Postinjury Multiple Organ Failure

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John Hunter Hospital
Newcastle
AUSTRALIA
ARDS  Ashbaugh & Petty  1970
EDITORIAL

MULTIPLE, PROGRESSIVE OR SEQUENTIAL SYSTEMS FAILURE
A Syndrome of the 1970’s

Arch Surg 1975
MULTIPLE ORGAN FAILURE

Ben Eiseman

42 ICU Patients at Denver General
- Big Hit → Resuscitate
- Tranquil Period for Several Days
- Pathologic “Domino-Effect” of MOF

Risk Factors
- Pre-existing Disease
- Shock
- Sepsis

SGO 1977
MOF OCCURS AS A RESULT OF UNCONTROLLED INFECTION

Abdominal Infection (50%)
Eiseman SGO 1977
Polk Surgery 1977
Fry Arch Surg 1980

USA “Knife and Gun Clubs”

? MOF → “Blind Lap”
MOF IN POLYTRAUMA PATIENTS

Eugene Faist

433 Trauma Patients from Munich
Multiple Injuries - 99% Blunt Mech
34 (8%) MOF → 19 (56%) Died

Early MOF
Massive Shock/Tissue Injury
Can Not Resuscitate

Late MOF
Shock/Tissue Injury
Resuscitated → ? MOF
Delayed Sepsis → MOF

J Trauma 1983
MOF OCCURS AS A RESULT OF AUTODESTRUCTIVE INFLAMMATION

Jan Goris

92 “SEPTIC” MOF PATIENTS

55 Trauma (All Blunt)
24 (44%)

37 Non-Trauma (GI Problems)
7 (19%)

No Focus of Infection Found at Autopsy

Arch Surg 1985
SYSTEMIC INFLAMMATORY RESPONSE

Infection
Tissue Injury
Shock
Pancreatitis
Limb Ischemia

SIRS
MOF
Die
Recover

“SEPSIS SYNDROME”
BACTERIAL TRANSLOCATION

“Passage of Viable Bacteria Through the Intact Mucosa of the GI Tract to MLNs and Other Organs”

Edwin A. Deitch

Important Factors
- Bacteria
- Physical Barrier
- Mucosal Immunity

Primary Insults → BT to MLNs
- Shock
- Burns
- Endotoxin

Pre-conditioners → Amplify BT
- Malnutrition
- Antibiotic
- Bowel Rest
- To Liver
- Spleen & Systemic Blood

J Trauma 1985
PORTAL VEIN SURVEILLANCE

20 Severely Injured Patients
11 Massive Transfusions
6 Major Abdominal Trauma
3 Multiple Pelvic & Extremity Fractures

6 Developed MOF \[\rightarrow\] 3 Died
PORTAL & SYSTEMIC BLOOD
Sampled at 0, 6, 12, 24, 48, 128 hrs

Blood Cultured

Blood Assayed
Endotoxin
Tumor Necrosis Factor
Interleukin-6
Complement $C_{3a}$
OUTLINE

• Definition
• The Problem
• History
• Epidemiology
• Predictors
• Prevention and Treatment strategy
• Future directions
BLOOD CULTURE RESULTS

Portal Cultures: 4% Positive
- 5 Coagulase Neg Staph
- 2 Propianibacterium Acnes
- 1 Acinobacter

Systemic Cultures: 0.5% Positive
- 1 Staph. Aureus
Tissue Injury

• Major
  - Enough itself to change homeostasis

• Minor
  - Not enough itself
  - Special injured area + physiologic response
Response to Major Trauma

- **SHOCK phase**: hypoperfusion, acute dysfunction
- **RESUS phase**: whole body I/R
- **SIRS phase**: hypermetabolic state
- **MOF phase**: result of over-activated and/or dysfunctional inflammation
Ringer's lactate
# Denver MOF Scale*

