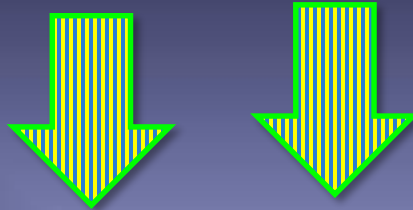


Intravenous  
Vitamin C



Severe Sepsis  
Acute Lung Injury

Alpha A. (Berry) Fowler, III, MD

Professor of Medicine

VCU Pulmonary Disease and Critical Care Medicine



**VCU**

V I R G I N I A   C O M M O N W E A L T H   U N I V E R S I T Y

I Have  
No Disclosures

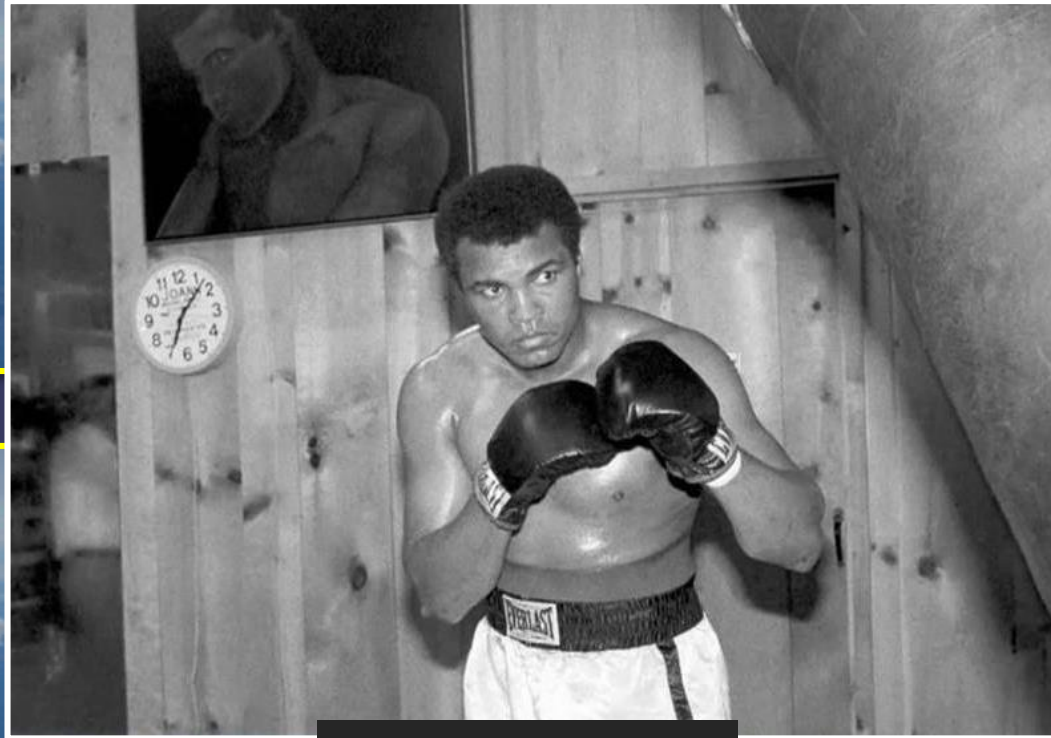
# Bacterial Sepsis

- Approximately 1 million people in the U.S. develop sepsis each year
- 35% to 40% of septic patients develop Acute lung injury
- 25% to 35% of septic lung-injured patients die

