In Collaboration With

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Inflammatory Response

- Activated immediately upon injury
- Persists in 25-35% of patients
- Primary cause of organ failure after shock episode from multiple sources
  - Tissue hypoperfusion
  - Mediators & catecholamines
  - Oxidative stress
  - Reperfusion injury
  - Gut injury
  - Coagulation cascade activation
MAJOR INSULT

↓

EBB PHASE

24-48 hr

Hypovolemia

Hypoxemia

Hypotension

FLOW PHASE

Resuscitation, Hemodynamic Stability

Acute Phase

3-6 days

Adaptive Phase

2nd hit

Cortisol

Catecholamines

Glucagon

Growth Hormone

Pro-Inflammatory Cytokines

Prostaglandins

Hypermetabolism

Increased REE

Catabolism of body tissues

↑ Gluconeogenesis

↑ VO2, CO
Hypermetabolism & Stress Starvation

- Weight loss
- Lactic Acidosis
- Negative Nitrogen Balance
- Hyperglycemia
- Insulin Resistance
- High serum insulin
- Malnutrition
Mediator Response
Balance between SIRS & CARS

**SIRS**
- Systemic Inflammatory Response Syndrome
- Pro-inflammatory activation of innate immunity
- Driven by mediators & antigen presenting cells
- Early defense against invading microorganisms

**CARS**
- Compensatory Anti-inflammatory Response Syndrome
- Microphage deactivation, decreased antigen production
SIRS (pro-inflammatory)  
Helper TH1 cells

MODS

CARS (anti-inflammatory)  
Helper TH2 cells
Single Hit
- MSOF from injury itself and/or resuscitation
- Severity of insult, host physiologic reserve, timing & quality of resuscitation

Double Hit
- Initial injury and successful resuscitation followed by secondary complications
- Shock, infection, return to surgery, myocardial infarction

Persistent Hit
- Initial hit & successful resuscitation followed by persistent alterations
- Infection, Ischemia, SIRS without infection, altered gut barrier integrity, hypermetabolism

Meakins JL. J Trauma 1990; 30:S165-8
Insult

IIR, SNS activation, Endothelial damage

Maldistribution of circulating volume

Imbalance of O₂ supply/demand

Metabolic derangement

Submaximal perfusion

Tissue hypoxia, ↓ ATP

Myocardial depression

Hyper-metabolism

Mediator action, Fluid imbalances

↑ Acidosis, Tissue damage

Severe depression

Exhaustion of stores

Severe hypotension

Organ dysfunction

Metabolic failure

MSOF

Huddleston VB. MSOF: A pathophysiologic approach. Boston, 1191:24
Catecholamine Response
• 1898: injection of adrenal medullary preparations, “Suprarenin”
• 1901: Crystalline form developed, “Adrenaline”
• 1940: Norepinephrine isolated
• 1953 Injection of catecholamines affects lymphocytes
  - Increase in number of normal lymphocytes
  - Significant increases in levels of “stress-lymphocytes” with NK capability, CD8
Where does this response originate from?

- Spleen is a reservoir ... but response still present in splenectomized patients
- Immune cells express catecholamine receptors for $\beta_2$
  - TH1 have more receptors than TH2
  - Receptiveness modulated by number of circulating catecholamines
Prolonged central adrenergic release

- ↓ antibody response (IgM, IgG)
- ↑ bacterial colonization in liver & spleen
- ↓ spleen & lung TNF and IL-6
- ↓ splenic & blood lymphocytes
- ↓ T cell antigen-antibody & NK cell activity
- ↓ Macrophage cytokine activity & nitric oxide release
- ↓ IgG release with chronic stress
EXOGENOUS

Dopamine

Dopexamine

\(\beta\) Adrenergic agonists

Epinephrine

Norepinephrine

Vessel Wall

CD4

NK cell

CD48

macrophage

B cell

ENDOGENOUS

Epinephrine

Norepinephrine

Oberbe, Current Medicinal Chemistry, 2006, 13(77), p. 1982
Oxidative Stress & Reperfusion

INJURY
Limb ischemia, MI, hypovolemia, shock, revascularization

REPERFUSION

ROI PRODUCTION

OVERWHELMED ANTI-OXIDANT DEFENSES

Bystander Injury
Cellular proteins & nucleic acids, lipid peroxidation, signaling
### Endogenous Antioxidant Defenses

<table>
<thead>
<tr>
<th>Enzymatic</th>
<th>Nonenzymatic</th>
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<tbody>
<tr>
<td>Superoxide dismutase</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Catalase</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>Vitamin A/β carotene</td>
</tr>
<tr>
<td></td>
<td>Glutathione</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
</tr>
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<td>Urate</td>
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</table>
Role of the Gut