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Pulmonary**</td>
<td>P/F &gt; 250</td>
<td>P/F 250-175</td>
<td>P/F 175-100</td>
<td>P/F &lt; 100</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Renal</td>
<td>Normal Cr &lt; 160</td>
<td>Cr &gt; 160</td>
<td>Cr &gt; 220</td>
<td>Cr &gt; 450</td>
</tr>
<tr>
<td>C. Hepatic</td>
<td>Normal T Bili &lt; 35</td>
<td>T Bili &gt; 35</td>
<td>T Bili &gt; 70</td>
<td>T Bili &gt; 140</td>
</tr>
<tr>
<td>D. Cardiac</td>
<td>No Inotropes</td>
<td>Minimal Inotropes (&lt;5)</td>
<td>Moderate Inotropes (5-15)</td>
<td>High Inotropes (&gt;15)</td>
</tr>
</tbody>
</table>

**Organ Failure Score** = A+B+C+D

MOF = Score > 3

POSTINJURY PMN APOPTOSIS

APOPTOTIC INDEX (%)

CTRL 0 1 2 3 4 5

POSTINJURY DAY

*
PMN APOPTOSIS AND INJURY SEVERITY

$r = -0.607$  
$p < 0.05$
HIGH RISK PATIENTS

Aptoptotic Index
MOF: $8 \pm 1$
No MOF: $27 \pm 6$

Aptoptotic Index Independently Predictive of MOF ($p=0.08$)
GASTRIC REGIONAL PCO$_2$

![Graph showing time course of PrCO$_2$ with two lines: one for ARDS/MOF (N=12) and one for NO ARDS/MOF (N=22). The graph includes error bars.]

**PrCO$_2$ (mmHg)**

TIME (hr)

0 4 8 12 16 20 24 28 32 36
Polytrauma Patients’ Inflammatory Markers 1-11 days from Injury

![Graph showing IL-6 and Control levels over 11 days.](image)
Polytrauma Patients’ Inflammatory Markers 1-11 days from Injury

ng/mL

- IL-8
- Control

0 0.1 0.2

1 2 3 4 5 7 9 11

days
<table>
<thead>
<tr>
<th></th>
<th>MOF + death</th>
<th>OF / MOF</th>
<th>No MOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>11</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>ISS</td>
<td>43</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Age</td>
<td>45</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>SBP&lt;90</td>
<td>36%</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>U of Blood</td>
<td>9</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Vent days</td>
<td>20</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Worst PO$_2$/FiO$_2$</td>
<td>134</td>
<td>181</td>
<td>289</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>20</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.8</td>
<td>5.0</td>
<td>3.1</td>
</tr>
<tr>
<td>A-III % of norm</td>
<td>49</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>Elastase</td>
<td>221</td>
<td>217</td>
<td>117</td>
</tr>
<tr>
<td>IL-6 (12 hours)</td>
<td>1969</td>
<td>703</td>
<td>177</td>
</tr>
<tr>
<td>IL-8 (12 hours)</td>
<td>1602</td>
<td>1101</td>
<td>301</td>
</tr>
</tbody>
</table>
Time Pattern of Post-Injury MOF

# MOF CASES

DAYS AFTER ADMISSION

3 4 5 6 7 8 9 10 11 12 13 >13
Polytrauma Patients’ IL-6 Concentration

- Early and Late MOF
- Early MOF
- Late MOF
- No MOF

(pg/mL)

A 24h 48h 3 4 5 6 7 8 9 10 11 12 13 14 days
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

TRAUMA

Tissue Injury
Shock
Host Factors
Second Hits

Severe SIRS
Moderate SIRS
Moderate CARS
Severe CARS

ALI → Early MOF

Infections → Late MOF
Bimodal Phenomenon

1. Refractory Shock
2. SIRS $\rightarrow$ Early MOF
3. Infections $\rightarrow$ Late MOF
ACUTE PREDICTION MODELS

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 of resuscitation

Second Hits
SECOND HITS

- Bad timing
- Transfusions
- Operations
- Diagnostics
- Transfusions
- Infections
- Complications
THE AGE OF THE TRANSFUSED BLOOD AND MOF

N = 513
MOF = 85

MTT 2001
N = 513
MOF = 85

Age of the blood ~ MOF risk

MTT 2001
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

TRAUMA

Severe SIRS → ALI → Early MOF
Moderate SIRS

Moderate CARS

Tissue Injury
Shock
Host Factors
Second Hits

Severe CARS

Infections → Late MOF
Trauma Deaths (%)

- Prehospital: 50%
- 0-48 hours: 30%
- 2-7 days: 5%
- >7 days: 10%

San Francisco 1977
O.K. But what to do with the patient?

