# Multi-organ Failure and Mechanisms of Acute Pancreatitis

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# Acute Pancreatitis (AP)

- AP is a sudden acute inflammatory condition of the pancreas
  - Linked to **trypsin** activation
  - Causes severe abdominal pain (typically with vomiting, but not headache)
  - Elevated serum pancreatic digestive enzyme levels
- In severe acute pancreatitis (SAP), there is up to 20% mortality
- Pathophysiology of SAP – poorly understood
  - Systemic inflammation (SIRS)  (limited with enteral nutrition)
  - Multi-organ failure (reduced with fluids / lactated Ringer's solution)
- The first 6 hours are critical (the "**golden**" hour)

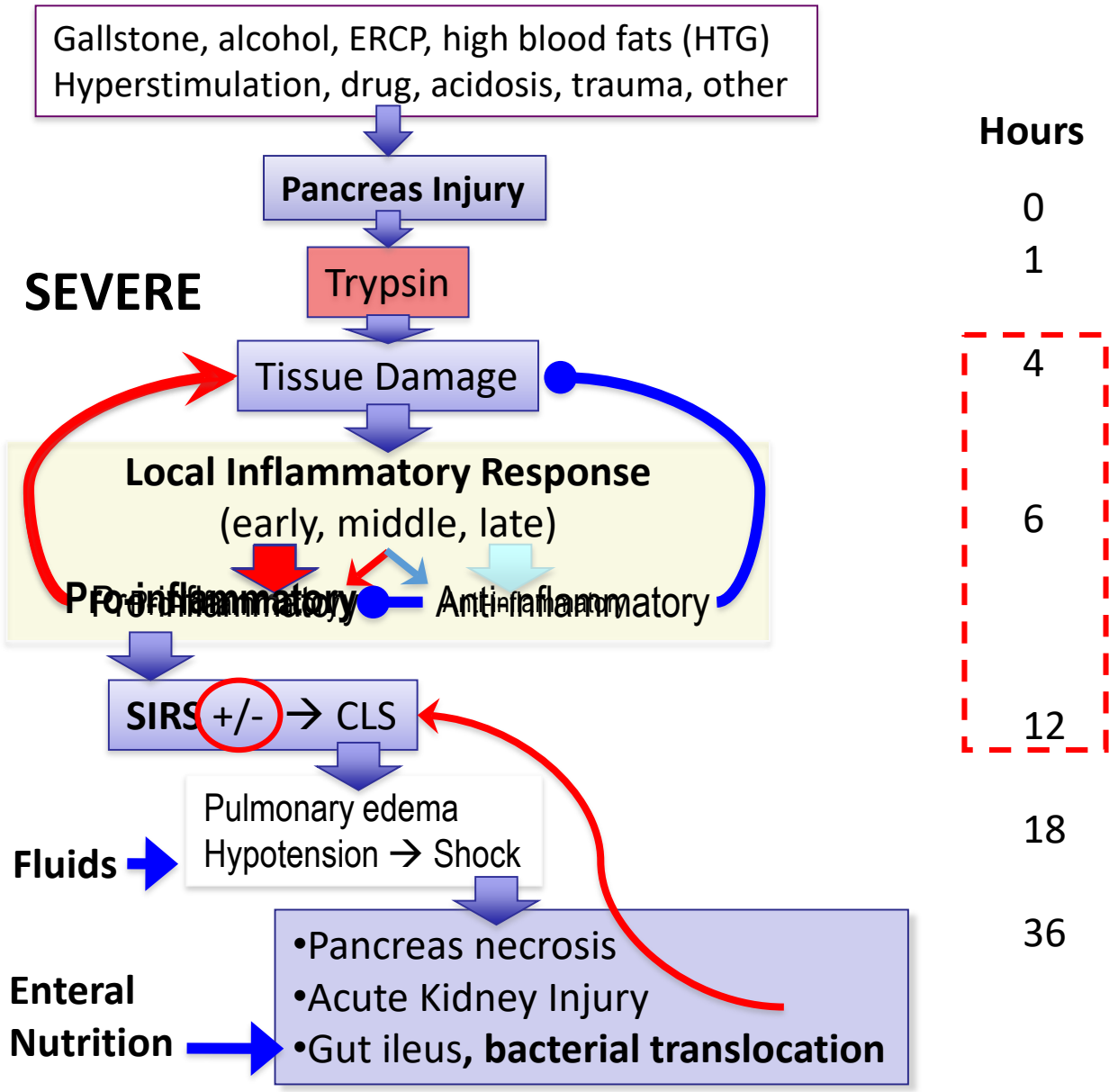
# Death requires systemic inflammation

- SIRS - systemic inflammatory response syndrome (”cytokine storm”):
- 2 or more of the following
  - *(1) temperature > 38 ° C or < 36 ° C*
  - *(2) HR > 90 BPM*
  - *(3) RR > 20 / min*
  - *(4) WBC > 12,000 or >10% Bands*
  - *(5) $PCO_2$ < 32 mmHg.*
- SIRS is also seen in Sepsis, Multiple Trauma, Burns (>25%), SARS-CoV-2
- **Organ failure requires *persistent* SIRS**
  - Buter et al. Br J Surg. 2002 Mar;89(3):298-302: PMID 11872053

