Multiple System Organ Failure

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Outline

• Definitions and Epidemiology: MODS
• Pathophysiology of MODS
• How do we get to MODS: SIRS/Sepsis
• Organ Failure: Clinical Assessment, Scoring
• Long Term and Patient Centered Outcomes

Multiple Organ Dysfunction Syndrome

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention:

➢ Primary: Direct Organ injury
  (ex. Trauma-pulmonary contusion)

➢ Secondary: Consequence of host response
  (ex. sepsis)


Disclosures

• None
• Unrelated: NIH funding HL120896
Multiple Organ Dysfunction Syndrome

INFECTION
TRAUMA
BURNS
PANCREATITIS

Systemic Inflammatory Response Syndrome (SIRS)

Organ Failure (MODS)

Resolution

Death

Matthay BMJ 2016 (image)

Epidemiology: Medical Patients

• Sepsis:
  ➢ Diagnosis/rate of sepsis doubled between 2000-2008
  ➢ Accounts for 50% of Admissions to the ICU
  ➢ Mortality in USA and Worldwide is 20-30%
  ➢ Major cause of acute organ failure
  ➢ Estimated annual total costs of $16.7 billion nationally

CDC.gov

Crit Care Med. 2001 Jul;29(7):1303-10

Epidemiology: Surgical Patients

• Trauma associated MOF:
  ➢ US incidence decreasing (17% in 2003, 10% in 2010)
  ➢ Mortality 36%
  ➢ Longer mechanical ventilation, ICU stays
  ➢ Estimated median cost per patient with MOF $77,000
double that of patient without MOF

• Surgical patients:
  ➢ account for 1/3 of sepsis patients in US
  ➢ Sepsis and septic shock 10x more common that peri-op
MI or PE

Sauaia A. J Trauma Acute Care Surg, 2014;76: 582-92
Dasta JF. Crit Care Med 2005; 33:1266-71
Angus DC. Crit Care Med 2001; 29: 1303-10
Moore LJ. Arch Surg 2010; 145: 695-700

SUMMARY: Epidemiology

• MODS is a syndrome, not a disease
• Sepsis accounts for the majority of ICU admissions and peri-operative complications
• Mortality from multiple organ failure of any cause is near 30%
Outline

- Definitions and Epidemiology: MODS
- **Pathophysiology of MODS**
- How do we get to MODS: SIRS/Sepsis
- Organ Failure: Clinical Assessment, Scoring
- Long Term and Patient Centered Outcomes

Genetic Predisposition

Discovery designs

<table>
<thead>
<tr>
<th>Year</th>
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<td>2005</td>
<td>ACE, IL6, F1F2, C02Z, ACPL, SERNAM, PLAUR</td>
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<td>AGA, COX4, CACNA, DLD</td>
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<td>TTP, BTG2, GADD45A, G2NAG, ADH1A, ECL2</td>
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<td></td>
<td>NAMPT, THBD, GGH, CADD, TDO, RB</td>
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<td>MTH1, GRM3, BTG2, RGC20</td>
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<tr>
<td></td>
<td>IFNRA, IRF3, NAMPT, SAMM56, CREB3L1, ANGPT2</td>
</tr>
<tr>
<td></td>
<td>APPH1, IAHN, PRKDC</td>
</tr>
<tr>
<td>2010</td>
<td>ALK1, LRAL, MAP3K11, MMT1, SPP2, ETS2</td>
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<tr>
<td></td>
<td>GATA4, CCNL2, SRP14</td>
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<tr>
<td></td>
<td>TFEB, TFEOZI, RHOA, FGFRA, ARSE</td>
</tr>
<tr>
<td></td>
<td>LINC0052, 50X4, GOSM, C17orf77, CCL26, CDOX, DKK1, DIXB, IL18, IL6, SERNAM</td>
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</table>

MODS Pathophysiology

Adapted from: Crit Care Clin. 2017;33:167-191
MODS: The role of uncontrolled infection

- With early antibiotic therapy does infection play a role in multiple organ failure?
- In patients with organ failure associated with “sterile” injury (ex. pancreatitis), does infection play a role?
- **Emerging concept of the pathobiome**