1. Is the patient high risk for MOF?

2. Does the patient have massive immune response?

3. Is the patient high-risk for second hits?
O.K. But what to do with the patient?

- Identify the risk (Tissue injury, Shock, Age)
- Monitor inflammatory response (IL-6, IL-8)
- Those who met with these:
  - Neutrophil elastase >85 ng/mL
  - Platelet count <180,000 /μL
  - CRP >11mg/dL

For Planned Interventions
Met inclusion criteria

On ICU admission:
- art, PA, NG tonometer catheters
- baseline ABG, Hb, lactate

DO$_2$I goal

Monitor:
- lactate, BD, PrCO$_2$
- bladder pressure Q 4h (reassess sooner if abnormal)

24 hours?

No

1) Hb (PRBC; Hb > 10 g/dL)
2) volume (LR; PAWP > 15 mmHg)

Yes

3) Optimize CI - PAWP (Starling curve)

Yes

4) low dose inotrope
5) vasopressor

Echo cardiography

No

stop resuscitation standard ICU care
Timeframes (%)

- Prehospital
- 0-48 hours
- 2-7 days
- >7 days

San Francisco 1977
San Diego 1987
<table>
<thead>
<tr>
<th></th>
<th>1º ACS</th>
<th>2º ACS</th>
<th>Non ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOF (%)</td>
<td>55</td>
<td>53</td>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>64</td>
<td>53</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<0.05 non ACS vs primary or secondary ACS

ACS is an independent risk factor for:

- MOF: odds ratio = 9.2
  95% confidence intervals: 3.8 - 22.8

- Mortality: odds ratio = 8.4
  95% confidence intervals: 3.5 - 20.6
POSTINJURY MOF OCCURS AS A RESULT OF A DYSFUNCTIONAL INFLAMMATORY RESPONSE

TRAUMA

Severe SIRS ➔ ALI ➔ Early MOF

Moderate SIRS

Tissue Injury
Shock
Host Factors
Second Hits

Moderate CARS

Infections ➔ Late MOF

Severe CARS
TIMING IS EVERYTHING

• The early vulnerable window of PMNs
  » Botha et al. Surgery 1995

• Amplified cytokine response after ACS compared to shock alone
  » Oda et al. J Trauma 2002

• ACS occurs between 6-8 hours during resuscitation and risk factor for MOF
  » Balogh et al. J Trauma 2003

• Laboratory data: ACS at 8hrs maximal organ injury
  » Rezende-Neto et al. J Trauma 2002
  » Rezende-Neto et al. SHOCK 2003
• Postinjury ACS is a preventable link between traumatic shock and MOF
  »Balogh et al. SHOCK 2003
Major Advancements

- Early advancements in organ support
- Preventive antibiotics
- Optimisation of Oxygen delivery
- Lung protective ventilation
- Insulin and Cortisol replacement
- Avoiding of supra-normal resuscitation
- Reassessment of Independent Predictors
Can we resuscitate better?