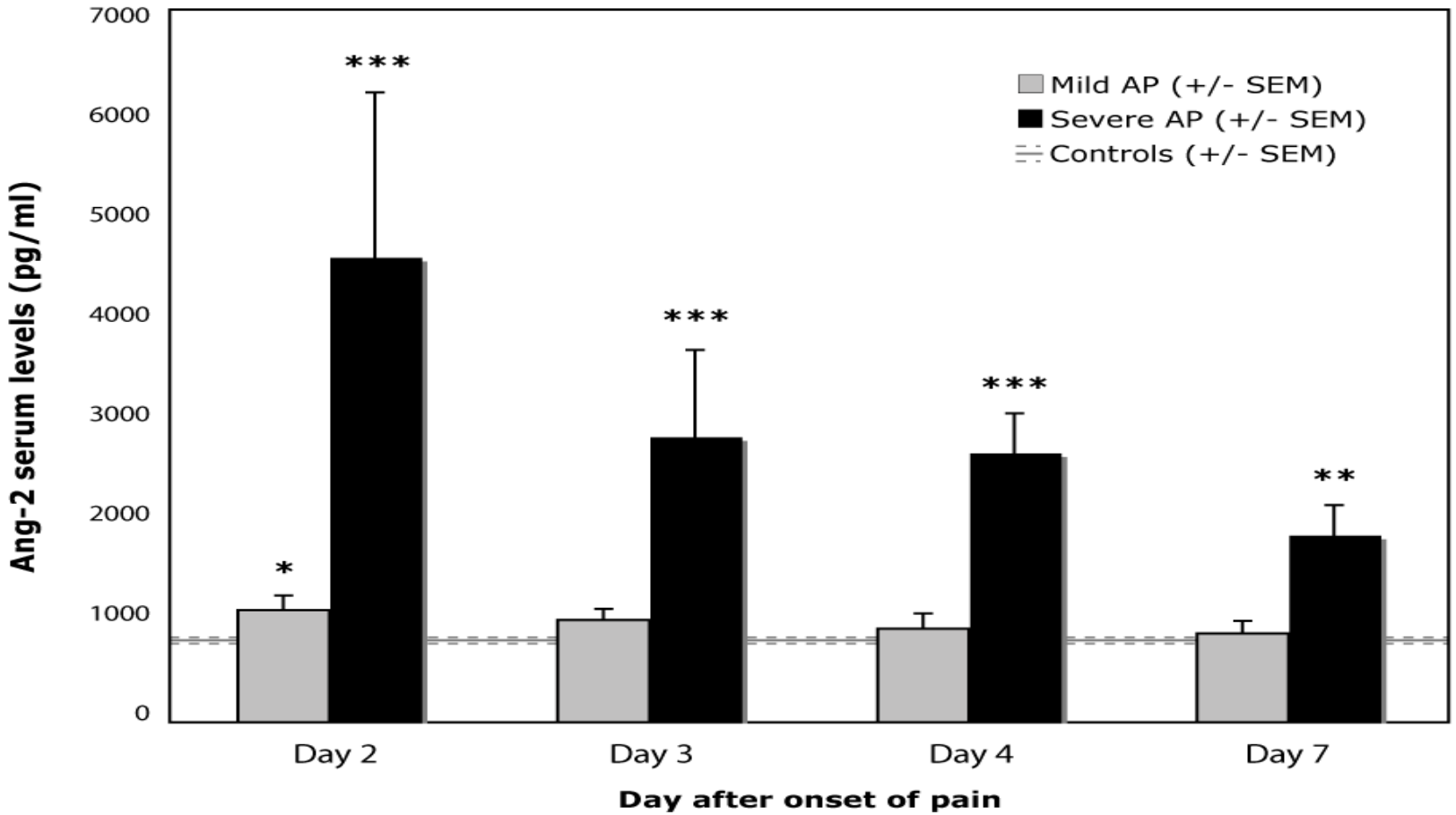
# Dynamic Process – 1st *48 hours!*

- Sequence
  - Injury
  - Pro-inflammatory
  - Anti-inflammatory
  - Resolution

- Severity
  - Major damage to the pancreas
  - "Cytokine Storm"
  - SIRS (sepsis physiology)
  - Capillary leak syndrome (CLS)
  - Multi-organ failure (MOF)



