



Multiple System Organ Failure

Carmen Mikacenic, MD
Assistant Professor
Pulmonary, Critical Care and Sleep Medicine
University of Washington

UW Medicine
HARBORVIEW
MEDICAL CENTER



Division of Pulmonary, Critical Care
& Sleep Medicine
University of Washington

Disclosures

- None
- Unrelated: NIH funding HL120896

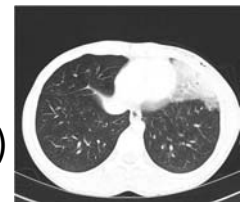
Outline

- **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

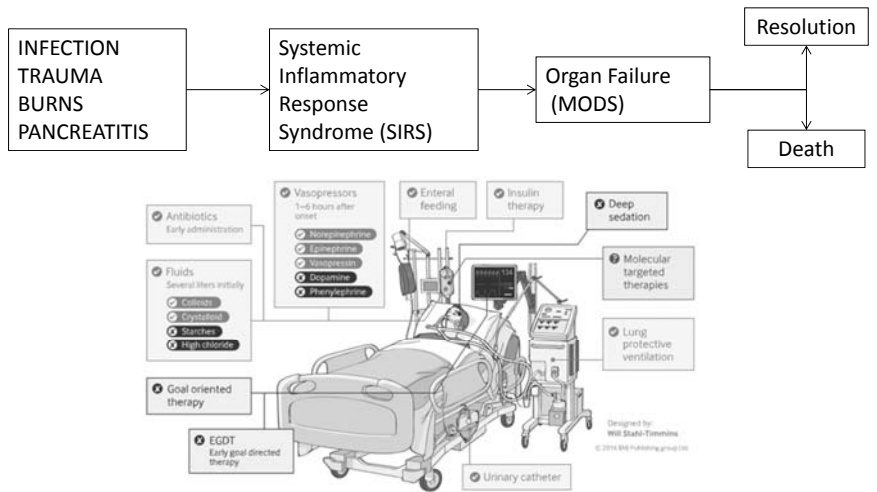
Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention:

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



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

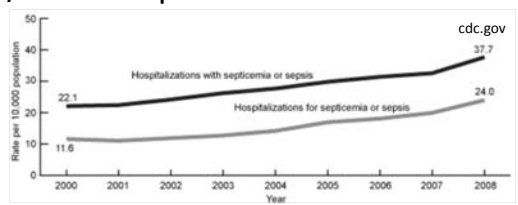
Multiple Organ Dysfunction Syndrome



Matthay.BMJ 2016 (image)

Epidemiology: Medical Patients

- Sepsis:
- Diagnosis/rate of sepsis doubled between 2000-2008

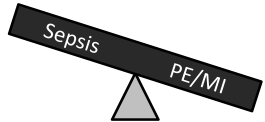


- Accounts for 50% of Admissions to the ICU
- Mortality in USA and Worldwide is 20-30%
- Major cause of acute organ failure
- Estimated annual total costs of \$16.7 billion nationally

Crit Care Med. 2001 Jul;29(7):1303-10
Lancet Resp Med. 2014 May;2(5):380-6

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 than 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