# 1 Fully Loaded Boeing 747

832 Passengers

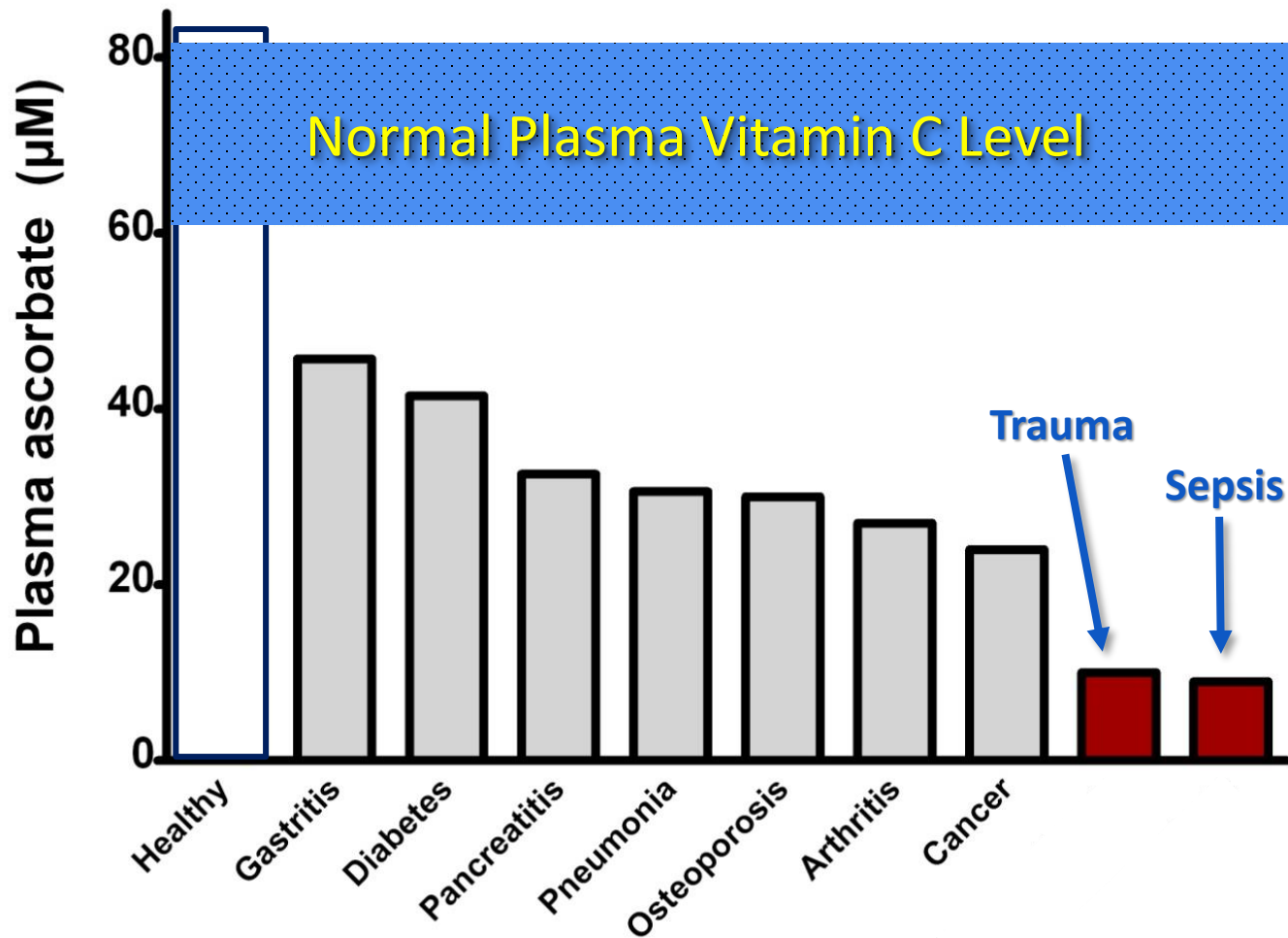
416 Passengers



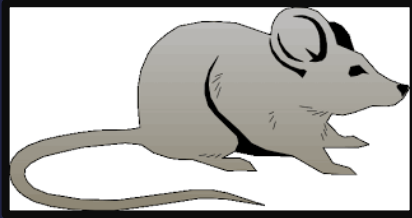
Muhammad Ali  
Sepsis - Pneumonia  
June 3, 2016