# Angiopoietin 2 and organ failure

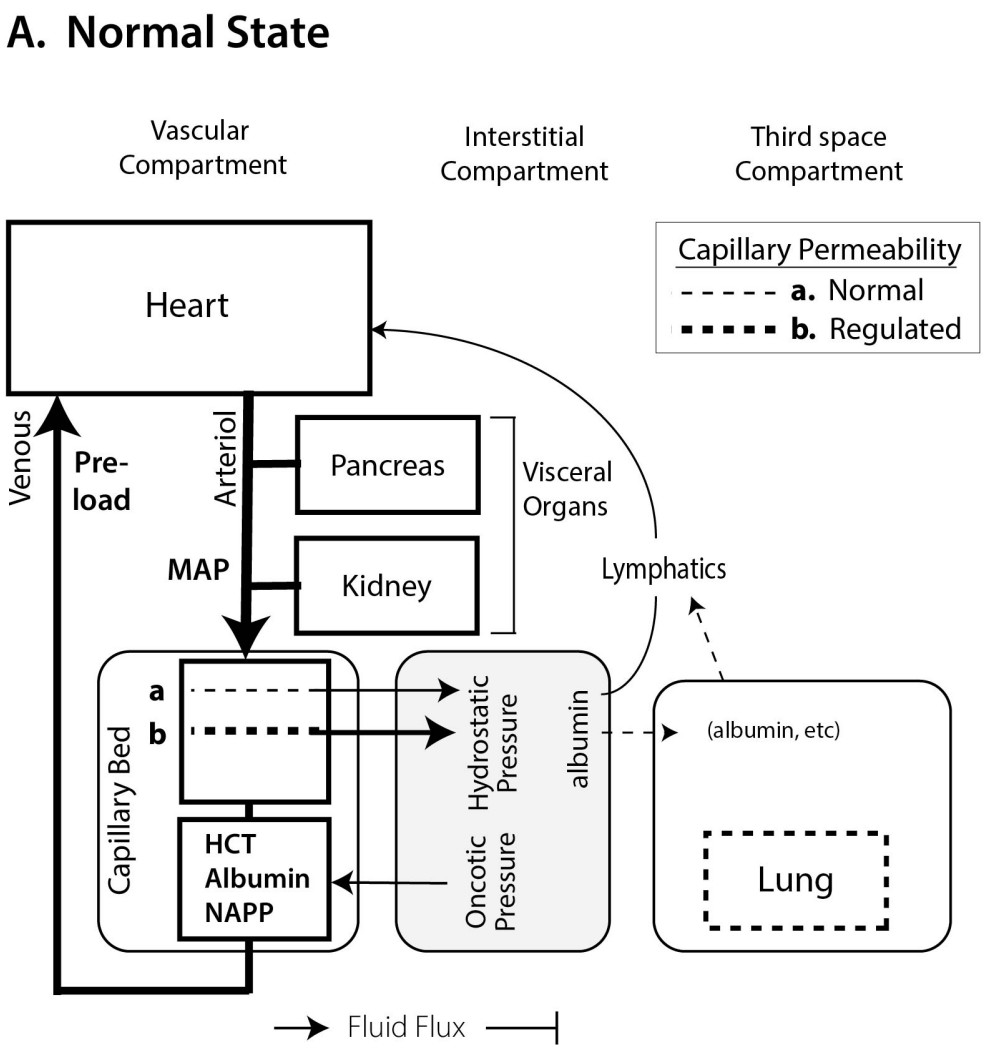



- Levels of Ang-2 were only elevated in patients with capillary leak and organ failure. Day 1 values predicts patient's final outcome

Whitcomb et al. *Am J Gastroenterol*. 2010 May 11;(epub May 21, 2010).

# Mechanism of Multi-organ Failure

- Lung
- Cardiovascular
- Kidney
- Pancreas




Komara NL, et al. Severe acute pancreatitis: Capillary permeability model linking systemic inflammation to multiorgan failure. *Am J Physiol Gastrointest Liver Physiol*. 2020; (in press).

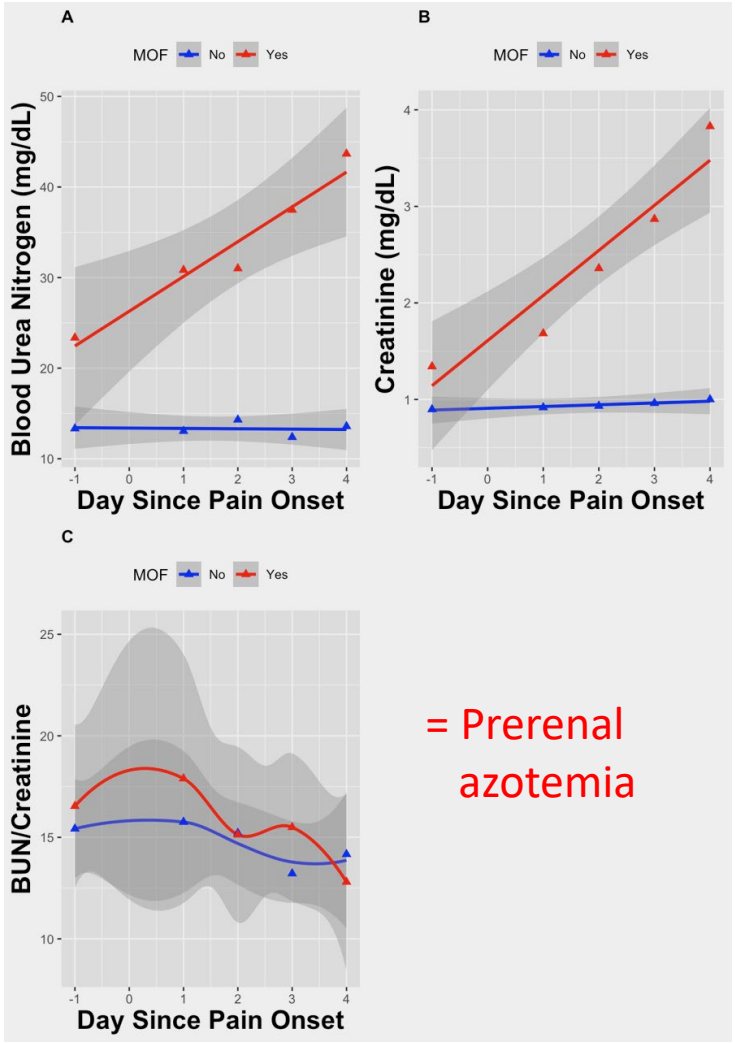
# Clinical Study of mild and severe AP patients