“Supra-normal” versus “Normal” trauma resuscitation
RESULTS

$\text{DO}_2\text{I}_600 \ N= 85 \quad \text{DO}_2\text{I}_500 \ N= 71$

The groups had similar demographics, ISS and severity of shock.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>ISS</th>
<th>BD (mEq/L)</th>
<th>Pre-ICU LR (L)</th>
<th>Pre-ICU PRBC (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{DO}_2\text{I}_600$</td>
<td>37 ±3</td>
<td>76</td>
<td>28 ±3</td>
<td>9 ±1</td>
<td>6 ±1</td>
<td>5 ±1</td>
</tr>
<tr>
<td>$\text{DO}_2\text{I}_500$</td>
<td>33 ±2</td>
<td>74</td>
<td>27 ±2</td>
<td>9 ±1</td>
<td>5 ±1</td>
<td>5 ±1</td>
</tr>
</tbody>
</table>

(mean ±SEM) were analyzed by t and $\chi^2$ tests; * denotes $p<.05$. 
Cardiac Index during ICU resuscitation

Cardiac Index (mL/min/m²)

Time (hours)

- DO2I > 600
- DO2I > 500
SvO2 During ICU Resuscitation

SvO2 (%) vs Time (hours)

- DO2I > 600
- DO2I > 500
Serum Lactate Concentration

![Graph showing the change in serum lactate concentration over time for two different conditions: DO2I > 600 and DO2I > 500.](image)

- X-axis: Time (hours)
- Y-axis: Serum Lactate (mmol/L)

The graph illustrates a decline in serum lactate levels over time for both conditions, with a more pronounced decrease for DO2I > 600 compared to DO2I > 500.
Timeframes (%)

- Prehospital
- 0-48 hours
- 2-7 days
- >7 days

Legend:
- San Francisco 1977
- San Diego 1987
- Denver 1992
Packed Red Blood Cell Transfusions

P = 0.07
Lactated Ringer's Infusions

P<0.05

DO2I>600

DO2I>500
Urinary Bladder Pressure

UBP (mm Hg)

DO2I > 600
DO2I > 500

P < 0.05

Time (hours)

1  5  9  13  17  21  25
GAPCO2 = Gastric Mucosal CO2 minus End Tidal CO2

P < 0.05
## RESULTS

<table>
<thead>
<tr>
<th>Group</th>
<th>IAH %</th>
<th>ACS %</th>
<th>MOF %</th>
<th>Death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO_{2}I_{600}</td>
<td>42*</td>
<td>16*</td>
<td>22*</td>
<td>27*</td>
</tr>
<tr>
<td>DO_{2}I_{500}</td>
<td>20</td>
<td>8</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

*(mean ±SEM) were analyzed by t and χ² tests; * denotes p < .05.*

_Balogh et al. Arch Surg 2003_
THE NISS PREDICTS BETTER POSTINJURY MOF THAN THE ISS

Balogh et al J Trauma 2000
<table>
<thead>
<tr>
<th>Region</th>
<th>Injury</th>
<th>AIS</th>
<th>ISS</th>
<th>NISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>Concussion</td>
<td>2</td>
<td>$2^2$</td>
<td></td>
</tr>
<tr>
<td>Face-Neck</td>
<td>Mandible fx</td>
<td>2</td>
<td>$2^2$</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>Left PTX (minor)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td>C-type pelvic fx</td>
<td>4</td>
<td>$4^2$</td>
<td>$4^2$</td>
</tr>
<tr>
<td></td>
<td>Left open femur fx</td>
<td>4</td>
<td>$4^2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right supracondylar fx</td>
<td>3</td>
<td>$3^2$</td>
<td></td>
</tr>
<tr>
<td>External</td>
<td>Multiple abrasions</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>41</td>
</tr>
</tbody>
</table>
The difference of ISS median values: $29 - 25 = 4$

ISS vs. NISS

AAST 1999
SEPARATION OF MOF AND nonMOF PATIENTS
BASED ON NISS  N=558

The difference of NISS median values: 42 - 29 = 13

ISS vs. NISS  AAST 1999
<table>
<thead>
<tr>
<th></th>
<th>Year: 2000</th>
<th>Year: 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Gender (male%)</td>
<td>76%</td>
<td>76%</td>
</tr>
<tr>
<td>Mechanism (Blunt%)</td>
<td>85%</td>
<td>97%</td>
</tr>
<tr>
<td>ISS</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>BD (mmol/L)</td>
<td>-9</td>
<td>-7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td>Crystalloid (L/24hrs)</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>PRBC (U/24hrs)</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>ACS (%)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>MOF (%)</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>
Denver MOF Database