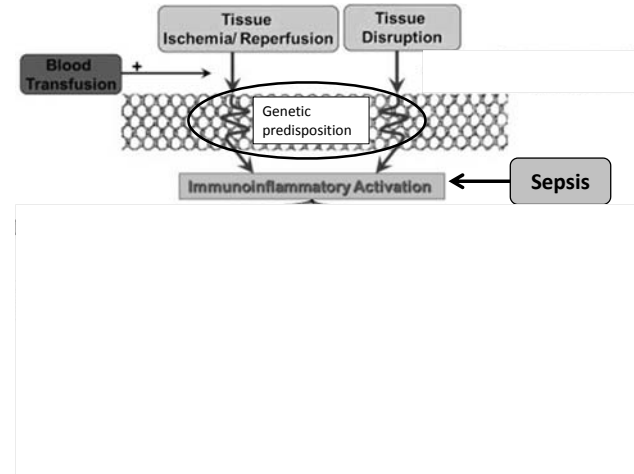
SUMMARY: Epidemiology

- 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

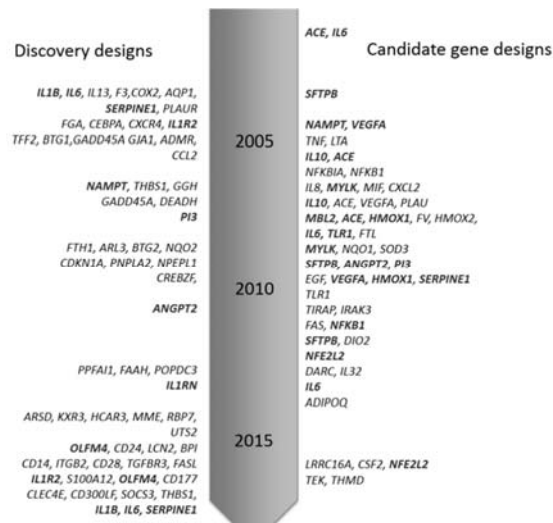
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MODS Pathophysiology



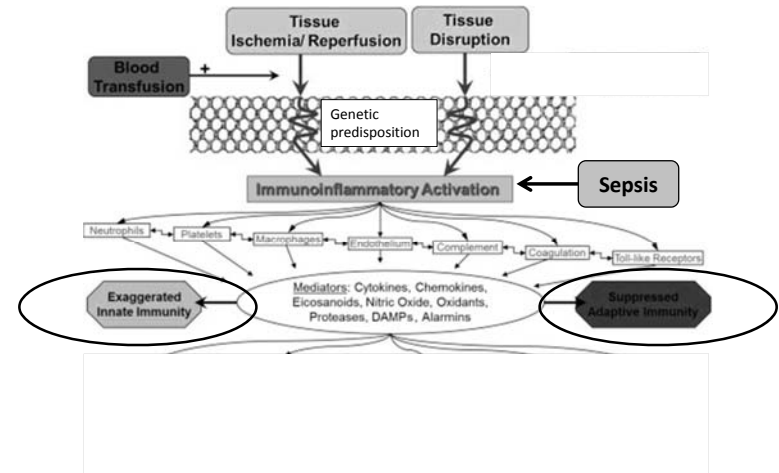
Adapted from: Crit Care Clin. 2017;33:167-191

Genetic Predisposition



AJRCCM May 2017

MODS Pathophysiology

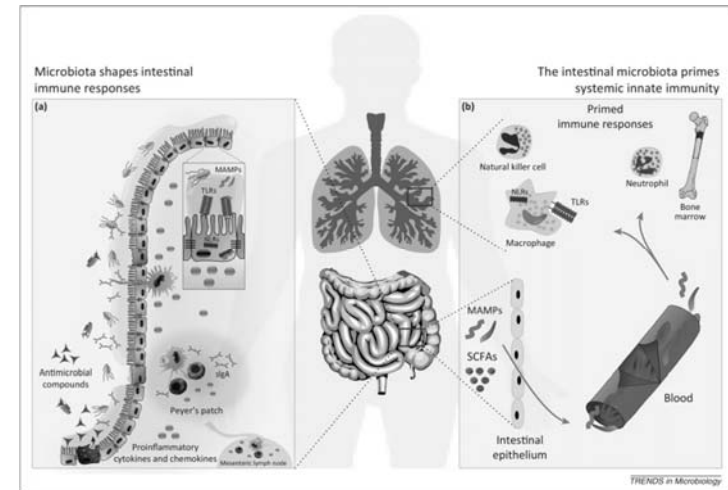


Adapted from: Crit Care Clin. 2017;33:167-191

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

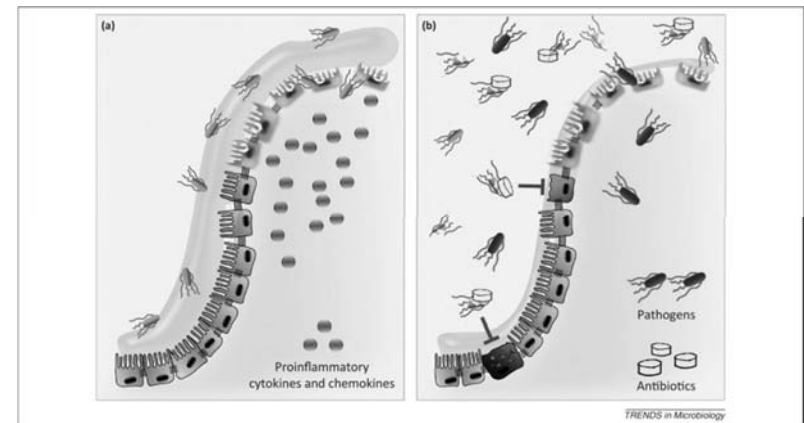


Trends in Microbiology 2013 May;21:221-9

MODS: The role of uncontrolled infection

- 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?