# Vitamin C in Disease



Surgical  
Sepsis



Surgical  
Sepsis



Vitamin C

20 Hours

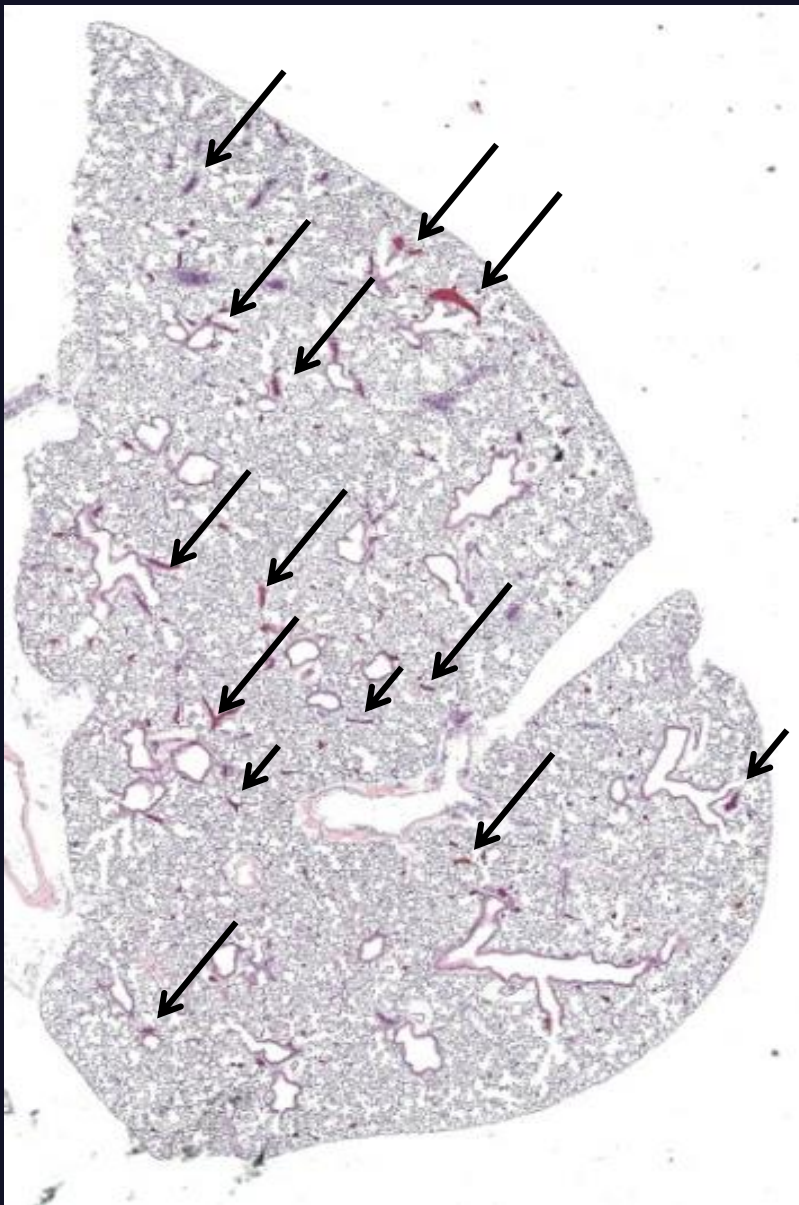


Detailed  
Study of  
Lung Tissue

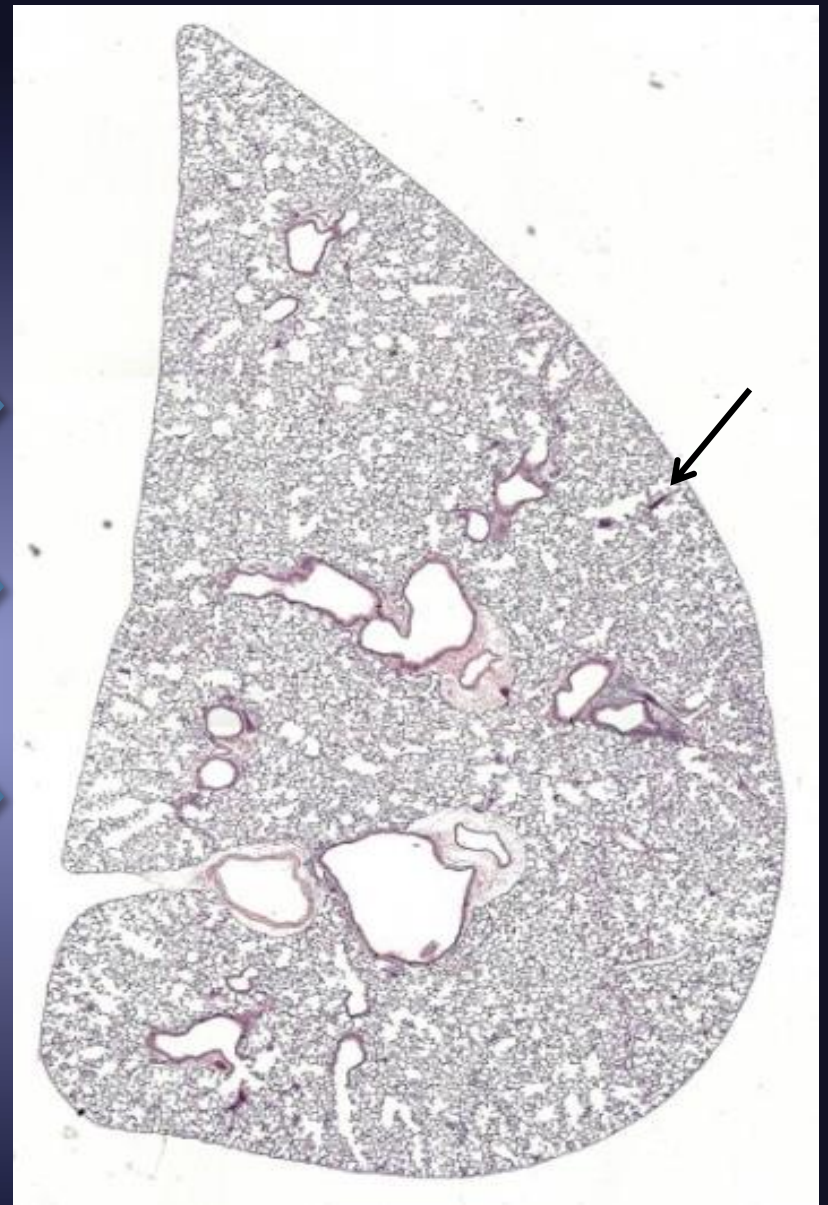
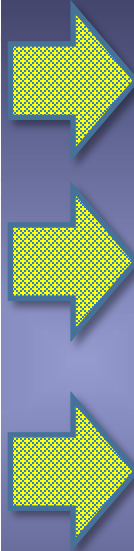
20 Hours