“Motor of Multiple Organ Failure”

• Reservoir of bacteria
  - $10^{12}$ total bacteria
  - $10^9$ potentially pathologic Gram Negative

• Enough endotoxin to kill host many times over

• Roles
  - Keep bacteria & toxins within lumen
  - Absorb nutrients
Normal Gut Barrier Function

- Prevention of bacterial overgrowth
- Normal mucous layer
- Peristalsis
- Cellular barrier
- Immune function
  - GALT
  - Cytokine release
  - Neutrophil activation
- Gut-liver axis
  - Endotoxin defense
  - Bile production
Gut Hypothesis for MOF

SHOCK, HYPOPERFUSION
↓
PREFERENTIAL SHUNTING
↓
O₂ DELIVERY TO SPLEEN, INTESTINAL MUCOSA
↓
ISCHEMIA
↓
APOPTOSIS OF VILLI CELLS, TRANSMURAL NECROSIS
↓
BREAKDOWN OF GUT BARRIER
Consequences of not using the gut

- Loss of functional & structural integrity
- Increased permeability
- Increased oxidative stress
- Perpetuates pro-inflammatory response
- Disruption of ecology of gut leading to bacterial overgrowth & systemic bacterial challenge
"Poking the Bear"

- Patients immunosuppressed
- Broad spectrum Abx allow colonization
- Antacids & H2 blockers allow colonization in stomach & upper airways
- Ileus allows intestinal stasis & overgrowth
- Hypoosmolar enteral feeding & TPN disrupt ecology of normal gut flora
- Hypotension & vasopressors result in splanchnic ischemia
Inflammation Communicates with Coagulation

Inflammatory Response to Infection

Thrombotic Response to Infection

Fibrinolytic Response to Infection
Clinical Presentation

- ARDS
- ATN
- Secondary Brain Injury
- “Septic” picture
- Hyperglycemia
- Gut failure
- Shock
- Infections
- Catabolic
Battle Strategies

• Timely and adequate resuscitation
• Antioxidant support
• Gut support & immunonutrition
Resuscitation

- Fluids
  - Hypertonic saline
  - Judicious use of blood products
  - Considered administration of vasopressors

- Adequate assessment of resuscitation
  - LA or BD, ABG
  - $\text{ScvO}_2$, $\text{SvO}_2$, $\text{StO}_2$, $\text{VO}_2\text{I}$
Gut Support

• Enteral nutrition
• Permissive underfeeding
• Immunosupport
Enteral Nutrition

- Maintains splanchnic blood flow
- Moderates the metabolic response
- Maintains gut permeability
- Prevents bacterial translocation
- Improves wound healing
- Decreases mortality
Permissive Underfeeding

• Nutrients may
  - Enable bacterial replication
  - Stimulate production of inflammatory cells
  - Increase cytokine production
  - Contribute to hyperglycemia & CO$_2$ production

• Recommendations
  - Begin enteral feeding in the first 24 hours following resuscitation
  - Advance to 33-66% of calculated intakes
  - Maintain at this level for 2-4 days
  - As hypermetabolism resolves, advance to goal over 3-5 days
Antioxidant Support

• Vitamin E
  - Major antioxidant
  - Interrupts lipid peroxidation
  - ↓ downstream ROI signaling pathways
  - Directly inhibits ROI production

• Levels fall steadily in first 24 hr

• Effects of infusion
  - ↓ lipid peroxidation, ↓ endotoxin response, ↓ pulmonary injury
  - ↑ ATP, ↑ viral protection, ↑ survival
Antioxidant Support

- Vitamin C (Ascorbic Acid)
- Role
  - Broadly scavenges ROI, but can be pro-oxidant as well
  - Helps Vitamin E work better
- Early loading doses
### Vitamin C

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<tr>
<td>Trauma ICU</td>
<td>Septic patients</td>
<td>Acute Trauma</td>
</tr>
<tr>
<td>Vit. C 1000 mg IV q 8 with Vit. E 1000 units PO q 8 hr</td>
<td>Early loading doses ↓ capillary leak</td>
<td>Vit C 1000 mg q 8h, Vit. E 1000 units q 8h, Se 200 mcg QD x 7 days</td>
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<tr>
<td>↓ Organ failure ↓ ICU LOS</td>
<td>↓ ↓ Hospital &amp; LOS days ↓</td>
<td>↓↓Mortality (6% vs. 8%) 30% relative risk reduction</td>
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**Toxicity should not be downplayed:**
- Oxalate stones (rare at moderate doses)
- False negative guiac (> 250 mg/d)
- May increase iron absorption in hemochromatosis
- Hemolysis with GRAM doses
Other Antioxidants & Immune Enhancing Nutrients

- Arginine
- Glutamine
- Selenium
- Omega 3s
- Vitamin D
Which antioxidants?