__Microbiome regulates immune responses__

Changes in microbiota associated with morbidity/mortality in SIRS
- Antibiotics induce disruption of the intestinal microbiome
- Cytokines and Chemokines have a direct effect on intestinal permeability
- Modulation of microbiome as therapy?
MODS Pathophysiology

SUMMARY: MODS Pathophysiology
- Initiating clinical event
- Genetic Predisposition
- Early pro-inflammatory response, endothelial leak, epithelial damage
- Danger signals, reactive oxygen species, coagulopathy, apoptosis -> organ injury
- Late Immunosuppression
- Altered microbiome/Pathobiome

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Multiple Organ Dysfunction Syndrome

INFECTION
TRAUMA
BURNS
PANCREATITIS
Systemic Inflammatory Response Syndrome (SIRS)
Organ Failure (MODS)
Resolution
Death
How do we identify this patient here?

Matthay.BMJ 2016 (image)
Two Patients Presenting to ED

Patient 1:
- 65 yo man presenting with cough, subjective fevers, chills, L sided pleuritic chest pain.

Patient 2:
- 40 yo male alcoholic with h/o duodenal ulcer with sudden onset abdominal pain.

Systemic Inflammatory Response Syndrome

- Designed to encapsulate physiologic host response
- Sensitive, Not Specific
- Two or more of:
  - Temperature >38°C or <36°C
  - Heart rate >90/min
  - Respiratory rate >20/min or PaCO₂ <32 mm Hg
  - White blood cell count >12 000/mm³ or <4000/mm³ or >10% immature bands

Do these patients have SIRS?

Do these patients have Sepsis?

Sepsis

Previous Clinical Criteria:
- SIRS + Infection
- Severe Sepsis: organ dysfunction
- Septic Shock: hypotension despite adequate resuscitation and tissue hypoperfusion

Proposed Clinical Criteria:
- Organ dysfunction caused by dysregulated host response to infection (SOFA ≥ 2)
- qSOFA RR ≥22/min, Δ mental status, SBP ≤100 mm Hg (ED patients)

SEPSIS Controversy

Why does it matter?

- SIRS may not capture everybody
- SIRS may be too sensitive
- Need early identification of sickest patients
- Need for uniform definition
- Sepsis and subsequent MOF are common, costly, and deadly

Two Patients Presenting to ED

Patient 1:
65 yo man presenting with cough, subjective fevers, chills, L sided pleuritic chest pain. ΔMS, SBP 70

Patient 2:
40 yo male alcoholic with h/o duodenal ulcer with sudden onset abdominal pain. ΔMS, SBP 70

Does these patients have Sepsis?

Resuscitation

- Medical/Surgical Emergency
- Code sepsis
- At least 30mL/kg of IV crystalloid fluid in the 1st 3 hours
- Ongoing Hemodynamic Monitoring
- Target SBP >65mmHg
- Measure and Follow Lactate

Resuscitation

- How much? What Target?
- Rivers: Early Goal Directed Therapy

Assessing Volume Status

- Dynamic measures > Static Measures
- Passive Leg raise
- Pulse Pressure Variation
- Stroke volume in response to bolus

Initial Laboratory Assessment

- Etiology:
- Blood cultures
- CXR
- Urine Culture
- Lipase
- Imaging
- Tissue hypoperfusion
- Lactate – Serial assessment > initial value
Antibiotics

- Antibiotics within 1 hour of recognition of sepsis or septic shock
- IV broad spectrum
- Narrow with clinical improvement, pathogen identification/sensitivities

Surgical Drainage and Debridement

- Definitive Source Control:
  - drainage of an abscess
  - debridement of infected necrotic tissue
  - removal of a potentially infected device
- No more than 6 to 12 hours after diagnosis – longer associated with increase in mortality

Two Patients

Patient 1:
65 yo man presenting with cough, subjective fevers, chills, L sided pleuritic chest pain.
IVF, Abx, monitoring

Patient 2:
40 yo male alcoholic with h/o duodenal ulcer with sudden onset abdominal pain.
IVF, Abx → To OR!

