Strategies For Translational Research

Frederick A. Moore MD

February 28, 2012
Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team

PICS – the New Predominant Phenotype of MOF
Strategies For Translational Research

Trauma Research: Historic Perspective

Participating in Multidisciplinary Translational Research

Creating a Multidisciplinary Translational Research Team

PICS – the New Predominant Phenotype of MOF

**Focus on the Process** not the Science
TRAUMA RESEARCH
Historic Perspective

Denver General (DG)

Inner City Hospital

THE KNIFE AND GUN CLUB
SCENES FROM AN EMERGENCY ROOM
Eugene Richards
TRAUMA RESEARCH
Chief of Surgery

Denver General (DG)

Ben Eiseman
TRAUMA SURGERY
Created Engaging Environment

Great operations

Brother John
TRAUMA SURGERY
Created Engaging Environment

Great operations
Surgical critical care

ECMO at DG
TRAUMA SURGERY
Created Engaging Environment

Great operations
Surgical critical care
Excellent research

Nutritional Support Team
TRAUMA SURGERY
Same Thing Happened Through Out USA

San Francisco General: William Blaisdell
Cook County Chicago: Robert Freeark
Shock Trauma Baltimore: R. Adams Cowley
Parkland Dallas: G.Tom Shires
Detroit Receiving: Charlie Lucas & Anne Leaderwood
Grady Memorial Atlanta: Harlan Stone
Buffalo General: John Border
King County New York: Gerald Shaftan
Charity New Orleans: F. Carter Nance
TRAUMA SURGERY
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Buffalo General: John Border
King County New York: Gerald Shaftan
Charity New Orleans: F. Carter Nance

Research was a Core Value of Trauma Surgery

#1: “Create the Culture”
Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research
MULTIPLE ORGAN FAILURE

B. Eiseman, m.d., f.a.c.s., R. Beart, m.d., and L. Norton, m.d., f.a.c.s.,
Denver, Colorado

#2: Pick a Topic
MULTIPLE ORGAN FAILURE

B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., and L. Norton, M.D., F.A.C.S.,
Denver, Colorado

Surg Gyn Obstet 1977

Important & Confusing Problem

MULTIPLE ORGAN FAILURE

Became DG’s Research Focus

Ben Eiseman
INJURY STRESS RESPONSE INDUCES

ACUTE PROTEIN MALNUTRITION

↓ Muscle Mass
↓ Visceral Protein
↓ Organ Function
↓ Immune Response

INFECTIONS

MULTIPLE ORGAN FAILURE
Hypothesis

ACUTE PROTEIN MALNUTRITION

↓ Muscle Mass
↓ Visceral Protein
↓ Organ Function
↓ Immune Response

INFECTIONS

MULTIPLE ORGAN FAILURE

Early Nutritional Support
Benefits of Immediate Jejunostomy Feeding after Major Abdominal Trauma—A Prospective, Randomized Study

ERNEST E. MOORE, M.D., AND TODD N. JONES, B.S.N.

Early TEN vs. Delayed TPN

Decreased Infections
TEN versus TPN following Major Abdominal Trauma—
Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N.,
BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

Early TEN vs. Early TPN

Decreased Infections
Early TEN vs. Early TPN

Decreased Infections

Is TEN good or is TPN bad?
# 3: Draw a cartoon

Gut: The Starter for MOF
Liver: The Motor for MOF

- Shock
- Delayed Enteral Feeding
- Endotoxin Bacteria
- Immune
- Stress
- ATN
- ARDS
- PGE$_2$
- IL-1
- TNF
- C$_3$a, C$_5$a
- O$_2^-$

Figure 1

**TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity**

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. McCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989
TEN versus TPN following Major Abdominal Trauma—Reduced Septic Morbidity

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., TODD N. JONES, R.N., BRIAN L. MCCROSKEY, M.D., AND VERLYN M. PETERSON, M.D.

J Trauma 1989

“Win-win” hypothesis:

Gut: The Starter for MOF
Liver: The Motor for MOF

Shock

Endotoxin
Bacteria

Kupffer Cell

Liver

C3a, C5a

IL-1 =

PGE2 =

TNF

O2-

ATN

ARDS

Immune

Stress

Delayed Enteral Feeding
“Win-win” hypothesis: bacterial translocation via portal vein

Gut: The Starter for MOF
Liver: The Motor for MOF

Shock

Endotoxin

Bacteria

Kupffer Cell

PGE$_2$

IL-1

TNF

C$_3$a, C$_5$a

O$_2^-$

ATN

ARDS

Immune

Stress

Injured Tissue

Delayed Enteral Feeding

Liver
Alden Harken

# 4: Be a Cheer Leader

TRAUMA RESEARCH CENTER
UNIVERSITY OF COLORADO

New Chairman

Intact Animal

Critically ill Patient

Cells & Organs

Genes & Molecules
Alden Harken

“Focus”

TRAUMA RESEARCH CENTER
DG SICU - CLINICAL CORE

Intact Animal

Critically ill Patient

Cells & Organs

Genes & Molecules
Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D., OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.

20 High Risk Torso Trauma Patients

Clinical Relevance

Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF
Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

FREDERICK A. MOORE, M.D., ERNEST E. MOORE, M.D., RENATO POGGETTI, M.D., OLIVER J. McANENA, M.D., VERLYN M. PETERSON, M.D., CHARLES M. ABERNATHY, M.D.