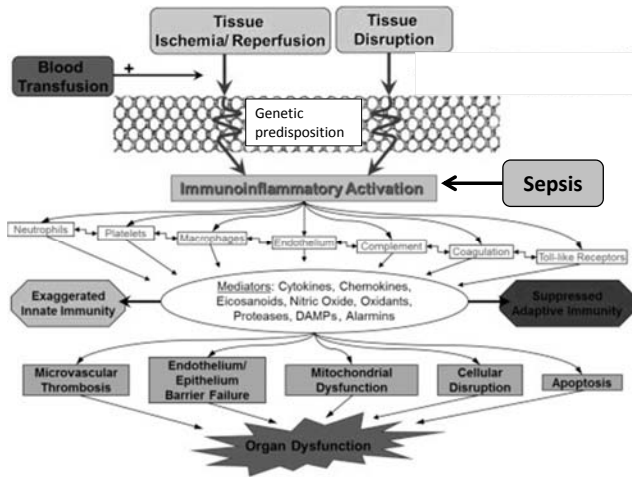
Pathobiome



Trends in Microbiology 2013 May;21:221-9

Trends in Microbiology 2013 May;21:221-9

MODS Pathophysiology



Adapted from: Crit Care Clin. 2017;33:167-191

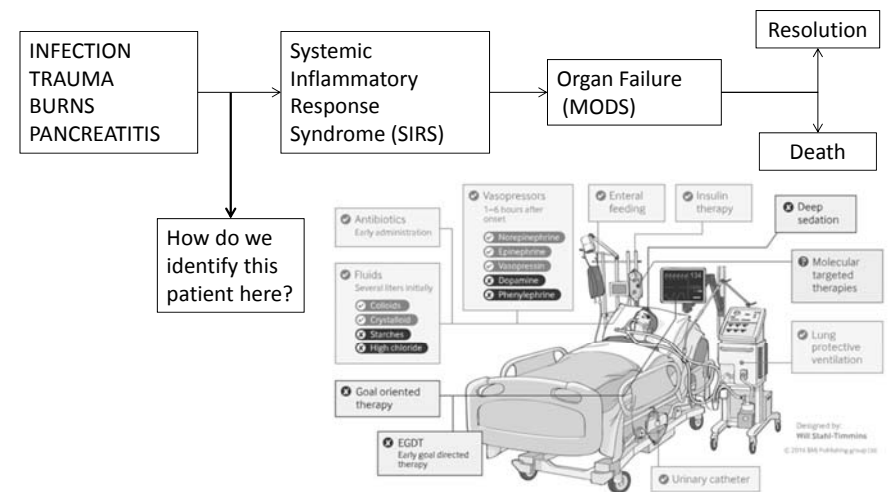
SUMMARY: MODS Pathophysiology

- 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



Matthay.BMJ 2016 (image)

Two Patients Presenting to ED

Patient 1:

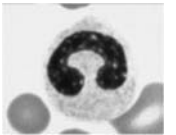
- 65 yo man presenting with cough, subjective fevers, chills, L sided pleuritic chest pain

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 $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Heart rate $>90/\text{min}$
 - Respiratory rate $>20/\text{min}$ or $\text{PaCO}_2 <32 \text{ mm Hg}$
 - White blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ immature bands



Bone RC et al. *Crit Care Med.* 1992;20:864-874.

Two Patients Presenting to ED

Patient 1:

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

T 39C, HR 110, RR 26

Patient 2:

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

T35C, HR 130, WBC 20K

Do these patients have SIRS?

Do these patients have Sepsis?

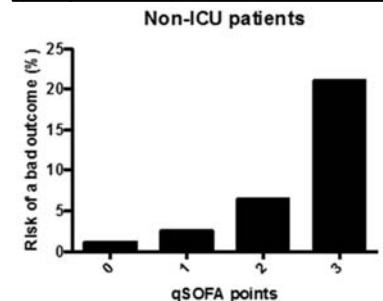
Sepsis

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 $\geq 22/\text{min}$, Δ mental status, SBP $\leq 100 \text{ mm Hg}$ (ED patients)



Bone RC et al. *Crit Care Med.* 1992;20:864-874.

Sepsis-3: What is the Meaning of a Definition?