Detailed  
Study of  
Lung Tissue



Septic Murine Lung

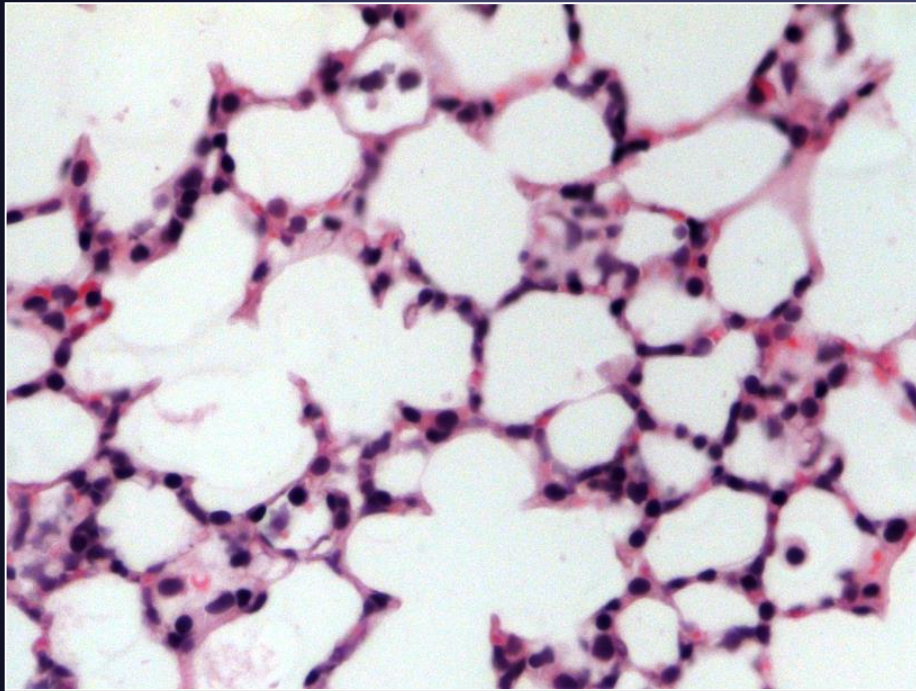


Vitamin C Treated Septic Lung

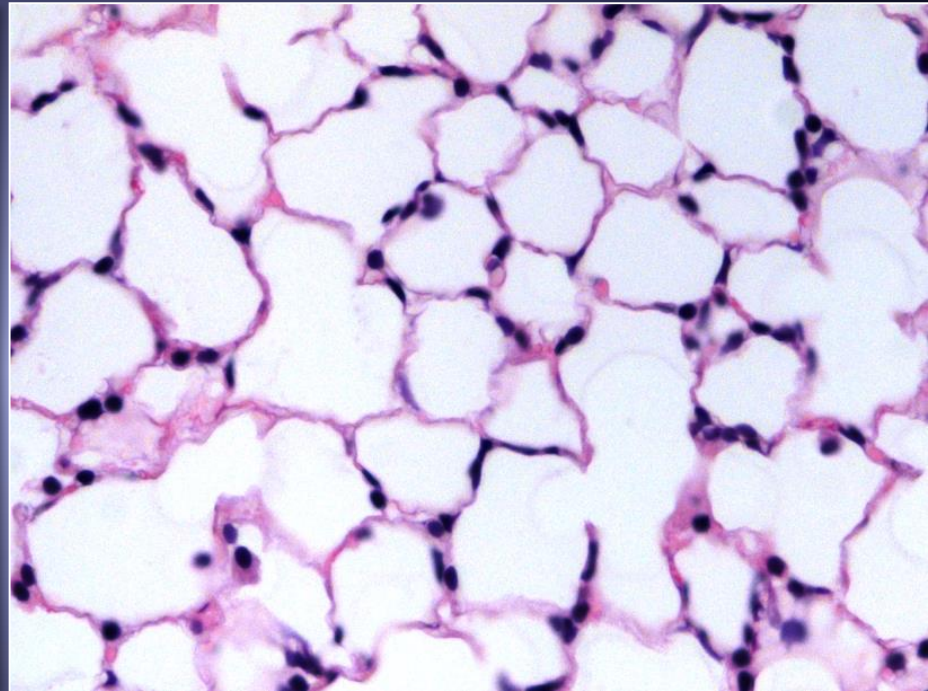


# Vitamin C

## Attenuates Histological Evidence Of Lung Injury

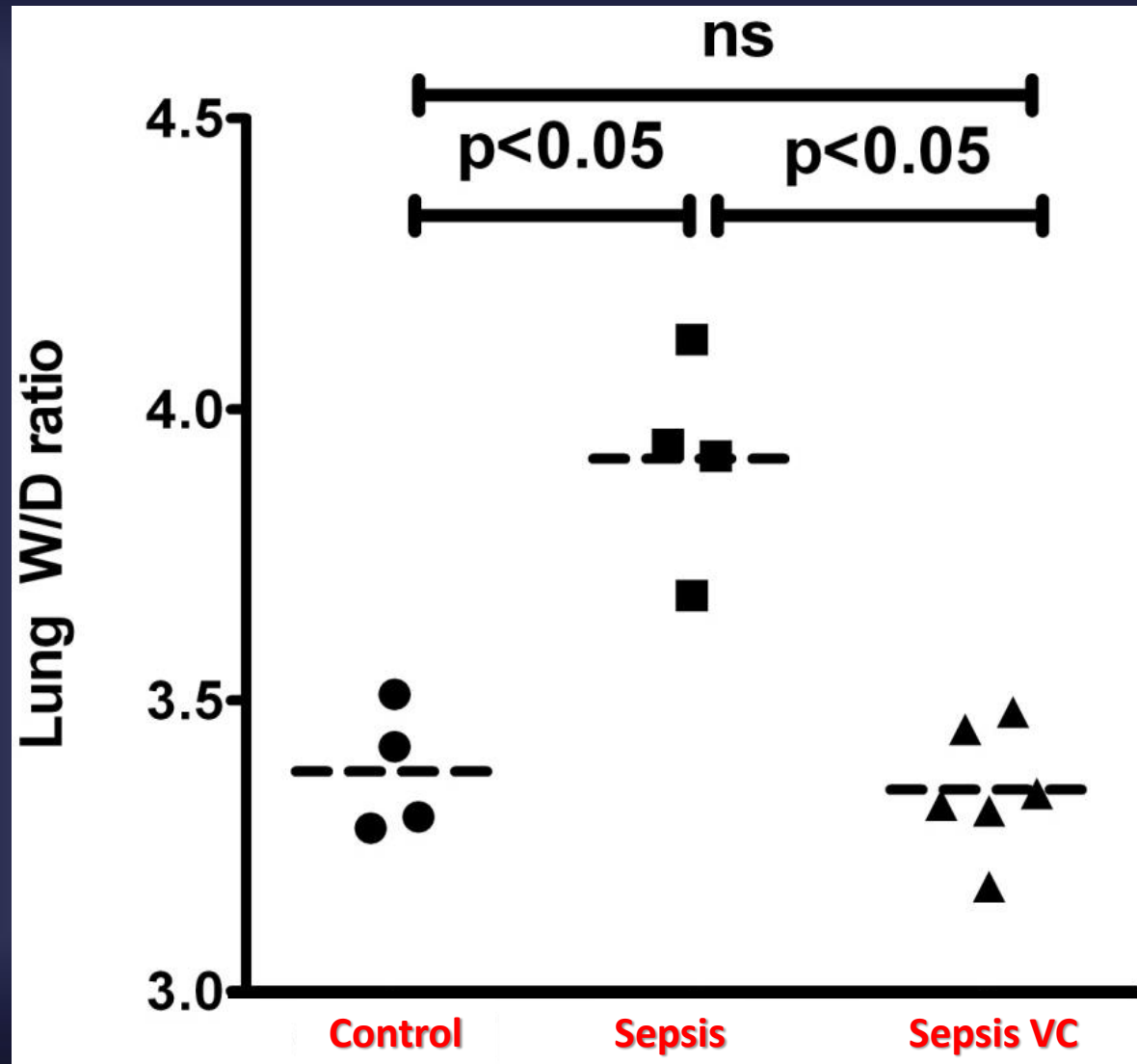


**Surgical Sepsis**



**Surgical Sepsis**  
**Vitamin C Treated**

# Lung Water



# Plasma Ascorbate Levels In Human Sepsis

- Subnormal levels a constant feature in septic patients
- Ascorbate levels correlate inversely with the incidence of multiple organ failure  
(low levels higher numbers of organs failed)
- Ascorbate levels correlate directly with survival  
(low levels low survival)