J Trauma 1991

20 High Risk Torso Trauma Patients
Portal Vein Catheters & Sampled Blood X 5 days

Hypothesis: bacterial translocation via portal vein is driving mechanism in MOF
Gut Bacterial Translocation via the Portal Vein: A Clinical Perspective with Major Torso Trauma

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J Trauma 1991

20 High Risk Torso Trauma Patients
Portal Vein Catheters & Sampled Blood X 5 days

Found no endotoxin or bacteria in portal vein
Back to the Drawing Board

First Hit
- Shock + Tissue Injury

Second Hit
- Vulnerable
- Protected
- Can not Resuscitate
- Early Death
- Recovery
- MULTIPLE ORGAN FAILURE
Cartoon for P-50 Trauma Center Grant

TRAUMA PRIMES CELLS

First Hit

Shock + Tissue Injury

Second Hit

MULTIPLE ORGAN FAILURE

Systemic Inflammatory Response

PRIMING

Can not Resuscitate

Early Death

PRECONDITIONING

Recovery
**The 2 Hit Hypothesis**

First Hit

- Shock + Tissue Injury

Systemic Inflammatory Response

- Can not Resuscitate
  - Early Death

Second Hit

- MULTIPLE ORGAN FAILURE

ACTIVATION

NEUTROPHIL PRIMING

PRECONDITIONING

Recovery
Lung Injury Is a Reversible Neutrophil-Mediated Event Following Gut Ischemia

Renato S. Poggetti, MD; Frederick A. Moore, MD; Ernest E. Moore, MD; Denis D. Bensard, MD; Benjamin O. Anderson, MD; Anirban Banerjee, PhD

# 5: Create clinically relevant lab model

Shock Induced Gut Ischemia Reperfusion

1st Research Fellow - Brazilian Trauma Surgeon
THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

45 Min SMA Occlusion

- Activates Gut PLA₂
- Sequesters PMN’s in Gut
- Primes Circulating PMN’s
- Sequesters PMN’s in Lung
- Causes Lung Injury

Pathophysiologic Sequence

J Trauma 1994
THE POSTISCHEMIC GUT SERVES AS A PRIMING BED FOR CIRCULATING NEUTROPHILS THAT PROVOKE MULTIPLE ORGAN FAILURE

Ernest E. Moore, MD, Frederick A. Moore, MD, Reginald J. Franciose, MD, Fernando J. Kim, MD, Walter L. Biffl, MD, and Anirban Banerjee, PhD

45 Min SMA Occlusion
- Activates Gut PLA$_2$
- Sequesters PMN’s in Gut
- Primes Circulating PMN’s
- Sequesters PMN’s in Lung
- Causes Lung Injury

Pathophysiologic Sequence

J Trauma 1994
POSTINJURY NEUTROPHIL PRIMING AND ACTIVATION STATES: THERAPEUTIC CHALLENGES

Botha AJ, Moore FA, Moore EE, Fontes B, Banerjee A, and Peterson VM:

*Shock* 1993

Abrie Botha

Pete Peterson

UK General Surgeon

Pediatric Hematologist
Postinjury neutrophil priming and activation: An early vulnerable window
Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Fernando J. Kim, MD, Anirban Banerjee, PhD, and Verlyn M. Peterson, MD, Denver, Colo.

Surgery 1995

Focused observational studies done DG SICU patients

Early Neutrophil Sequestration after Injury: A Pathogenic Mechanism for Multiple Organ Failure
Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Angela Sauaia, MD, Anirban Banerjee, PhD, and Verlyn M. Peterson, MD

J Trauma 1995

Proof of Concept

Sequential systemic platelet-activating factor and interleukin 8 primes neutrophils in patients with trauma at risk of multiple organ failure.
Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Chistopher C Silliman, MD and Verlyn M. Peterson, MD

Br J Surg 1996
Postinjury neutrophil priming and activation: An early vulnerable window
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Abraham J. Botha, MD, Frederick A. Moore, MD, Ernest E. Moore, MD, Christopher C Silliman, MD and Verlyn M. Peterson, MD

Br J Surg 1996
Early Predictors of Postinjury Multiple Organ Failure

Angela Sauaia, MD; Frederick A. Moore, MD; Ernest E. Moore, MD; James B. Haenel, RRT; Robert A. Read, MD; Dennis C. Lezotte, PhD

Arch Surg 1992

Angela Sauaia

Brazilian Internist

# 6: Develop a Clinical Database
Early Predictors of Postinjury Multiple Organ Failure

Host Factors
- Age > 55 years

Tissue Injury
- ISS > 25

Shock Indices
- Blood Transfusion > 6 units
- ED Base Deficit > 8mEq/L
- Lactate > 2.5 mmol/L after 12 hrs

ACUTE PREDICTION MODELS

Angela Sauaia
Multiple Organ Failure Can Be Predicted as Early as 12 Hours after Injury

Angela Sauaia, MD, PhD, Frederick A. Moore, MD, Ernest E. Moore, MD, Jill M. Norris, PhD, Dennis C. Lezotte, PhD
And Richard F. Hamman, MD DrPH

J Trauma 1998

ACUTE PREDICTION MODELS

Host Factors
  Age > 55 years

Tissue Injury
  ISS > 25

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  ED Base Deficit > 8mEq/L
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Validated
Multiple Organ Failure Can Be Predicted as Early as 12 Hours after Injury

Angela Sauaia, MD, PhD, Frederick A. Moore, MD, Ernest E. Moore, MD, Jill M. Norris, PhD, Dennis C. Lezotte, PhD, and Richard F. Hamman, MD DrPH

J Trauma 1998

“Win, Win” Collaboration

Denver MOF Database
Postinjury Multiple Organ Failure: A Bimodal Phenomenon

Frederick A. Moore, MD, Angela Sauaia, MD, Ernest E. Moore, MD, James B. Heanel, RRT, Jon M. Burch, MD and Dennis C. Lezotte, PhD

J Trauma 1996

Denver MOF Database

Temporal distribution of the onset of MOF

- Early MOF
- Late MOF
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

Trauma

Severe SIRS

Moderate SIRS

Early MOF

Moderate Immunosupression

Severe Immunosupression

Infections ➔ Late MOF

2nd Hits
Pulmonary Aspiration
Femur Fx Rodding
PRBC Transfusion
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

Trauma

Severe SIRS

Moderate SIRS

Early MOF

Innate Immunity

Neutrophils

Moderate Immunosupression

Severe Immunosupression

Infections ➔ Late MOF
Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS)

Roger C. Bone, MD

Ann Intern Med 1996

Roger Bone

Adaptive Immune Response
Lymphocytes

CARS

COMPENSATORY ANTI-INFLAMMATORY RESPONSE SYNDROME
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

Trauma

Severe SIRS
Moderate SIRS

Early MOF

Severe CARS
Moderate CARS

Infections

Late MOF
Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team
Hermann Hospital

UT Houston Medical School

Medical Director of Trauma 1996 to 2006
NIGMS Sponsored P-50 Trauma Center Grant (TRC)

Gut Inflammation and Ileus

Norm Weisbrodt  Frank Moody

Physiologist  Surgeon
Decreased ileal muscle contractility and increased NOS II expression induced by lipopolysaccharide (LPS).

