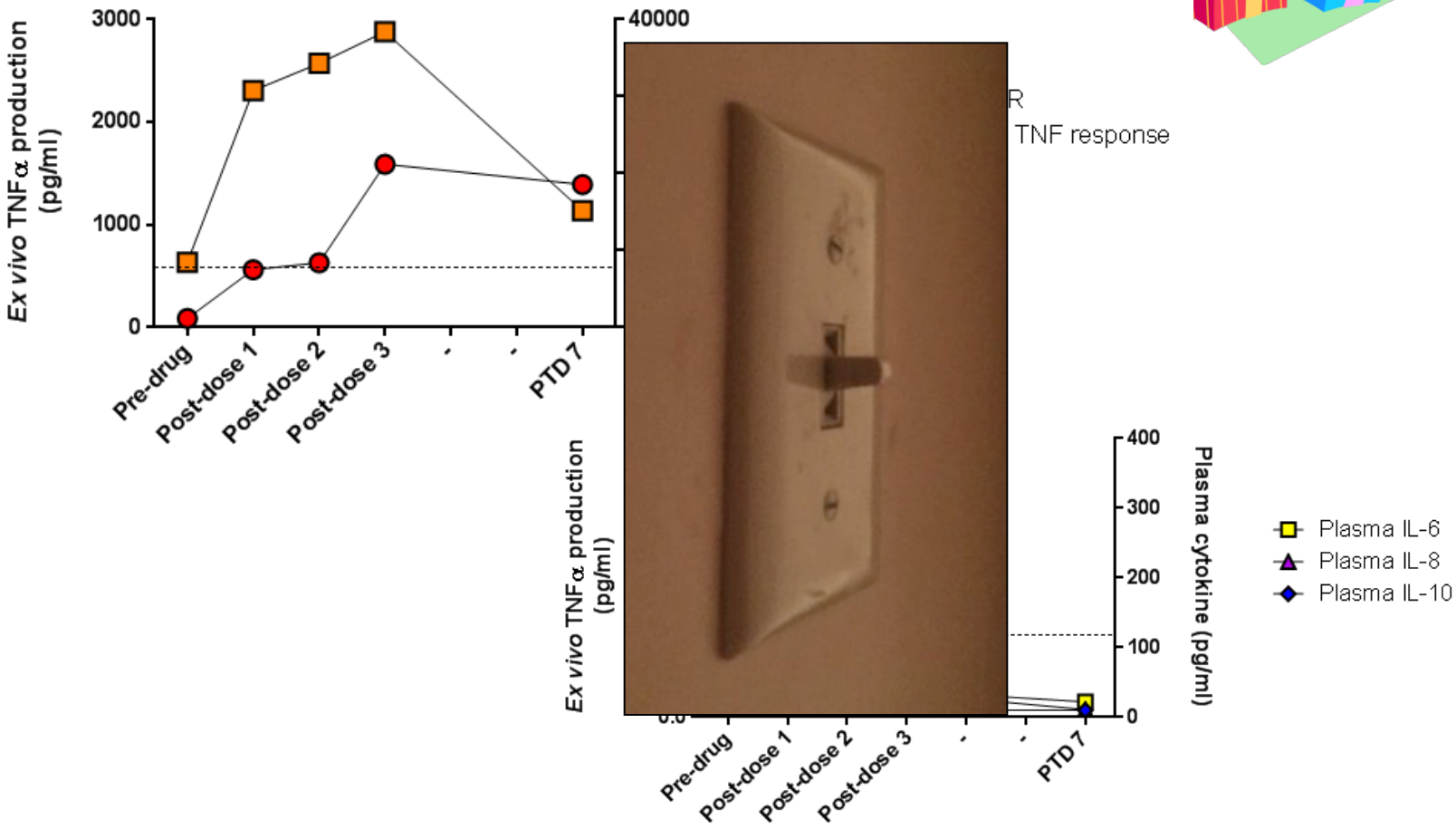
- Dose-finding (dose-escalation) study to identify the lowest immunostimulatory, tolerable dose (LITD).
- LITD: Restoration of immune function to levels *not* considered to be risk factors for secondary infection by the **end of treatment** (the morning after the 3rd dose) *and* **persisting through post-trauma day 7.**
  - *Ex vivo* TNFα production capacity > 600 pg/ml (normal 1000)
  - Monocyte HLA-DR expression > 8000 mol/cell (normal > 8000)
- Why the focus on the first week?
  - Observational study: Infections occurred a median of 5 (4 – 8) days after injury.

GIFT Study



- Starting with ⅛ of the FDA-approved dose.
- Escalating through ¼ or ½ of the FDA-approved dose in subsequent cohorts if needed.
- 4 strata based on Tanner stage and severe TBI status

GIFT Study


Ex vivo TNFα production (pg/ml)
3000
2000
1000
0
Pre-drug
Post-dose 1
Post-dose 2
Post-dose 3
PTD 7
40000
R
TNF response
Ex vivo TNFα production (pg/ml)
400
300
200
100
0
Plasma cytokine (pg/ml)
Plasma IL-6
Plasma IL-8
Plasma IL-10

Future of front line immune care?

- Reversal of shock in the field
  - Saves lives
  - Saves organ function
  - Saves immune function???
- Early (even empiric?) treatment for high risk groups
  - Severe TBI: Nearly all GIFT subjects with severe TBI have developed severe immune suppression.
  - GM-CSF can be given subcutaneously and comes lyophylized.
- Move immune function testing from regional medical centers to field hospitals and beyond? Point of care?

Summary

- Trauma is indeed pro-inflammatory, but…..
- A compensatory anti-inflammatory response often follows that is, when severe, associated with increased infection risk.
- This can be quantified in the laboratory:
  - Monocyte HLA-DR expression (innate)
  - *Ex vivo* stimulated TNFα production capacity (innate)
- We need to learn what *causes* "immunoparalysis"
- Strategies exist that can allow for modification of immune function to promote a balanced immune response
  - Shock reversal
  - Patient-specific immune monitoring
  - Targeted immunostimulation

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Questions?

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