- Preadmission and daily hematocrit (HCT), blood urea nitrogen (BUN), creatine (Cr), albumin (Alb), and total protein (TP) were collected, and non-albumin plasma protein (NAPP = TP minus the Alb) was calculated
- Subjects served as their own controls for trajectory analysis.
- Of 57 SAP subjects, 18 developed MOF (5 died), and 39 were non-MOF (0 died).
- Hemoconcentration. Compared with *preadmission* levels, admission HCT increased in **MOF +5.00** [25%-75% interquartile range, IQR] versus **non-MOF -0.10** [-1.55, 1.40] ($P < 0.002$)
- HCT > +3 distinguishing MOF from non-MOF (odds ratio 17.7, $P = 0.014$).
- HCT in MOF vs non-MOF using population-based cutoff of >40%, >43% men, >36% women, >44% or >47% = **nonsignificant!** (huge variance in baseline HCT)

Komara NL, Paragomi P, Greer PJ, Wilson AS, Breze C, Papachristou GI, et al. Severe acute pancreatitis: Capillary permeability model linking systemic inflammation to multiorgan failure. *Am J Physiol Gastrointest Liver Physiol.* 2020. PMID:32877220

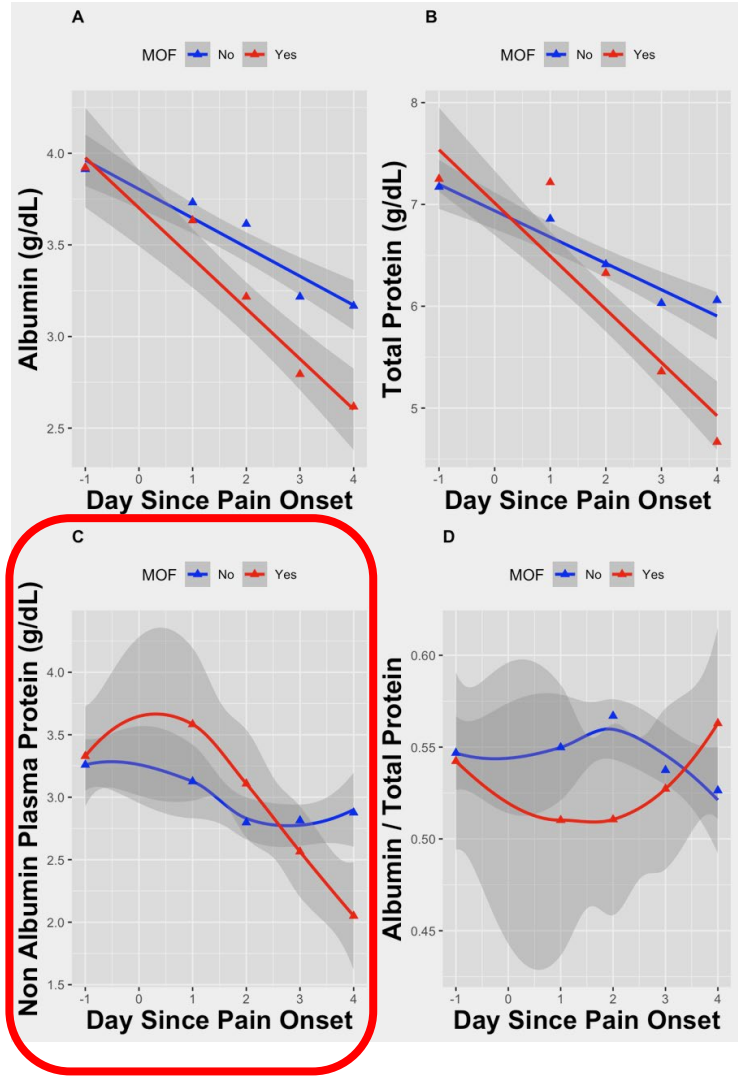
# Biomarkers of MOF: Kidney dysfunction and Capillary leak

BUN and Creatinine




= Prerenal azotemia

Albumin, Total Protein and TP minus Alb (NAPP)

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# Mechanism of Capillary Leak

Hypotheses:

A. Endothelial Cell Dysfunction
B. Hydrolysis of plasma proteins by active enzymes

# Acute pancreatitis study (DoD)

UPMC Study

- Serial blood samples from AP patients classified by Revised Atlanta Criteria (RAC) with or without OF by Modified Marshal Score (MMS) were compared.
- **18 AP subjects** (99 samples) were classified as **OF** (n=7) and **non-OF** (n=11).
- Cultured human intestinal microvascular **endothelial** cells (HIMEC) were treated with patient serum.
- **Proteolysis** was measured by amino acid and metabolite (AA/M) metabolomics.