NORMAN W. WEISBRODT, THOMAS A. PRESSLEY, YONG-FANG LI, MALGORZATA J. ZEMBOWICZ, SANDRA C. HIGHAM, ARTUR ZEMBOWICZ, ROBERT F. LODATO, AND FRANK G. MOODY

Focus: Sepsis Induced Ileus  
Am J Physiology 1996

Physiologist

Surgeon
Preparation for Intestinal Transit Studies

Unanesthetized & Unrestrained
**SMALL INTESTINAL TRANSIT**

Administer LPS or Sham

Wait at least 5 hours

1. Fluorescent Tracer into Duodenum
2. **30 min**
3. Divide Intestine into 10 equal Segments
4. Recover Tracer from each segment

---

**Sham**

- Segments 1, 2, 3, and 6 are white.
- Segments 4, 5, 7, 8, 9, and 10 are white.

**LPS**

- Segments 4, 5, 7, 8, and 9 are yellow.
- Segments 1, 2, 3, 6, 10 are white.

---

Calculate Geometric Center
Inducible Nitric Oxide Synthase Mediates Gut Ischemia/Reperfusion-Induced Ileus Only after Severe Insults

Heitham T. Hassoun, M.D.,* Norman W. Weisbrodt, Ph.D.,† David W. Mercer, M.D.,* Rosemary A. Kozar, M.D., Ph.D.,* Frank G. Moody, M.D.,* and Frederick A. Moore, M.D.,* 2

Heitham Hassoun

“Diamond in the Rough”

1st UT Research Fellow
Inducible Nitric Oxide Synthase Mediates Gut Ischemia/Reperfusion-Induced Ileus Only after Severe Insults

Heitham T. Hassoun, M.D.,* Norman W. Weisbrodt, Ph.D.,† David W. Mercer, M.D.,*
Rosemary A. Kozar, M.D., Ph.D.,* Frank G. Moody, M.D.,* and Frederick A. Moore, M.D.*.2

Role of iNOS in gut I/R induced ileus

Denver SMAO rodent model

Measured intestinal transit

Characterized gut inflammation

Different iNOS blockers

1st UT Research Fellow
# 7: Write Review Articles & Propose New Paradigms

Our “Story of Life”

Research Focus: Role of the gut in MOF
POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,* Norman W. Weisbrodt,† and Frederick A. Moore*

*Department of Surgery, † Division of Nephrology, Department of Medicine. ‡ Department of Integrative Biology, Pharmacology, and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

Bruce Kone
Chair of Medicine

David Mercer
Chief LBJ

Frank Moody
PI of P 50 grant

Norm Weisbrodt
Chair of Physiology

# 8: Align Institutional “Super Stars”
GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE

Shock

Moderate SIRS

Reperfusion

Resuscitation
Laparotomy
ICU Therapies
Disuse

↓ ↓ ↓

Blood Flow
Gastric Emptying
Small Bowel Ileus
Colonization
Permeability
Immunity

↑ ↑ ↑

Early MOF

Aspiration

Translocation

Late MOF

Infections
Toxins

Moderate CARS

Severe CARS

Moderate SIRS

Severe SIRS

Gut Ischemia

GUT DYSFUNCTION

SEPSIS
Poster Kids

NIGMS T-32 Research Training Grant

Formal Training for Translational Research

Bioethics
Statistics
Epidemiology
Clinical Trial Design
Outcomes Research

# 9: Train the next Generation to be Translational Scientists
NIGMS K-08 Grants

Chuck Cox  Rosemary Kozar  Emily Robinson

Previous UT Surgery Residents
NIGMS K-08 Grants

Chuck Cox
Rosemary Kozar
Emily Robinson

NIH Lab Training at Other Institutions
NIGMS K-08 Grants

Assistant Professors worked on the TRC Projects

Chuck Cox  Rosemary Kozar  Emily Robinson
Rosemary Kozar
Critical Care Fellow 1999

UT-Houston Surgery Resident
PhD Baylor College of Medicine
Trauma Surgeon  Hahnemann University Philadelphia,
GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE

Shock

Moderate SIRS

Early MOF

Moderate CARS

Gut Ischemia

Gut Dysfunction

Reperfusion

Resuscitation
Laparotomy
ICU Therapies
Disuse

↓↓ ↓↓ Blood Flow
↓ Gastric Emptying
↓ Small Bowel Ileus
↓↓ Immunity

↑↑ ↑↑ Colonization
↑ Permeability

Aspiration

Translocation

Infections Toxins

Late MOF

Severe SIRS

Severe CARS

SEPSIS
GUT IS THE INSTIGATOR & VICTIM OF THIS RESPONSE

Shock

Moderate SIRS

Gut Ischemia

Resuscitation
Laparotomy
ICU Therapies
Disuse

Reperfusion

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Blood Flow
↓ Gastric Emptying
Small Bowel Ileus
↑ Colonization
↑ Permeability
↓↓ ↓↓ Immunity

Aspiration
Translocation

Infections Toxins

Early MOF

Moderate CARS

GUT DYSFUNCTION

Severe SIRS

Moderate SIRS

Reperfusion

Moderate CARS

Severe CARS

Aspiration
Translocation

Late MOF

SEPSIS
ICU THERAPIES

Early Enteral Nutrition

Sedation & Analgesia

Stress Gastritis Prophylaxis
Enteral Feeding Following Major Torso Trauma: From Theory to Practice