- **Inclusion Criteria**
  - Age > 16
  - ISS > 15
  - Survival > 48h
  - SICU Admit < 48h from Injury
  - No Isolated Head

- **Patients**
  - 8/18/91 - Present
  - n=1277 as of 9/15/03
  - 72% Male
  - 72% Blunt Mechanism
  - 9% Mortality Rate

Acknowledgement: DHMC Staff and David Ciesla for the following slides
Injury Severity Over 10 Years

$R^2 = 0.5547$
10 Year MOF Rate by ISS

% of Patients With MOF

ISS > 40
ISS 25-40
ISS 15-25

MOF Severity and Duration

MOF Score vs. Duration (Days)


SD ≈ 2
SD ≈ 2.5
Mortality Due to MOF

% Mortality due to MOF

R² = 0.4908

Conclusions

- **MOF Rate**
  - Postinjury MOF remains a serious clinical problem
  - MOF rates among the most severely injured are decreasing. ISS less predictive.

- **MOF Duration and severity**
  - People are getting better faster.

- **Mortality Rate**
  - Mortality rates of patients with MOF is decreasing
  - Mortality due to MOF is decreasing.

- **Risk Factors**
  - Risk for development of MOF based on earlier models needs to be reassessed given changes in MOF presentation.
Future Directions

- Reassessment of Independent predictors
- Comparing epidemiology among centres
- Understanding the role of immune-monitoring
- Improvements in fluid resuscitation
HUMAN POLYMERIZED HEMOGLOBIN

- Volume = 500 mL
- Mass Hb = 50 grams
- [Hb] = 10 g/dL
- P_{50} = 28–30 torr
- Met[Hb] < 3%
- Tetramer < 1%
- T_{1/2} = 24 hours
- Shelf life ≥ 1 year

Gould, J Trauma 1997
$O_2^-$

Johnson, J Trauma
2001
<table>
<thead>
<tr>
<th>TIME</th>
<th>CAUSE</th>
<th>INTERVENTIONS</th>
<th>MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.W.I.</td>
<td>Wound toxins</td>
<td>undefined</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>W.W.II.</td>
<td>Blood loss</td>
<td>Normal BP</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Korea</td>
<td>Blood loss</td>
<td>Normal BP</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Blood loss Extracellular fluid</td>
<td>Urine output Crystalloids</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>Mid1970</td>
<td>Shock</td>
<td>Advanced organ support capabilities</td>
<td>Sequential organ failure</td>
</tr>
<tr>
<td></td>
<td>Age sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid1980</td>
<td>Uncontrolled infection</td>
<td>Prevent and treat septic complications</td>
<td>Infectious models</td>
</tr>
<tr>
<td>Early1980</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polk/Fry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late1980</td>
<td>Systemic inflammation</td>
<td>Control inciting event, attenuate early inflammation</td>
<td>Inflammatory models</td>
</tr>
<tr>
<td></td>
<td>Bacterial translocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>SIRS/CARS</td>
<td>Supra-normal Resuscitation endpoints, Avoid secondary events</td>
<td>Dysfunctional inflammation</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Early2000</td>
<td>SIRS/CARS Resuscitation related problems</td>
<td>Abandoning supra-normal resuscitation Avoid of resuscitation related complications</td>
<td>Dysfunctional inflammation</td>
</tr>
</tbody>
</table>
ELASTASE

Johnson, J Trauma
2001
Newcastle Epidemiology

- 2006: 25 patients met inclusion criteria
- 60% male, Age: 39 years, ISS: 27
- 3 patients (12%) had MOF
- Duration: 2.3 days, Severity: 5.7 points
- No Mortality
- 18 vs 7 days on ICU
- The previous predictors are not applicable
Head injury/Exsanguination

- San Francisco 1977
- San Diego 1987
- Denver 1992
- Newcastle 2005