Summary: SIRS/SEPSIS

- qSOFA for rapid detection in ED
- qSOFA may be insufficient in other settings
- Early Resuscitation
- Early Antibiotics
- Early surgical intervention
Outline

- Definitions and Epidemiology: MODS
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- How do we get to MODS: SIRS/Sepsis
- **Organ Failure: Clinical Assessment, Scoring**
- Long Term and Patient Centered Outcomes

Risk Factors Associated with Development of Organ Failure

- Advanced Age
- Male Gender
- Alcoholism
- Existing Comorbidities

Organ Failure Assessment

- Complete Blood Counts
- Liver Function Tests
- Renal Function Monitoring (Cr and UOP)
- Hemodynamic monitoring
- Mental Status (GCS, Delirium – CAM ICU)
- Multiple different scoring systems....

SOFA: Sequential Organ Failure Assessment

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory PaO₂/FIO₂, mmHg</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200*</td>
<td>≤100*</td>
</tr>
<tr>
<td>Congestion plasma&lt;10^9/μl</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤100</td>
<td>≤50</td>
<td>≤20</td>
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<tr>
<td>Liver bilirubin, mg/dl</td>
<td>&lt;1.2</td>
<td>1.2~1.9</td>
<td>2.0~5.9</td>
<td>6.0~11.9</td>
<td>&gt;12.0</td>
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<tr>
<td>Cardiovascular hypertension</td>
<td>No hypertension</td>
<td>MAP&lt;70 mmHg</td>
<td>Dop&lt;5 or Dop&lt;5 (any dose)</td>
<td>Dop&gt;5, Epi&lt;0.1 or Noepi&lt;0.1</td>
<td>Dop&gt;15, Epi&gt;0.1 or Noepi&gt;0.1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>15</td>
<td>13~14</td>
<td>10~12</td>
<td>6~9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal creatinine, mg/dl or urine output, ml/dl</td>
<td>&lt;1.2</td>
<td>1.2~1.9</td>
<td>2.0~3.4</td>
<td>3.4~4.9 or &lt;500</td>
<td>&gt;5.0 or &lt;200</td>
</tr>
</tbody>
</table>

*SOFA: Sequential Organ Failure Assessment, Intensive Care Med. 1996;22(7):707-710
MODS: Multiple Organ Dysfunction Score

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Score</th>
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<tbody>
<tr>
<td>Respiratory (PaO2/FiO2 ratio)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Renal (serum creatinine)</td>
<td>≤100</td>
</tr>
<tr>
<td></td>
<td>101–200</td>
</tr>
<tr>
<td></td>
<td>201–350</td>
</tr>
<tr>
<td></td>
<td>351–500</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
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<tr>
<td>Hepatic (serum bilirubin)</td>
<td>≤20</td>
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<td>21–60</td>
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<td>61–120</td>
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<td></td>
<td>121–240</td>
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<td></td>
<td>&gt;240</td>
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<td>Cardiovascular (PAR)</td>
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<td>10.1–15.0</td>
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<td>20.1–30.0</td>
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<td>&gt;30.0</td>
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<tr>
<td>Hematologic (platelet count)</td>
<td>≤10.0</td>
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<td>10.1–15.0</td>
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<td>20.1–30.0</td>
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<td>&gt;30.0</td>
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<td>Neurologic (Glasgow Coma Score)</td>
<td>15</td>
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<td>13–14</td>
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<td></td>
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<td></td>
<td>7–9</td>
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<td>≤6</td>
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Critical Care Med. 1995;23:1638-1652

Denver Post-injury MOF Score

<table>
<thead>
<tr>
<th>Table 1 Denver post-injury MOF score</th>
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<tbody>
<tr>
<td>Organ System</td>
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<tr>
<td>Pulmonary</td>
</tr>
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<td>Renal</td>
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<td>Hepatic</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Small</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Large</td>
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</table>

Arch Surg. 1994;129:39–45

Dysfunction of Organ Systems

- Refractory Shock
- ARDS
- AKI
- GI dysfunction
- Liver dysfunction
- CNS dysfunction
- Coagulopathy/DIC

Matthay JCI 2012

Two Patients

Patient 1:
- Hypotension x 24 hrs, now resolved
- Creatinine: 4.5
- Platelets: 56K
- PaO2/FiO2: 90
- MAP 50 on Norepi, Vasopressin

Patient 2:
- Hypotension x 24 hrs, now resolved
- Creatinine: 4.5
- Platelets: 56K
- PaO2/FiO2: 90
- MAP 50 on Norepi, Vasopressin
Dysfunction of Organ Systems

- **Refractory Shock**
- ARDS
- AKI
- GI dysfunction
- Liver dysfunction
- CNS dysfunction
- Coagulopathy/DIC

Refractory Shock

A Norfolk doctor found a treatment for sepsis. Now he's trying to get the ICU world to listen.