New Horizons 1999

Margaret M. McQuiggan, MS, RD, CSM; Robert G. Marvin, MD; Bruce A. McKinley, PhD, FCCM; Frederick A. Moore, MD, FCCM

Maggie McQuiggan

ENTERAL FEEDING PROTOCOL

Background & Rationale

Patient & Formula Selection

Enteral Access

Formula Advancement

Managing GI Intolerance

Monitoring Effectiveness

ICU Dietician

Nurse Driven
### Phase I – 17 Shock Resuscitation Patients

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Early</th>
<th>Late</th>
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</thead>
<tbody>
<tr>
<td>Good</td>
<td>82 %</td>
<td>65 %</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>6 %</td>
</tr>
<tr>
<td>Poor</td>
<td>18 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Abandon EN</td>
<td>0</td>
<td>12 %</td>
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</tbody>
</table>
### Phase I – 17 Shock Resuscitation Patients

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<td>18 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Abandon EN</td>
<td>0</td>
<td>12 %</td>
</tr>
</tbody>
</table>

### Phase II - 49 Major Trauma Patients at 4 Level I Centers

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>84 %</td>
<td>80 %</td>
</tr>
<tr>
<td>Moderate</td>
<td>16 %</td>
<td>16 %</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>4 %</td>
</tr>
<tr>
<td>Abandon EN</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Nonocclusive Bowel Necrosis Occurring in Critically Ill Trauma Patients Receiving Enteral Nutrition Manifests No Reliable Clinical Signs for Early Detection

Robert G. Marvin, MD, Bruce A. McKinley, PhD, Margaret McQuiggan, RD, Christine S. Cocanour, MD, Frederick A. Moore, MD, Houston, Texas

Am J Surg 1999
Rationale for Enteral Feeding Protocol
JEJUNAL NUTRITION

Metabolic Stress

Dysmotility

Bacterial Colonization

Increased Energy Demand

Distention

Intraluminal Toxins

Microvascular Ischemia

Mucosal Injury Local Inflammation

NONOCCLUSIVE BOWEL NECROSIS
JEJUNAL NUTRITION

Metabolic Stress

Increased Energy Demand

Microvascular Ischemia

Dysmotility

Distention

Bacterial Colonization

Intraluminal Toxins

Mucosal Injury Local Inflammation

NONOCCLUSIVB BOWEL NECROSIS
# 8: Align Institutional “Super Stars”

Use Senior Scientists as Mentors

Acting Dean of Medical School

Expert on GI Epithelial Transport
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>ATP Consumed With Absorption</th>
<th>Can be Used by Cell to Produce ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Yes</td>
<td>Yes, aerobic &amp; anaerobic</td>
</tr>
<tr>
<td>Fructose</td>
<td>No</td>
<td>Yes, aerobic &amp; anaerobic</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Yes</td>
<td>Yes, aerobic only</td>
</tr>
<tr>
<td>Alanine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Arginine</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Create Jejunal Sacs

Fills Them With

1. Mannitol  (Osmotic Control)
2. Glucose
3. Fructose
4. Glutamine
5. Alanine
6. Arginine

SMAO Model
45 min ischemia
30 min reperfusion
Deconvolution Microscopy

**Glucose**
- ATP Consumer: +
- Aerobic: +

**Fructose**
- ATP Producer: +
- Anaerobic: +

**Glutamine**
- ATP Producer: +
- Aerobic: +
- Anaerobic: -
Deconvolution Microscopy

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>Alanine</th>
<th>Arginine</th>
</tr>
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<tbody>
<tr>
<td>ATP Consumer</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ATP Producer</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aerobic</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Anaerobic</td>
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<td>-</td>
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The Type of Sodium-Coupled Solute Modulates Small Bowel Mucosal Injury, Transport Function, and ATP After Ischemia/Reperfusion Injury in Rats

ROSEMARY A. KOZAR,* STANLEY G. SCHULTZ,† HEITHAM T. HASSOUN,* ROLAND DESOIGNIE,* NORMAN W. WEISBRODT,† MARIAN M. HABER,‖ and FREDERICK A. MOORE*
The Type of Sodium-Coupled Solute Modulates Small Bowel Mucosal Injury, Transport Function, and ATP After Ischemia/Reperfusion Injury in Rats

Gastroenterology 2002

ROSEMARY A. KOZAR,* STANLEY G. SCHULTZ,† HEITHAM T. HASSOUN,* ROLAND DESOIGNIE,* NORMAN W. WEISBRODT,† MARIAN M. HABER,‖ and FREDERICK A. MOORE*

Norio Sato

Research Fellow
INJURIOUS PRO-INFLAMMATION

Gut I/R

AP-1   NFkB

iNOS

PMN Influx & Injury
ENTERAL FORMULA SUPPLEMENTED WITH

Glutamine

Arginine

Nucleotides

Omega-3 fatty acids

CLINICAL BENEFITS OF AN IMMUNE-ENHANCING DIET FOR EARLY POSTINJURY ENTERAL FEEDING

Frederick A. Moore, MD, a Ernest E. Moore, MD, a Kenneth A. Kudsk, MD, b Rex O. Brown, PharmD, b Robert H. Bower, MD, c Mark J. Koruda, MD, d Christopher C. Baker, MD, d and Adrian Barbul, MD e

J Trauma 1994
ENTERAL FORMULA SUPPLEMENTED WITH
- Glutamine
- Arginine
- Nucleotides
- Omega-3 fatty acids

Protected

Injurious

CLINICAL BENEFITS OF AN IMMUNE-ENHANCING DIET FOR EARLY POSTINJURY ENTERAL FEEDING

Frederick A. Moore, MD, a Ernest E. Moore, MD, a Kenneth A. Kudsk, MD, b Rex O. Brown, PharmD, b Robert H. Bower, MD, c Mark J. Koruda, MD, d Christopher C. Baker, MD, d and Adrian Barbul, MD e

J Trauma 1994
HOW DO GLUTAMINE AND ARGinine MODULATE Gut I/R?