# Comparison of AP patients +/- OF

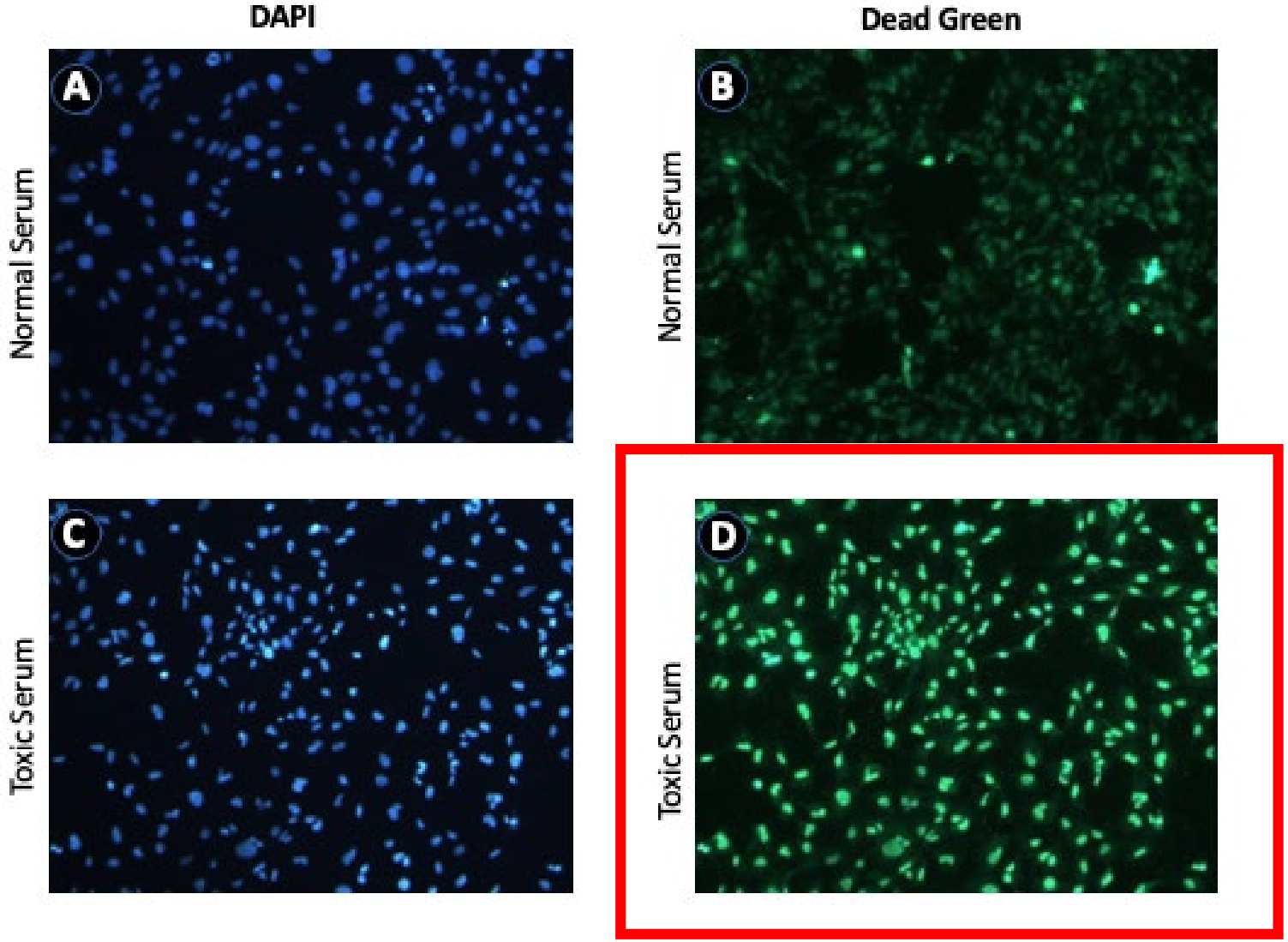
| Characteristic | All (n=18) | with OF (n=7) | without OF (n=11) | P-value |
|---|---|---|---|---|
| Age, years, median (IQR) | 48.5(36.75,60.5) | 65(42,68) | 41(34,52) | **0.033** |
| Gender (Male/Female) | 11/7 | 5/2 | 6/5 | 0.474 |
| White race, n (%) | 15 (83.3) | 6 (85.7) | 9 (81.8) | 0.415 |
| BMI, median (IQR) | 32.4(25.05,35.5) | 33.3(31.3,35.3) | 30.1(24.6,40.9) | 0.441 |
| Active smoking, n (%) | 5 (27.8) | 2 (28.6) | 3 (27.3) | 0.952 |
| Active alcohol, n (%) | 8 (44.4) | 3 (42.9) | 5 (45.5) | 0.914 |
| Charlson, median (IQR) | 0.5(0,2.25) | 2(1,4) | 0(0,1) | **0.011** |
| Etiology (1/2/3/3/4/5) | 6/2/3/6/1 | 3/0/2/1/1 | 3/2/1/4/1 | 0.513 |
| SIRS, median (IQR) | 2.5(2,3) | 2(2,4) | 3(2,3) | 0.703 |
| HCT, %, median (IQR) | 45.95(40.95,50.1) | 43.7(42.1,49.8) | 46(32.9,51.1) | 0.856 |
| BUN, mg/dl, median (IQR) | 16(10.75,25.75) | 31(20,37) | 12(10,17) | **0.013** |
| Creatinine, mg/dl, median (IQR) | 1.1(0.7,1.675) | 1.6(1.3,2.6) | 0.8(0.7,1.3) | **0.02** |
| RAC (1/2/3) | 4/9/05 | 0/2/5 | 4/7/0 | **0.003** |
| Pancreatic necrosis, n (%) | 10 (55.6) | 5 (71.4) | 5 (45.5) | 0.28 |
| ICU admission, n (%) | 14 (77.8) | 7 (100) | 7 (63.6) | 0.07 |
| LOS, days, median (IQR) | 14.5(7,29.5) | 31(17,35) | 7(6,15) | **0.003** |
| Mortality, n (%) | 0 (0) | 0 (0) | 0 (0) | 1 |