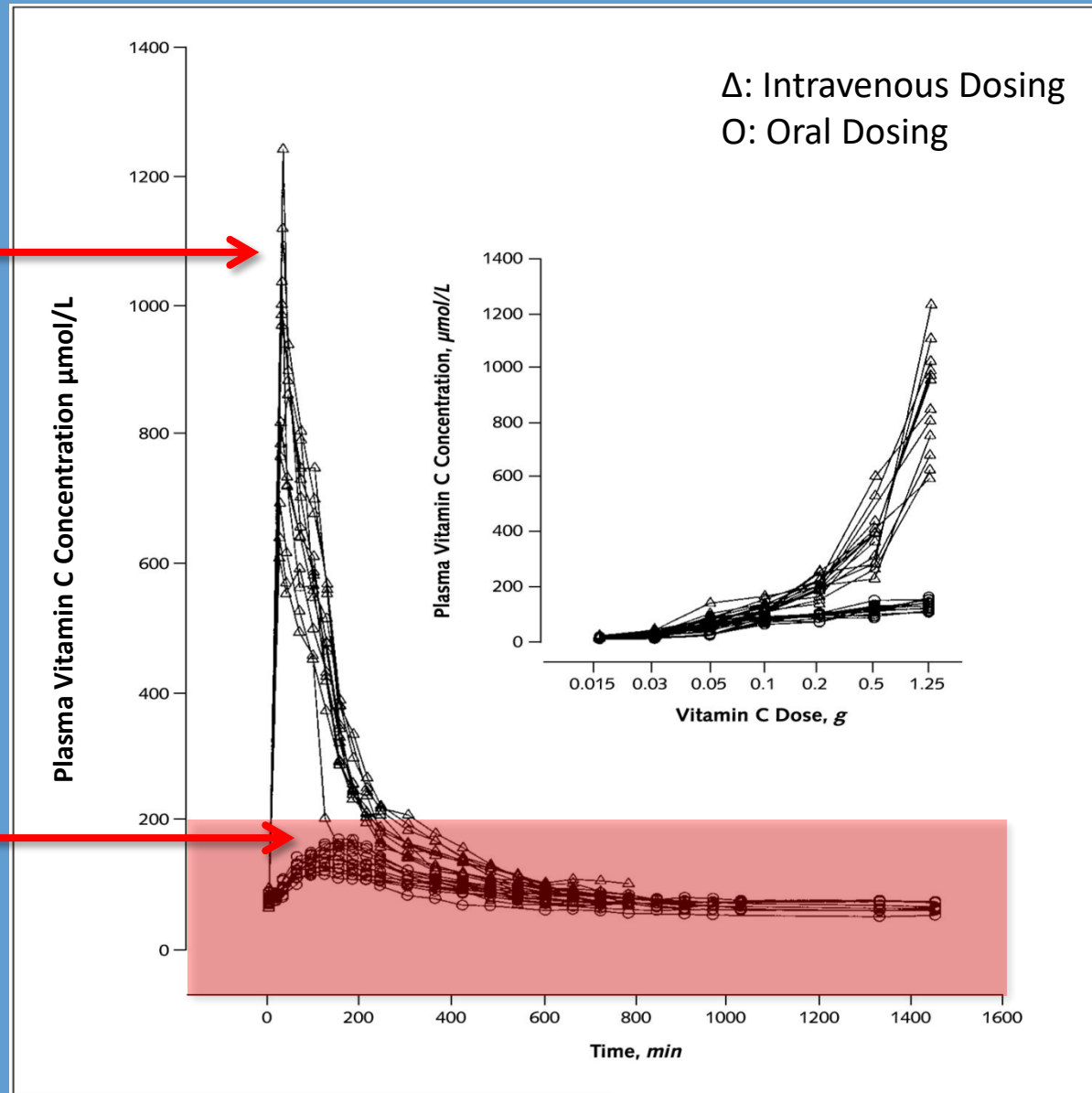
Borrelli et al. Crit Care Med. 1996, 24 (3): 392-397, PMID: 8625625.

# Phase I Safety Trial

- Severe Sepsis
- IRB (April 2010) Enrollment (August 2010)
- Septic Patients: Geographic MRICU patients
- Randomized, double blind, placebo-controlled
- **AE:** Systemic hypotension, tachycardia, nausea
- 1) Placebo, 2) 50 mg/kg/24 hr, 3) 200 mg/kg/24 hr
- IV VitC → ¼ dose infused 6 hours → D5%W
- Blood Draw (0, 12, 24, 36, 48, 72, 96 hours)