- PPAR
- AP-1
- NFKB
- iNOS
- HO - 1
- PMN Influx & Injury
GLUTAMINE INDUCES PPAR AND HAS NO EFFECT ON HO-1

Gut I/R

↑ PPAR

↑ AP-1

↑ NFκB

↓ iNOS

↓ PMN Influx & Injury

HO - 1
ARGinine inhibits PPAR and has no effect on HO-1

Gut I/R

↓ PPAR

↓ AP-1

↑ iNOS

↑ PMN Influx & Injury

HO - 1

NFκB

↑ iNOS
Differential Induction of Transcription Factor AP-1

Gut I/R

↑ PPAR

↑ AP-1

NFκB

Ho - 1

Novel Mechanism

↓ iNOS

↓ PMN Influx & Injury
Differential Induction of Transcription Factor AP-1

Gut I/R

↓ PPAR

↓ AP-1

↑ iNOS

↑ PMN Influx & Injury

Novel Mechanism
Differential induction of PPAR-γ by luminal glutamine and iNOS by luminal arginine in the rodent postischemic small bowel

N. Sato,^1^ F. A. Moore,^1^ B. C. Kone,^2^ L. Zou,^2^ M. A. Smith,^1^ M. A. Childs,^1^ S. Moore-Olufemi,^1^ S. G. Schultz,^3^ and R. A. Kozar^1^

Norio Sato

Funded R-01 Grant - 2007

Glutamine activates PPAR γ via the LOX pathway

Arginine inhibits PPAR γ via the c-jun pathway
Enteral Glutamine During Active Shock Resuscitation Is Safe and Enhances Tolerance

Margaret McQuiggan, MS, RD; Rosemary Kozar, MD, PhD; R Matthew Sailors; Chul Ahn, PhD; Bruce McKinley, PhD; and Frederick A. Moore, MD

Translational Research Project
Pilot Validation Study
Prospective & Randomized
**Enteral Feeding Protocol**  
Started After Shock Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Early Glutamine (n=10)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Intolerance Episodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>High nasogastric output</td>
<td>5</td>
<td>23             *</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>3</td>
<td>12             *</td>
</tr>
<tr>
<td><strong>Total instances of intolerance</strong></td>
<td>8</td>
<td>42             *</td>
</tr>
<tr>
<td><strong># Patients requiring TPN PID #7</strong></td>
<td>0</td>
<td>4              *</td>
</tr>
</tbody>
</table>

* p < 0.05
The Methodist Hospital (TMH)

Chief of Acute Care Surgery 2006 - 2011
March 1, 2004

H. Gill Cryer, M.D., President
American Association for the Surgery of Trauma (AAST)
Gregory J. Jurkovich, M.D., Chairman
AAST Committee for the Speciality of Trauma, Surgical Critical Care and Emergency Surgery
UCLA Medical Center
Department of Surgery
10833 Le Conte Avenue, CHS 72-178
Los Angeles, CA 90095

Dear Gill and Greg:

I apologize for the very slow response to your letter of December 23 but your request has led to a great deal of discussion within the Board both during our January Meeting and in the period subsequently on a more informal basis. Your request for an Advisory Council to represent Trauma and Critical Care has stimulated a broader discussion of the general procedure for evolving new Advisory Councils in other areas, and has pointed out the need for us to have some specific guidelines for dealing with this on a continuing basis. At the January Meeting, the Board adopted a resolution to become more heavily involved in the oversight of post-residency fellowships and the development of Advisory Councils in various areas will be a part of this entire plan. Chairman Ron Maier is appointing a group of Directors who will specifically meet to formulate guidelines for this in the next several weeks and then bring this issue back to the Board at its meeting in June. Hopefully, they will be in a position to be adopted at that time, so we can go forward with the creation of additional Advisory Councils. I think it is extremely likely that an Advisory Council in the area of Trauma, Critical Care, and Emergency Surgery will be created once these guidelines are formulated. At that time, we would look forward to sitting down with representatives of the AAST to determine the specifics of that structure.

In the meantime, I urge you to consider within your organization the way in which trauma surgery, surgical intensive care, and emergency surgery can be combined, and how each of these areas should be represented within the structure of the American Board of Surgery. Although each is closely related to the other, they are not synonymous, and our current processes for issuing certificates in Surgical Critical Care do not entirely meet the needs of the other two areas. If the AAST could help with the development of a cohesive plan for integrating and addressing these it would be helpful to the Board as well.

If you want to discuss this further, please give me a call at any time. The Board is entirely sympathetic with your request and looks forward to entering into a productive dialogue in order to move the issue forward.

Sincerely,

Frank R. Lewis, Jr., M.D.
Executive Director
Division of Surgical Critical Care and Acute Care Surgery

Joe Sucher  Krista Turner  Laura Moore  Rob Todd
Barbara asked: “what is going to be your research focus”
# Sepsis in general surgery: a deadly complication

Laura J. Moore, M.D., Frederick A. Moore, M.D., Stephen L. Jones, M.D., Jiaqiong Xu, Ph.D., Barbara L. Bass, M.D.

*Am J Surg* 2009

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>30-Day Mortality</th>
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</thead>
<tbody>
<tr>
<td><strong>n=363,897 Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Sepsis</td>
<td>96.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.3%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Severe Sepsis/Shock</td>
<td>1.6%</td>
<td>34%</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>0.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.2%</td>
<td>32%</td>
</tr>
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</table>

NSQIP 2005-2007 Database Analysis General Surgery
# Sepsis in general surgery: a deadly complication

Laura J. Moore, M.D., Frederick A. Moore, M.D., Stephen L. Jones, M.D., Jiaqiong Xu, Ph.D., Barbara L. Bass, M.D.