# Cultured HIMEC Cells (Endothelial cells)

- Serum samples from admission through up to 7 days was collected under EDRN protocol.
- Human intestinal microvascular endothelial cells (HIMEC) were cultured.
- HIMECs were cultured with serum for 24 hours.
- Endothelial cell stress and viability were measured.

# Results: Endothelial DEAD Green Viability assay

- HIMECs cultured with serum from OF patients **DIED**!

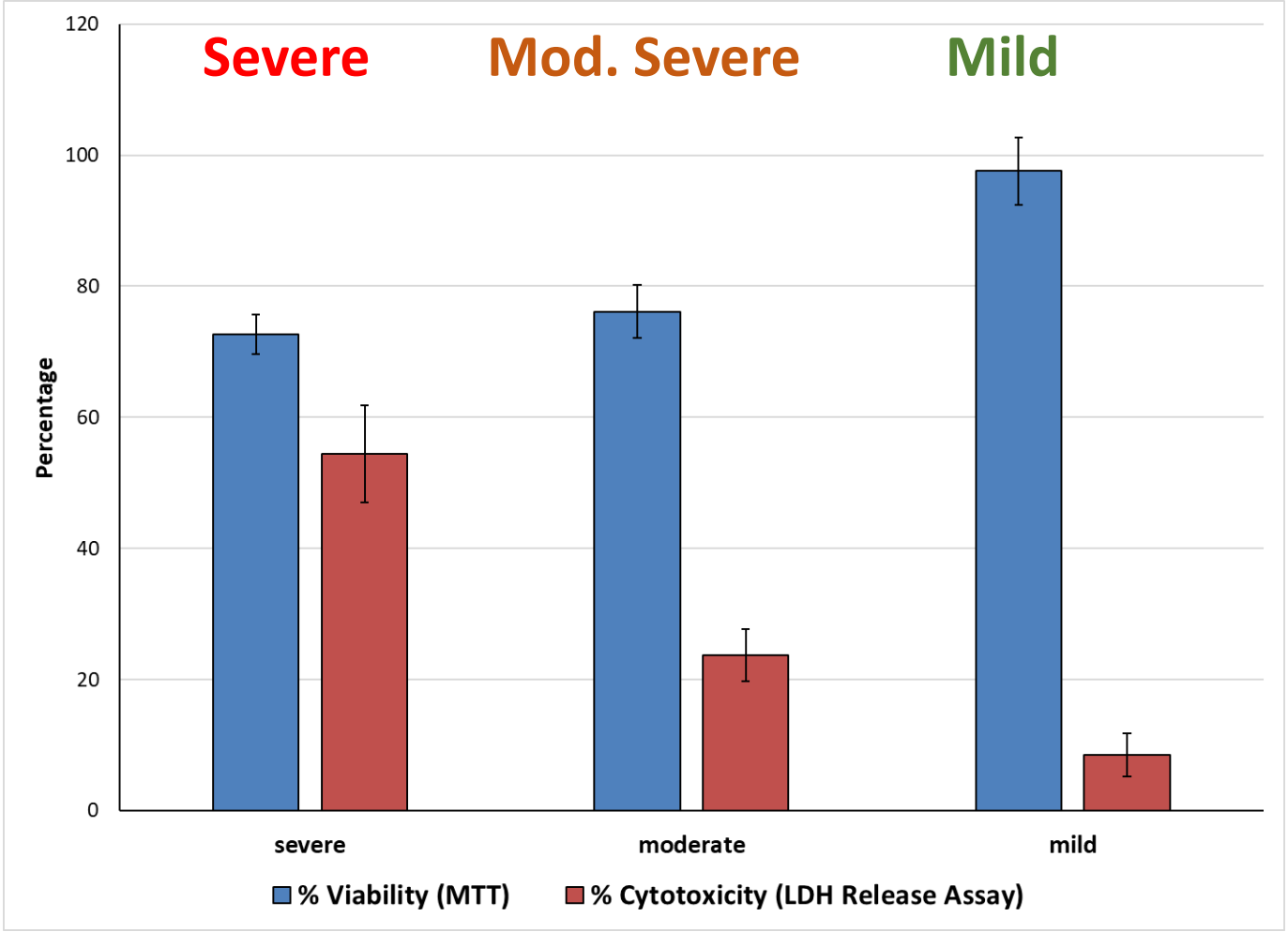


# Endothelial Cells + patient serum

Viability

Cytotoxicity

- **MTT and Lactate Dehydrogenase (LDH) Release Cellular Viability Assays.**
- serum from patients with mild, moderate and severe acute pancreatitis for 24 hours.