The Cocktail

- Vitamin C
  1.5 gm q 6h x 4 days or until ICU D/C
- Hydrocortisone
  50 mg q 6h x 7 days or until ICU D/C
- Intravenous Thiamine
  200 mg q 12h x 4 days or until ICU D/C
- Treatment group 7 months (9% mortality) vs historical controls for past 7 months (40% mortality)
- No Randomized Trial Exists -> Proceed with caution

Dysfunction of Organ Systems

- Refractory Shock: Pressors, +/- steroids
- ARDS: 6cc/kg, Plateau pressure <30, higher PEEP, fluid restrictive, prone position, paralytics
- AKI: RRT
- GI dysfunction: Early Enteral Feeding
- Liver dysfunction: Supportive
- CNS dysfunction: Daily Spontaneous Awakening, Day/Night reorientation
- Coagulopathy/DIC: Supportive
Summary

• Multiple scoring systems exist for multiple organ failure:
  - SOFA in medical patients
• There is still no cure for septic shock
• Care for most organ injury remains supportive

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• Definitions and Epidemiology: MODS
• Pathophysiology of MODS
• How do we get to MODS: SIRS/Sepsis
• Organ Failure: Clinical Assessment, Scoring
• Long Term and Patient Centered Outcomes

Long Term Consequences for Patients

PICS: Post-Intensive Care Syndrome
• >50% of critical care survivors
• Increased moderate to severe cognitive impairment
• New functional disability
• ICU acquired weakness
• Affects family members

Risk for Poor Long Term Outcome

• Pre-illness Determinants:
  ➢ Age
  ➢ Poor mobility
  ➢ Cognitive Function
  ➢ ADLs
  ➢ Geriatric syndrome
  ➢ Social functioning
  ➢ Depression

• Hospitalization Factors:
  ➢ Environment
  ➢ Restricted Mobility
  ➢ Undernutrition
  ➢ Enforced Dependence
  ➢ Polypharmacy
• Post-Hospital Factors:
  ➢ Environment
  ➢ Resources
  ➢ Community Support
  ➢ Quality of Discharge Planning

References:
JAMA 2010; 304:1787–94
JAMA 2010; 303:763-70
Image NY Times 2010.
Early mobility

- Muscle loss higher in MOF versus single organ failure:
  -15.7 vs. -3.0 percent by day 7
  -8.7 percent vs. -1.8 percent by day 3
- Minimize Sedation
- PT and OT even in most complicated patients can be feasible and safe
- Better if instituted early in ICU stay
  - Within 3d: higher survival, shorter delirium
  - After 4d: no improvement in long term physical function
- Multidisciplinary Approach
- Discuss mobility goals daily

Family Engagement

- Family presence on ICU rounds is beneficial and does not interfere with communication
- Increased nursing satisfaction with team communication and family relationships
- No difference between palliative care specialist discussion versus team lead discussions in family anxiety/depression
- PTSD higher in PC-Led discussions BUT did not examine full PC consult, ICU physicians were often not present

ICU Discharge Planning: Cost savings?

- Early re-hospitalization costs Medicare $26 billion/year

ICU to Floor Transition: Readmission Prevention

- Communication: direct verbal between ICU and floor physician
- Engagement: Critical Care nurses in discharge planning
- Needs Assessment: Mobility (PT/OT), Psych
- Family Outreach: 68% report desire for increased opportunity to ask questions
THRIVE initiative

- Connect with ICU survivors
- Resources

Summary: Long Term Outcomes

- A significant number of MODS survivors will have long term deficits
- Considering this while patients are in the ICU may offer benefits

MODS

- Multiple Organ Dysfunction Syndrome is common, costly, and associated with high mortality
- Definitions are a moving target
- Resuscitation, antibiotics, surgical intervention, and supportive care are often necessary
- Patients who survive may have prolonged deficits

Thank you

- Questions?