Am J Surg 2009

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<th>Condition</th>
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</thead>
<tbody>
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NSQIP 2005-2007 Database Analysis General Surgery
Do The Math

<table>
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<tr>
<th>Condition</th>
<th># Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>8,350</td>
</tr>
<tr>
<td>Severe Sepsis/ Shock</td>
<td>5,977</td>
</tr>
<tr>
<td>PE</td>
<td>1,078</td>
</tr>
<tr>
<td>MI</td>
<td>615</td>
</tr>
</tbody>
</table>
# Cases

- Sepsis: 8,350 cases
- Severe Sepsis: 5,977 cases
- PE: 1,078 cases
- MI: 615 cases

# Deaths

- Sepsis: 449 deaths
- Severe/Shock: 2,012 deaths
- PE: 98 deaths
- MI: 193 deaths
Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis*

Mitchell M. Levy, MD; R. Phillip Dellinger, MD; Sean R. Townsend, MD; Walter T. Linde-Zwirble; John C. Marshall, MD; Julian Bion, MD; Christa Schorr, RN, MSN; Antonio Artigas, MD; Graham Ramsay, MD; Richard Beale, MD; Margaret M. Parker, MD; Herwig Gerlach, MD, PhD; Konrad Reinhart, MD; Eliezer Silva, MD; Maurene Harvey, RN, MPH; Susan Regan, PhD; Derek C. Angus, MD, MPH; on behalf of the Surviving Sepsis Campaign

IHI Surviving Sepsis Campaign

Audit of Compliance and Effect on Mortality

(15,002 patients at 166 hospitals over 2 year implementation)
Compliance 6 hr Resuscitation Bundle = 12 %
Compliance 24 hr management Bundle = 18 %
Compliance 6 hr Resuscitation Bundle = 12 %  \rightarrow  32 %
Compliance 24 hr management Bundle = 18 %  \rightarrow  37 %

Percent

Resuscitation
Management
Mortality

Quarter
1 2 3 4 5 6 7 8

37% 31%
2/3 of patients did not receive evidence based care
Surviving Sepsis Campaign Guidelines 2008

Grades of Evidence

Grade 1A
- Vent Weaning SBT Protocol
- DVT/PUD Prophylaxis
- No Renal Dose Dopamine
- No High Dose Steroids

Grade 1B
- Broad Spectrum Antibiotics within 1 hour
- Conservative Transfusions
- IV Insulin Therapy
- Sedation Protocol
- Avoid Bicarbonate
- ALI Vent Protocol

Grade 1C
- Early Goal Directed Therapy
- Cultures prior to antibiotics
- Early Source Identification
- De-escalate antibiotic Rx
- Norepinephrine or Dopamine

Grade 1D
- Source Control within 6 hours
- Fluid Challenge for Hypovolemic
- Limit Antibiotics to 7-10 days
- Consider Limiting Support

19 Recommendations
Difficult to Remember and Prioritize 19 Recommendations

Information overload !!!
Difficult to Remember and Prioritize 19 Recommendations

Information overload !!!

This may be a physician extender
Computerized Clinical Decision Support (CCDS)

Potential Solution for this Dilemma

This may be a physician extender
Computerized Decision Support for Mechanical Ventilation of Trauma Induced ARDS: Results of a Randomized Clinical Trial

Bruce A. McKinley, PhD, Frederick A. Moore, MD, R. Matthew Sailors, PhD, Christine S. Coganour, MD, Alicia Martinez, RN, Roberta K. Wright, RRT, Alan S. Tennesen, MD, C. Jane Wallace, RN, PhD, Alan H. Harris, MD, and Thomas D. East, PhD

Bruce McKinley

Bioengineer

Matt Sailors

Informatics Expert
Computerized Clinical Decision Support (CCDS)
Proof of Concept

Mechanical ventilation of ARDS

Shock resuscitation

ICP management

Surviving Sepsis Campaign
DEVELOPMENT PROCESS

- Domain Expert
- Consensus Group
- Published References

Me

Knowledge Engineering

Algorithms

Knowledge Base

Matt

Programmer

User Training (Classroom & Bedside)

Clinical Use at Bedside

- Prototypes for Testing
- Feedback to Knowledge Base Creators
- Feedback to Programmer

Bedside Testing of Knowledge Base

Formal Testing of Knowledge Base
Fellow Using CCDS Application: Open Loop System

#10: Use CCDS to Control Confounding Variable Care
Difficulty in Diagnosis
Early Signs are not Recognized

A change in mental status: acute delirium

Hyperventilation: respiratory alkalosis

Hypotension & ↓ urine output: need for fluid bolus

Fever or hypothermia (especially in the elderly)
Validation of a Screening Tool for the Early Identification of Sepsis

Laura J. Moore, MD, Stephen L. Jones, MD, Laura A. Kreiner, MD, Bruce McKinley, PhD, Joseph F. Sucher, MD, S. Rob Todd, MD, Krista L. Turner, MD, Alicia Valdivia, RN, and Frederick A. Moore, MD

J Trauma 2009

Sepsis Screening Champion
% MORTALITY
Severe Sepsis/Septic Shock

Methodist SICU

- 2006 Pre: 35%
- 2007 Paper Protocol: 24%
- 2008 Paper Protocol: 23%
- 2009 CCDS Protocol: 14%
- NSQIP: 34%
- SSC 8th QTR: 31%
Linc Moldawer PhD

Dr NIH Inflammation
Strategies For Translational Research

Trauma Research: Historic Perspective

Performing Translational Research

Creating a Translational Research Team

PICS – the New Predominant Phenotype of MOF
Epidemiology of MOF has again changed
2nd Peak in MOF Disappeared *(Why?)*

The Changing Pattern and Implications of Multiple Organ Failure after Blunt Injury With Hemorrhagic Shock

Denver MOF Database

Arch Surg 2005

Glue Grant Database

Crit Care Med 2012
Recognition That Traditional ICU Care is Harmful

High Tidal Volume Mechanical Ventilation
Liberal Blood Transfusion Practices
High Volume Crystalloid Resuscitation
Intermittent Dialysis
Early TPN

Late MOF/Deaths are iatrogenic
More Consistent Implementation of Evidence Based Care

IHI Surviving Sepsis Campaign

Our CCDS for Early Sepsis Management

Glue Grant Experience of Increasing SOP Compliance
Benchmarking Outcomes in Critically Injured Trauma Patients

Joseph Cuschieri, MD; Jeffery L. Johnson, MD; Jason Sperry, MD; Michael A. West, M, PhD; Ernest E. Moore, MD; Joseph P. Minei, MD; et.al and the Inflammation and Host Response to Injury Large Scale Collaborative Research Program.