# Metabolomics*

- 187 ammino acids and AA metabolites AA/M analytes identified
- 120 significantly changed in concentration in OF ($p \leq 0.05$, ANOVA).
- **Increases were associated with OF** (115 increased versus 5 decreased; **$p < 2.2e^{-16}$**)
- 15 of 16 AA metabolic pathways involved
- **Results**: non-specific, unregulated proteolysis.

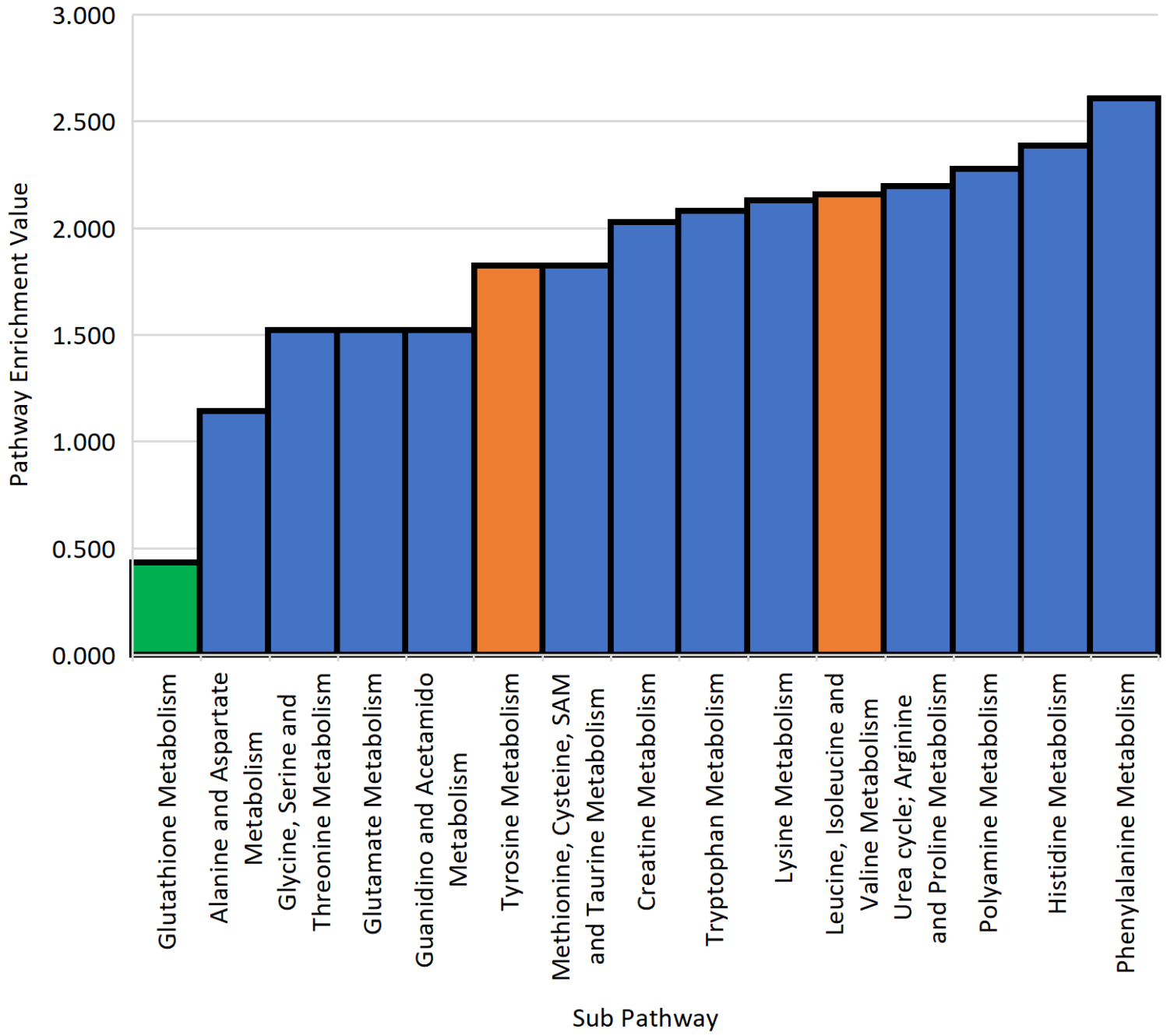
*Metabolon, Inc., Morrisville, NC, USA.

# AA Pathways

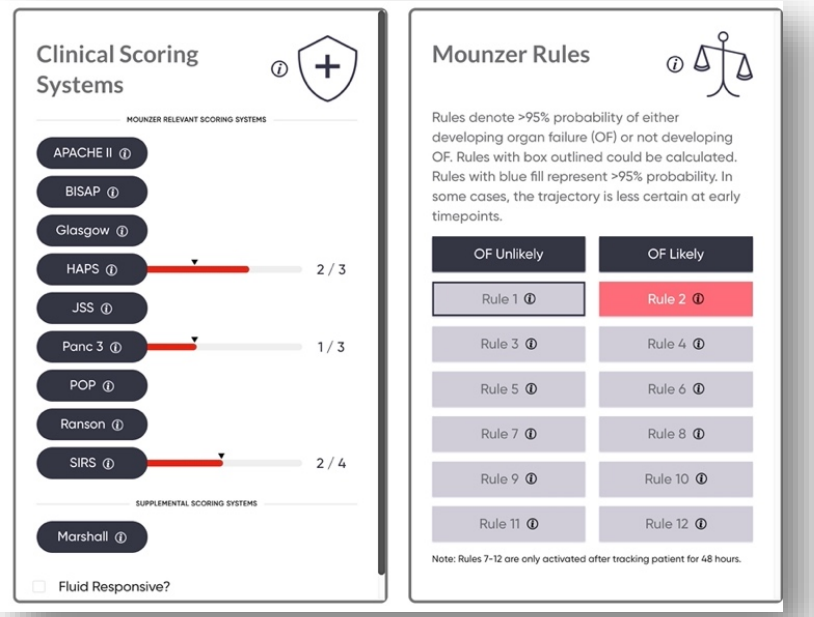
**Ratio of AA/M levels in organ failure (OF) versus no organ failure (no-OF) based on amino acid sub pathway.**