John C. Marshall, MD
Departments of Surgery and Critical Care Medicine
Keenan Research Centre for Biomedical Science of the
Li Ka Shing Knowledge Institute
St. Michael's Hospital



qSOFA does not replace SIRS in the definition of sepsis

Jean-Louis Vincent, Greg S. Martin, and Mitchell M. Levy

Critical Care

BioMed Central

SEPSIS Controversy

CHEST

New Sepsis Criteria
A Change We Should
Not Make

Steven Q. Simpson, MD, FCCP
Kansas City, KS



ATS Journals

OPENING THE DEBATE ON THE NEW SEPSIS DEFINITION
Defining Sepsis: A Case of Bounded Rationality and
Fuzzy Thinking?

Derek C. Angus M.D., M.P.H. ¹

OPENING THE DEBATE ON THE NEW SEPSIS DEFINITION
Change Is Not Necessarily Progress: Revision of the
Sepsis Definition Should Be Based on New Scientific
Insights

Irene Cortés-Puch M.D. ¹ and Christiane S. Hartog M.D. ^{2,3}

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?



ALTERED
MENTAL STATUS



FAST RESPIRATORY
RATE



LOW BLOOD
PRESSURE

Qsofa.org

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

Surviving Sepsis Guidelines. Crit Care Med. 2017; 45: 1-67.

Resuscitation

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

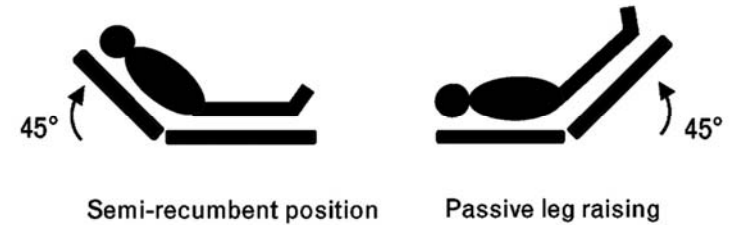
ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

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

Patient 1



Patient 2



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



Crit Care 2014; 18:R8
Crit Care 2014; 18:R42

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

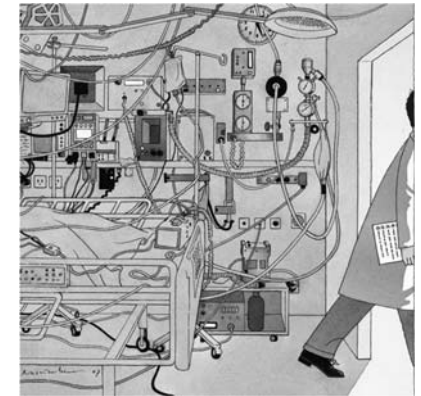


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Risk Factors Associated with Development of Organ Failure

- Advanced Age
- Male Gender
- Alcoholism
- Existing Comorbidities



New Yorker. Illustration by Nascimbene

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

Variables	SOFA score				
	0	1	2	3	4
Respiratory PaO ₂ /FiO ₂ , mmHg	>400	≤400	≤300	≤200*	≤100*
Coagulation platelets×10 ³ /μl [†]	>150	≤150	≤100	≤50	≤20
Liver bilirubin, mg/dl [†]	<1.2	1.2~1.9	2.0~5.9	6.0~11.9	>12.0
Cardiovascular hypotension	No hypotension	MAP [‡] <70 mmHg	Dop [§] ≤5 or Dob ^{**} (any dose) [†]	Dop >5, Epi ^{††} ≤0.1, or Norepi ^{††} ≤0.1 [†]	Dop >15, Epi >0.1, or Norepi >0.1 [†]
Central nervous system GCS ^{§§} scale	15	13~14	10~12	6~9	<6
Renal creatinine, mg/dl or urine output, ml/dl [§]	<1.2	1.2~1.9	2.0~3.4	3.4~4.9 or <500	>5.0 or <200

MODS: Multiple Organ Dysfunction Score

Organ System	Score				
	0	1	2	3	4
Respiratory ^a (P_{O_2}/F_{iO_2} ratio)	>300	226-300	151-225	76-150	≤75
Renal ^b (serum creatinine)	≤100	101-200	201-350	351-500	>500
Hepatic ^c (serum bilirubin)	≤20	21-60	61-120	121-240	>240
Cardio-vascular ^d (PAR)	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Hematologic ^e (platelet count)	>120	81-120	51-80	21-50	≤20
Neurologic ^f (Glasgow Coma Score)	15	13-14	10-12	7-9	≤6