What timeframes?

What combinations?

What doses?

When does toxicity develop?
Probiotics

“Live microorganisms in which, when administered in adequate amounts, confer a health benefit on the host”

- Human Origin
- Viable & hardy in human GI tract
- Acid & bile stable
- Adhesion to mucosa
- Clinically demonstrated benefit
- Safe

L. casei
L. acidophilus
L. Salivarius
B. bifidum
S. boulardii

Ventilator associated pneumonia
Pancreatitis
VRE
Clostridium difficile
Infectious diarrhea
Probiotics

- Inhibit growth of pathogenic enteric bacteria
- Block epithelial attachment or invasion by pathogens
- Eliminate pathogenic toxins
- Improve epithelial & mucosal barrier function
- Alter host immune response
- Monostrain vs. multistrain?
- Pre, pro, or synbiotic?
- Quantity and quality for desired effect?
- How to assess the activity & viability?
- Probiotic safety?
- When are probiotics contraindicated?
Application to Practice in the Burn Trauma Patient

32 year old, self extrication from house fire (25’ fall), LOC at scene, found down by Medics

Injuries: R. humerus fx, R. clavicle fracture, R. pneumothorax, Grade II splenic lac, SDH, inhalation injury and approx 80% TBSA Burn
ED Presentation

- NIBP 140/50, HR 150
- Mechanically ventilated, FiO2 100%
- R. Apical Chest tube placed
- HCT 50, LA 10, K+ 6.0, Gluc 180
- ABG 7.20/30/250/18
- + Methamphetamine
- Foley placed
- Abbreviated ‘trauma train’
- Immediately transferred to BICU
ICU arrival - Hour 1

- NIBP 145/90  HR 120
- Secure airway
  - Carbonaceous sputum
- Access establishment
  - Infusing LR @ 1500cc/hr
- UOP 20cc/hr
- Burn assessment recalc to 70%
  - Full thickness - face, torso, BUE, BLE
  - Undetermined - perineum, buttocks
- Full spine precautions
Congruence (Parkland/ Baxter) Formula

2-4 mL / kg / % TBSA = mL of LR in first 24 hrs post burn injury

½ in the 1st 8 hrs

¼ in the 2nd 8 hrs

¼ in the 3rd 8 hrs
...according to Congruence Formula

3mL x 70Kg x 70% TBSA = 14,700 ml Ringers Lactate in 24 hours

- 7,350 mL over the first 8 hrs
  - 920 mL/hr  (6L in 4 hours)

- 3,675 mL over the second 8 hrs
  - 459 mL/hr

- 3,675 mL over the third 8 hrs
  - 459 mL/hr
Lung Injury Complication

- Methamphetamine lung injury requires 2x fluid resuscitation
- Ventilatory support - ↑PEEP, ↑FiO2, LPV
- Smoke inhalation
  - CO poisoning = shift to left
  - Meth + heat = caustic lung trauma
  - Pulmonary edema
- ARDS
Hour 8

- LR infusing at 1500L/hr
- Wound care
- Enteral Feedings trickling
- Access established
- Insulin gtt @ 8u/hr
- Morphine 10mg/hr  Midazolam 2mg/hr
- Room: 95°F  Patient 35.6°C
- Family being located
Treatment Criteria

- 35% burn
- $\uparrow$ fluids without response
- $\downarrow$ UOP (<30cc/hr >2hr)
- $\downarrow$ Cardiac output
- Labs
- Other considerations
  - Age, inhalation injury, electrical injury, tissue trauma, co-morbidities, delay in resuscitation
Components of Plasma
albumin, clotting factors, Ig, cytokines, complement
Hypothesis

• Treat within first 24hr
  - Heightened inflammatory cascade
  - Patient at risk of hypoperfusion
• Filters blood of accumulated cytokines
  - TNF (Tissue necrosis factor)
  - PGI-2 and PGE-2 (prostaglandins)
  - Bradykinins (potent vasodilator)
  - Reduces leak at capillary level
• Creates a bridge for treatment
Plasmaphoresis in Action

• Pre treatment (Hour 12 since injury)
  - Failing resuscitation
  - Increasing ventilatory needs

• Labs: INR 3.2  Plts 80,000  HCT 22%
  BD - 7.1

Plasmaphoresis Ordered
Post treatment

- INR 2.1
- HCT 22
- Plts 80,000
- BD -5.1

Patient Presentation

- NIBP 110/60  MAP 76
- HR 110
- UOP 32cc/hr
THANK YOU!!

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