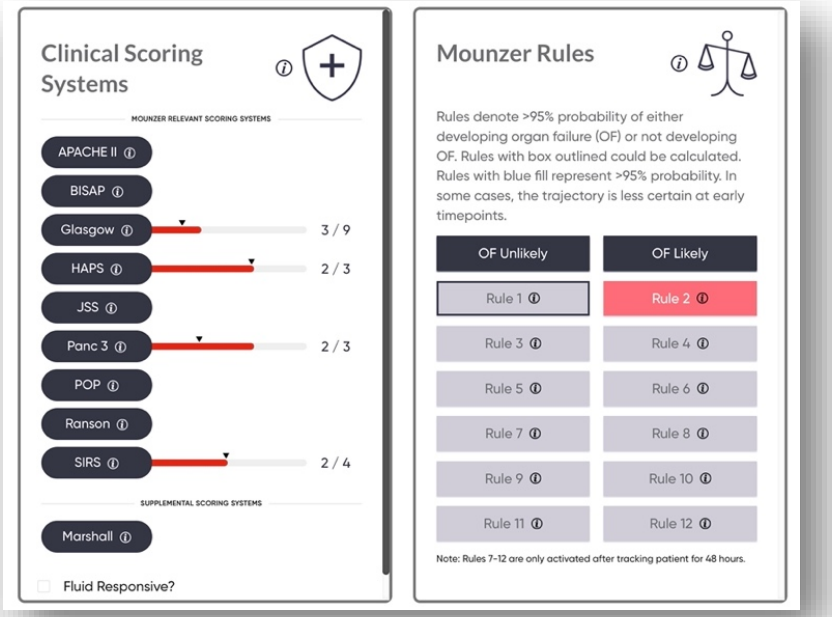
**Green** - The marked reduction is the glutathione metabolism pathway indicates consumption of detoxification compounds in phase II metabolism.

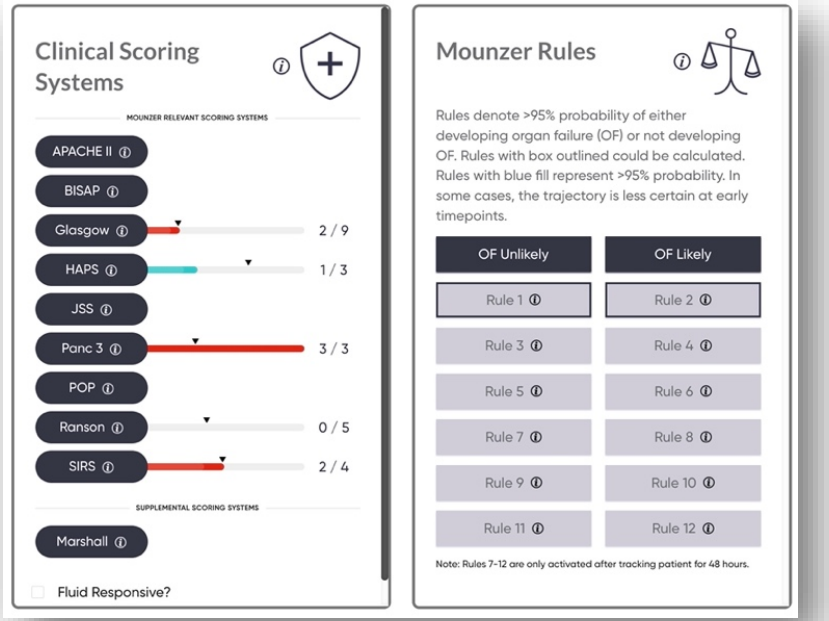
**Orange** – Key pathologic pathways in catecholamines and BCAAs.



# 3 patients with RAC mild/moderate AP → Toxic serum




- Three patients initially classified by RAC with mild or moderate-severe diseases progressed to more severe AP. Patients 1 and 2 had prolonged ICU courses, with patient 3 in the ICU for 7 days for HTG-AP.
- The **ADAPT** severity calculator was accurate during the first 12-24 yours of admission.
- RAC classification is *post hoc*, and may misclassify patients early in the course of disease.

# Summary / Conclusions

- Serum from AP subjects with OF is toxic to endothelial cells causing CLS
- High AA/M levels indicate unregulated proteolysis in OF patients
- Both CLS and Proteolysis may contribute to loss of plasma albumin and total protein.
- RAC is inaccurate in early classification of AP patients with toxic serum and emerging OF.

# Questions?

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