IV

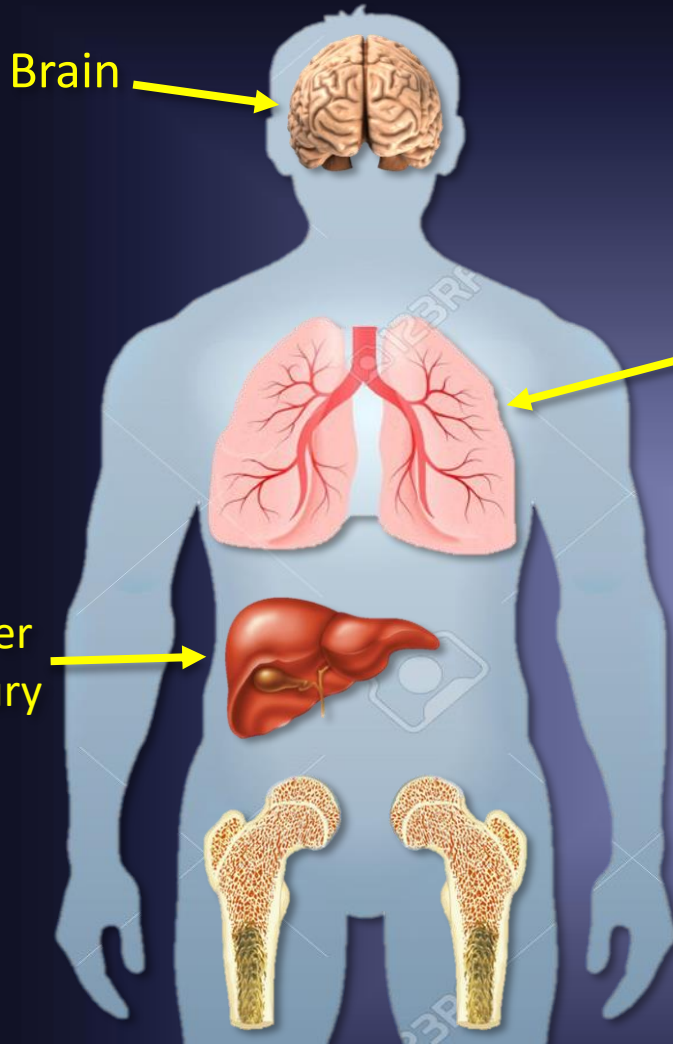
Oral





# Assessing Organ Injury

## SOFA SCORE



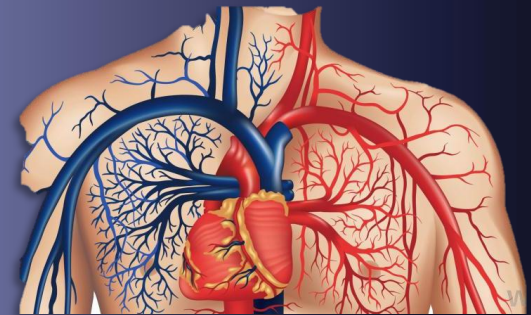
Liver  
Injury

Bone Marrow  
Dysfunction

Respiratory  
Failure



Renal  
Failure



Shock

Extent of  
Pharmacologic Support

# Sequential Organ Failure Assessment Score

## SOFA

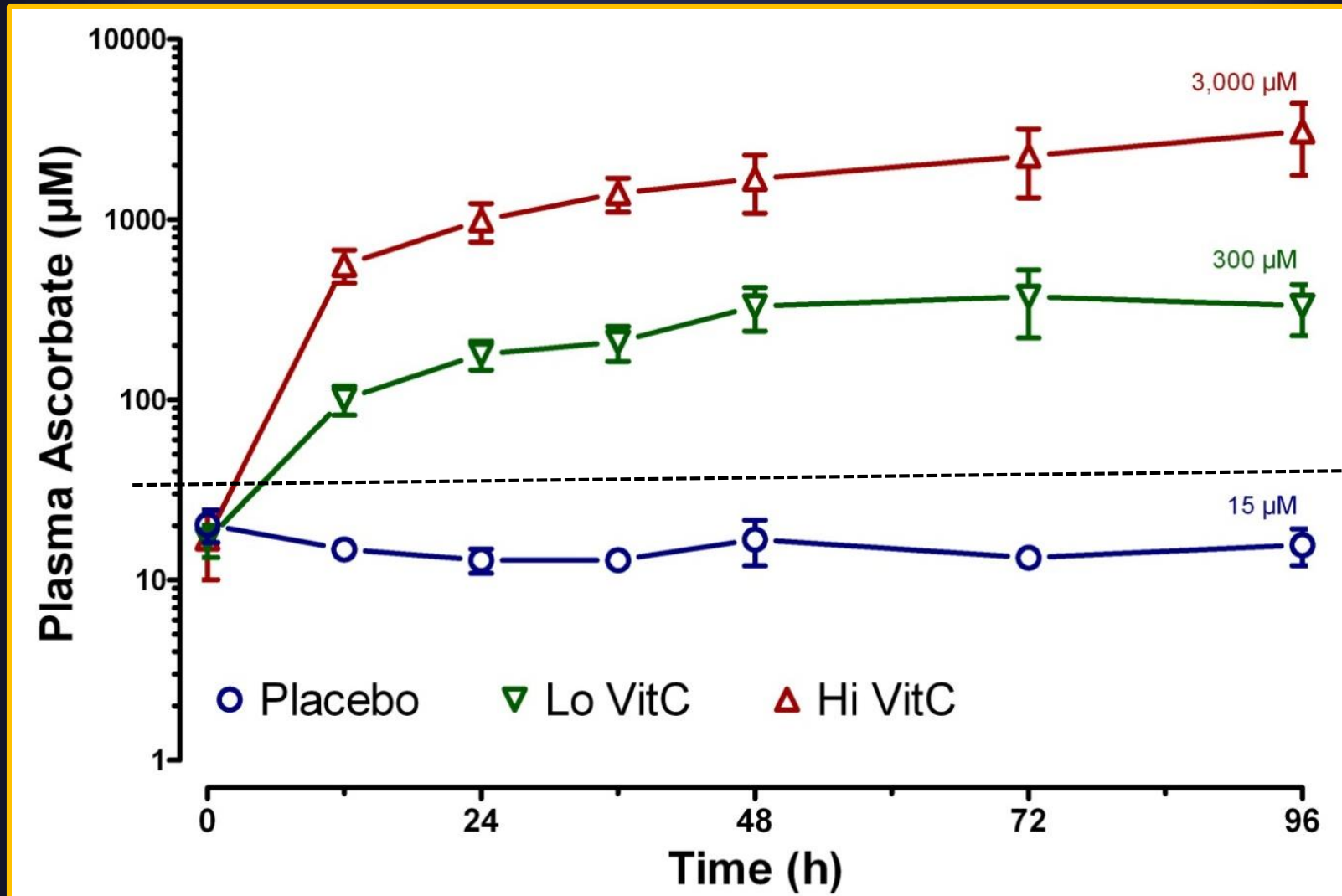
Lung (PaO <sub>2</sub> /FiO <sub>2</sub> mm/Hg)		Brain (Coma)		Cardiovascular (Shock)		Liver (Bilirubin)		Bone Marrow (Platelet)		Renal Failure (Creatinine)	
< 400	1	13-14	1	MAP<70 Mm/Hg	1	1.2-1.9	1	<150	1	1.2-1.9	1
< 300	2	10-12	2	Dopamine ≤ 5 µg/kg	2	2.0-5.9	2	<150	2	2.0-3.4	2
< 200 mechanically ventilated	3	6-9	3	Norepi ≤ 0.1 µg/kg	3	6.0-11.9	3	<50	3	3.5-4.9	3
< 100 mechanically ventilated	4	<6	4	Norepi ≥ 0.1 µg/kg	4	>12	4	<20	4	>5	4
Organ Failure Scores											