Ann Surg in press

Decreasing Mortality with Increasing Compliance to SOPs

Driven By Quarterly Audits & Feedback

Mortality Rate (%) against Study Year from 2005 to 2009.
CARS is not Compensatory
Basic Lab Observations

Circulating Cytokine/Inhibitor Profiles Reshape the Understanding of the SIRS/CARS Continuum in Sepsis and Predict Mortality

Marcin F. Osuchowski, Kathy Welch, Javed Siddiqui, Daniel G. Remick

J Immunology 2006

Simultaneous Pro- & Anti-inflammation

Block Pro-inflammation & Improve Mortality
CARS is not Compensatory
Basic Lab Observations

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Marcin F. Osuchowski, Kathy Welch, Javed Siddiqui, Daniel G. Remick

J Immunology 2006

Simultaneous Pro- & Anti-inflammation
Block Pro-inflammation & Improve Mortality

But has no Effect on Anti-inflammation & CARS
Glue Grant Hypothesis Tested in Humans

SIRS - Excessive Innate Immune Response

CARS – Suppression Adaptive Immune Response

Looking at the Genomic Response After Severe Blunt Trauma
A Genomic Storm – 75% of Genes Up or Down Regulated

A. Heat Map of Gene Expression After Severe Trauma
A Genomic Storm – 75% of Genes Up or Down Regulated

A. Heat Map of Gene expression After Severe Trauma

B. Up-regulated Innate Immunity
- Integrin signaling
- Leukocyte extravasation
- FcγReceptor mediated phagocytosis
- IL-10 signaling
- Toll-like receptor signaling
- Ephrin Receptor signaling
- IL-6 signaling
- TREM1 signaling
- Actin Cytoskeleton signaling
- B cell receptor signaling

C. Down-regulated Adaptive Immunity
- Ca²⁺ T cell apoptosis
- iCOS-iCOSL signaling in T cells
- CTLA4 signaling in CD8 T cells
- CD28 signaling in T cells
- T cell receptor signaling
- CD8 T cell mediated apoptosis
- Role of NFAT in immune response
- IL-4 signaling
- Primary immunodeficiency signaling
- Purine Metabolism
**Significant Findings**

The SIRS/CARS phenomenon cannot be confirmed.

There is no evidence of a 2\(^{nd}\) hit

Exaggerated and prolonged expression of genes involved in both innate and adaptive immunity discriminates complicated outcome

Simultaneous pro- & anti-inflammation
NEW PHENOTYPE OF MOF EMERGES?

Prolonged ICU stays

Manageable Organ Dysfunctions & no Overt Late MOF

Recurrent Infections (i.e. Hits) with Milder SIRS
NEW PHENOTYPE OF MOF EMERGES?

- Prolonged ICU stays
- Manageable Organ Dysfunctions & no Overt Late MOF
- Recurrent Infections (i.e. Hits) with Milder SIRS
- Persistent Acute Phase Response & ↓↓ # Lymphocytes
- Decreased Lean Body Mass – a Wasting Disease
NEW PHENOTYPE OF MOF EMERGES?

Prolonged ICU stays

Manageable Organ Dysfunctions & no Overt Late MOF

Recurrent Infections (i.e. Hits) with Milder SIRS

Persistent Acute Phase Response & ↓↓ # Lymphocytes

Decreased Lean Body Mass – a Wasting Disease

Poor Wound Healing & Decubitus Ulcers

Transfer to LTACs for Indolent Deaths
Induction of myeloid-derived suppressor cells (MDSC)

- Released from bone marrow after inflammatory insults
- Immature innate immune cells
- Poor antigen presentation but cause inflammation
Induction of myeloid-derived suppressor cells (MDSC)

Released from bone marrow after inflammatory insults

Immature innate immune cells

Poor antigen presentation but cause inflammation

Express arginase 1 which depletes arginine

Suppress T-cell responses that require arginine
A Novel Regulatory Cell Population
Myeloid Derived Suppressor Cells (MDSCs)

Historically referred to as “natural suppressor cells”

Arise with chronic inflammation and immunologic stress

Highly conserved response to various inflammatory insults
**Insults that promote MDSC expansion**
- Injury
- Infection
- Tumor Growth
- Inflammation

**Factors that promote MDSC expansion**
- G/M/GM-CSF
- SCF
- IL-1β
- IL-6
- IL-10
- IL-12
- IL-13
- IL-17
- S100A8/9
- Prostaglandins
- VEGF
- SAA
- CCL2

**Hemopoietic Stem Cells**
- Released from Bone Marrow & Populate Other Hemopoietic Organs

**Granulocytes**

**Macrophage**

**Dendritic Cell**

**Common Lymphoid Progenitor**

**Common Myeloid Progenitor**

**Myeloid derived suppressor cells**
A. Clinical Response

Pro-Inflammation

Anti-Inflammation

Early innate immunity

Chronic Low Grade Inflammation

Fulminant death

Early MOF

Insult

SIRS

PICS

CARS

Persistant Inflammation

Protein Catabolism/Cachexia

Recovery

Indolent Death

Persistent Inflammatory/immunosuppression Catabolism Syndrome (PICS)
Pro-Inflammation

A. Clinical Response

Early innate immunity

Chronic Low Grade Inflammation

Fulminant death

Early MOF

B. Individual Cell Response

Macrophage Activation

TRegs

MDSCs

Dendritic Cells

T Effector Cell Number and Function

Protein Catabolism/Cachexia

Defects in Adaptive Immunity

Persistent Inflammation

Persistent Inflammation

Recovery

Insult

CARS

SIRS

PICS

Indolent Death
A. Clinical Response

- Insult
- Pro-Inflammation
- Anti-Inflammation

Early innate immunity → Chronic Low Grade Inflammation

- SIRS
- PICS
- Persistent Inflammation
- Protein Catabolism/Cachexia

Early MOF → Fulminant death → Indolent Death

Changes in Cell Populations:
- Macrophage Activation
- Macrophage Paralysis
- TRegs
- MDSCs
- Dendritic Cells
- T Effector Cell Number and Function
Potential PICS Patients