Critical Care Med. 1995;23:1638-1652

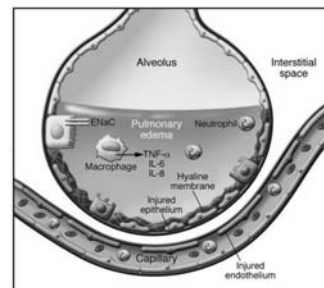
Denver Post-injury MOF Score

Organ System	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary				
P_{aO_2}/F_{iO_2} ratio	>250	250-200	200-100	≤100
Renal				
Creatinine (mg/dL)	≤1.8	1.9-2.5	2.51-5.0	>5.0
Creatinine (μmol/L)	<159	160-221	222-442	>442
Hepatic				
Bilirubin (mg/dL)	≤2.0	2.0-4.0	4.1-8.0	>8.0
Bilirubin (μmol/L)	<34	34-68	69-137	>137
Cardiac				
	No inotropes	Only 1 inotrope at a small dose ^a	Any inotrope at moderate dose or >1 agent, all at small doses ^a	Any inotrope at large dose or >2 agents at moderate doses ^a
		Small	Moderate	Large
Milrinone	<0.3	0.4-0.7	>0.7	
Vasopressin	<0.03	0.03-0.07	>0.07	
Dopamine	<5	6-10	>10	
Dobutamine	<5	6-10	>10	
Epinephrine	<0.06	0.06-0.15	>0.15	
Norepinephrine	<0.11	0.11-0.5	>0.5	
Phenylephrine	<0.6	0.6-3	>3	

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:



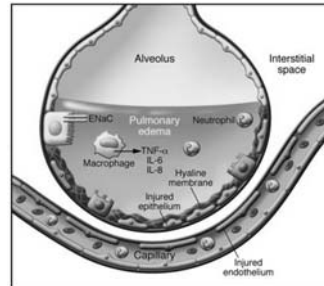
- > P_{aO_2}/F_{iO_2} : 90
- > MAP 50 on Norepi, Vasopressin

Patient 2:

- > Hypotension x 24 hrs, now resolved
- > Creatinine: 4.5
- > Platelets: 56K

Dysfunction of Organ Systems

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



Matthay JCI 2012

Refractory Shock

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

By Elizabeth Simpson
The Virginian-Pilot
Mar 23, 2017



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

Chest. 2016 Dec 6. pii: S0012-3692(16)62564-3.

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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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



JAMA 2010; 304:1787-94
JAMA 2010; 303:763-70
Crit Care Med. 2009;37(10 Suppl):S309-15
Image NY Times 2010.

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

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 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



JAMA. 2013;310(15):1591-1600.
 Crit Care Med 2007; 35: 139-145
 Lancet 2009; 373: pp. 1874-1882
 AJRCCM 2015; 193: 1101-1110
 Chestnet.org

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

Original Investigation
Effect of Palliative Care–Led Meetings for Families of Patients With Chronic Critical Illness
 A Randomized Clinical Trial

Shannon S. Carson, MD, Christopher E. Cox, MD, MPH, Sylvan Wallenstein, PhD, Laura C. Hanson, MD, MPH, Marion Davis, MD, James A. Tulsky, MD, Emily Chal, MD, Judith E. Nelson, MD, JD

JAMA. 2016;316:51-62.

ICU Discharge Planning: Cost savings?

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

	National Readmission Data ^a		
	No. of All Index Admissions Readmitted Within 30 Days	Estimated Mean Length of Stay (95% CI), d ^b	Estimated Mean Cost per Readmission (95% CI), \$ ^b
Admissions associated with 30 d readmission	1 187 697	6.4 (6.4-6.5)	8242 (8225-8258)
Primary Analyses^c			
Sepsis	147 084	7.4 (7.3-7.4)	10 070 (10 021-10 119)
Acute myocardial infarction	15 001	5.7 (5.6-5.8)	9424 (9279-9571)
Heart failure	79 480	6.4 (6.4-6.5)	9051 (8990-9113)
Pneumonia	59 378	6.7 (6.6-6.7)	9533 (9466-9600)
Chronic obstructive pulmonary disease	54 396	6.0 (5.9-6.0)	8417 (8355-8480)

N Engl J Med. 2009;360:1418–1428.
 J Am Heart Assoc 2017;6:e004072
 JAMA 2017;317(5):530-531.

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

J Clin Nurs 2005;21:39–46
 J Hosp Med 2007;2:314–23

THRIVE initiative

- Connect with ICU survivors
- Resources



<http://www.mycucare.org/Thrive/>
<http://www.icusteps.org/>

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?