Persistent Inflammatory Hits

Burns ( > 30 % BSA )

Smoldering surgical sepsis

Necrotizing pancreatitis

Severe blunt trauma ( ISS > 25 )

Major surgery complicated by sepsis
Clinical Determinants of PICS

- **Persistent**
  - Prolonged hospitalization > 14 days
- **Inflammation**
  - C-reactive protein > 150 μg/dl
- **Immunosupression**
  - Total lymphocyte count < 800/mm³
- **Catabolism**
  - Weight loss of > 10% during hospitalization or BMI < 18
  - Creatinine Height Index < 80%
  - Albumin < 3.0 gm/dl
  - Pre-albumin < 10 mg/dl
  - Retinol binding protein < 10 μg/dl
<table>
<thead>
<tr>
<th>Clinical Determinants of PICS</th>
<th>Research or Laboratory Methodologies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persistent</strong></td>
<td><strong>Inflammation</strong></td>
</tr>
<tr>
<td>- Prolonged hospitalization &gt;14 days</td>
<td>- Luminex™ for cytokine concentrations- IL-6, IL-10, IL-1ra, procalcitonin</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>- Leukocyte genome expression patterns, e.g. ARG1, NOS2, IL-1RA, SILR2, MMP8, MMP9, MMP2</td>
</tr>
<tr>
<td>- C-reactive protein &gt; 150 μg/dl</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosupression</strong></td>
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</tr>
<tr>
<td>- Total lymphocyte count &lt; 800/mm³</td>
<td>- ‘Paralyzed Monocyte’</td>
</tr>
<tr>
<td><strong>Catabolism</strong></td>
<td>- Reduced ex vivo cytokine production</td>
</tr>
<tr>
<td>- Weight loss of &gt;10% during hospitalization or BMI &lt; 18</td>
<td>- Reduced HLA-DR expression</td>
</tr>
<tr>
<td>- Creatinine Height Index &lt; 80%</td>
<td>- Reduced phagocytosis</td>
</tr>
<tr>
<td>- Albumin &lt; 3.0 gm/dl</td>
<td>- Anergy or Exhausted T cell</td>
</tr>
<tr>
<td>- Pre-albumin &lt; 10 mg/dl</td>
<td>- Expression of suppressor molecules, e.g. PDL-1, CTLA-4, BTLA, HVEM</td>
</tr>
<tr>
<td>- Retinol binding protein &lt; 10 μg/dl</td>
<td>- Reduced T-cell proliferation</td>
</tr>
<tr>
<td></td>
<td>- $T_{H2}$ polarization</td>
</tr>
<tr>
<td></td>
<td>- Increased Treg numbers and suppressor activity</td>
</tr>
</tbody>
</table>
Summary

Myeloid derived suppressor cells drive persistent inflammation & catabolism that characterizes PICS

Better understand these cells & how to modulate them

Understand how co-morbid conditions contribute to PICS

Embrace early immunonutrition

Develop strategies for anabolic nutrition
Conclusion
Strategy # 1

Translational research needs to be a core value

Create the Culture

Thank You Dr Eiseman
Conclusion

Strategy #2

Pick a Topic and Stick with it

I have been studying MOF for over 25 years
Conclusion

Strategy # 2

Pick a Topic and Stick with it

and the story just gets better as the syndrome evolves
Conclusion
Strategy # 3
Draw cartoons and generate “win:win” hypotheses

Figure 1
Gut: The Starter for MOF
Liver: The Motor for MOF

Shock

Endotoxin
Bacteria

Gut

Kupffer Cell

Liver

PGE_2 =

C_3a, C_5a

IL-1 =

TNF

O_2

ATN

ARDS

Injured Tissue

Delayed Enteral Feeding

Immune

Stress

Thank You Gene
Conclusion
Strategy # 4

Be a Cheer Leader and Focus on Your Patients

Intact Animal

Critically ill Patient

Cells & Organs

Genes & Molecules

Thank You Dr Harken
Conclusion
Strategy # 5
Create clinically relevant lab models

Pathophysiologic Sequence

Denver SMAO Model

Thank you Renato
Conclusion
Strategy # 6

Develop a clinical database & study epidemiology

Denver MOF Database

Thank You Angela
Conclusion
Strategy # 7

Write review articles & propose new paradigms

POST-INJURY MULTIPLE ORGAN FAILURE: THE ROLE OF THE GUT

Heitham T. Hassoun,* Bruce C. Kone,† David W. Mercer,* Frank G. Moody,* Norman W. Weisbrodt,‡ and Frederick A. Moore*

Department of Surgery, †Division of Nephrology, Department of Medicine, ‡Department of Integrative Biology, Pharmacology and Physiology, University of Texas-Houston Medical School, Houston, Texas 77030

The Role of the Gut in Late MOF

Thank You Heitham
Conclusion
Strategy # 8

Develop “win, win” research relationships

Foreign research fellows

Institutional “super stars”

Use senior scientists as mentors

Too Many to Thank
I call it this the “alignment of the stars”

Surround yourself with smart people who think differently
Conclusion
Strategy # 9

Train the next generation to be translational scientists

Formal Didactics
- Bioethics
- Statistics
- Epidemiology
- Clinical Trial Design
- Outcomes Research

Basic Laboratory Studies
- Critical Thinking
- Hypothesis Driven Research

Thank You David
Conclusion
Strategy # 10

Use CCDS to control confounding effect of variable care

Thank You Bruce
“The connection between cause and effect has no beginning and can have no end.”

Leo Tolstoy
War and Peace
“The connection between cause and effect has no beginning and can have no end.”

Leo Tolstoy
War and Peace

“Imagination is more important than knowledge.”

Albert Einstein
Growing PICS Research Team at UF