**SOFA Score = Sum of Organ Failure Scores**

# Phase I Safety Trial

- 31 patients screened – 24 enrolled and randomized
- Placebo: (4M, 4F, age 54-68 yrs)
- Lo-VitC: (5M, 3F, age 30-70 yrs)
- Hi-VitC: (4M, 4F, age 44-92 yrs)
- SOFA - Placebo: 13.1, SOFA - Lo-Vit C: 11.6  
SOFA Hi-Vit C - 12.2

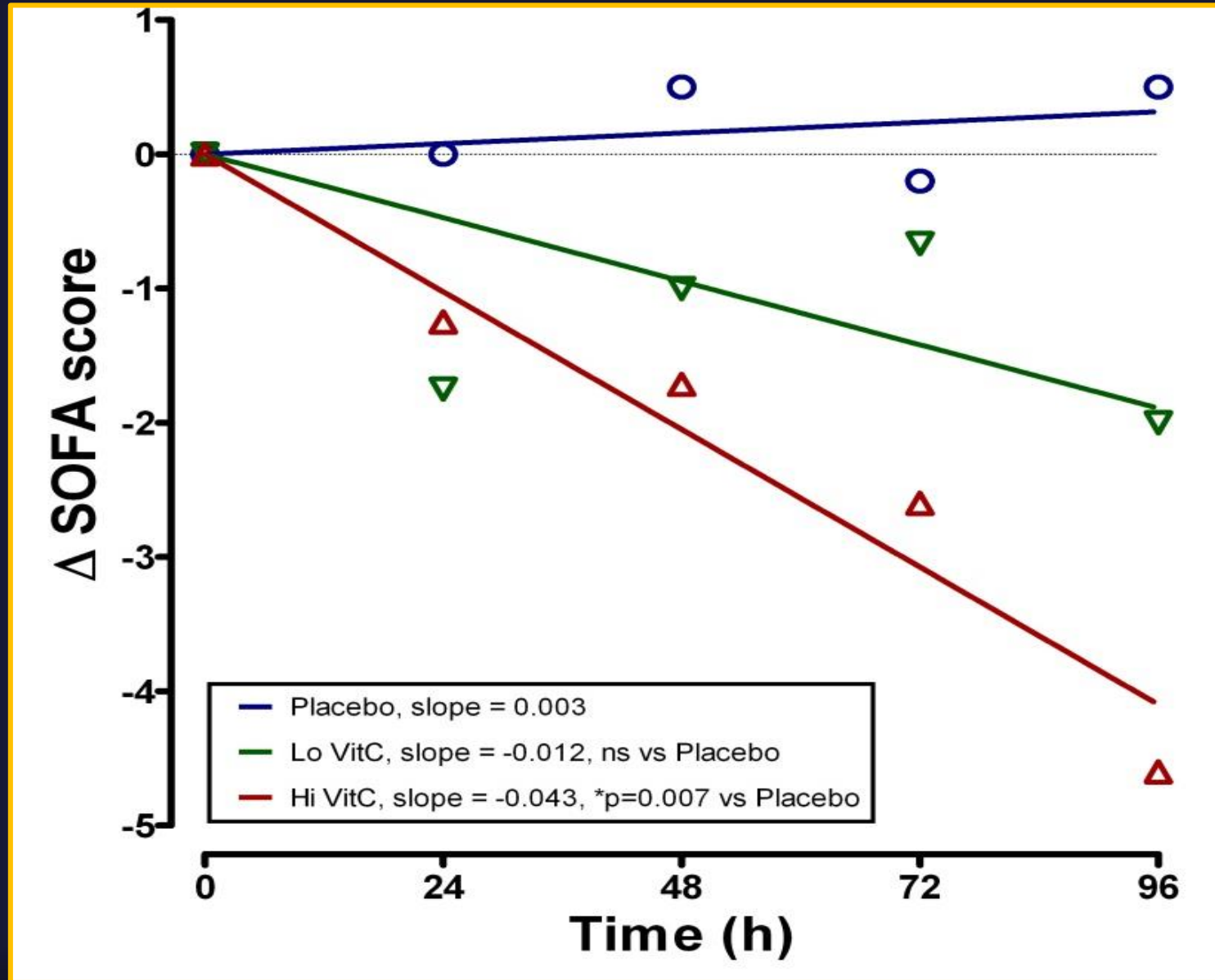
# Plasma Vitamin C Levels

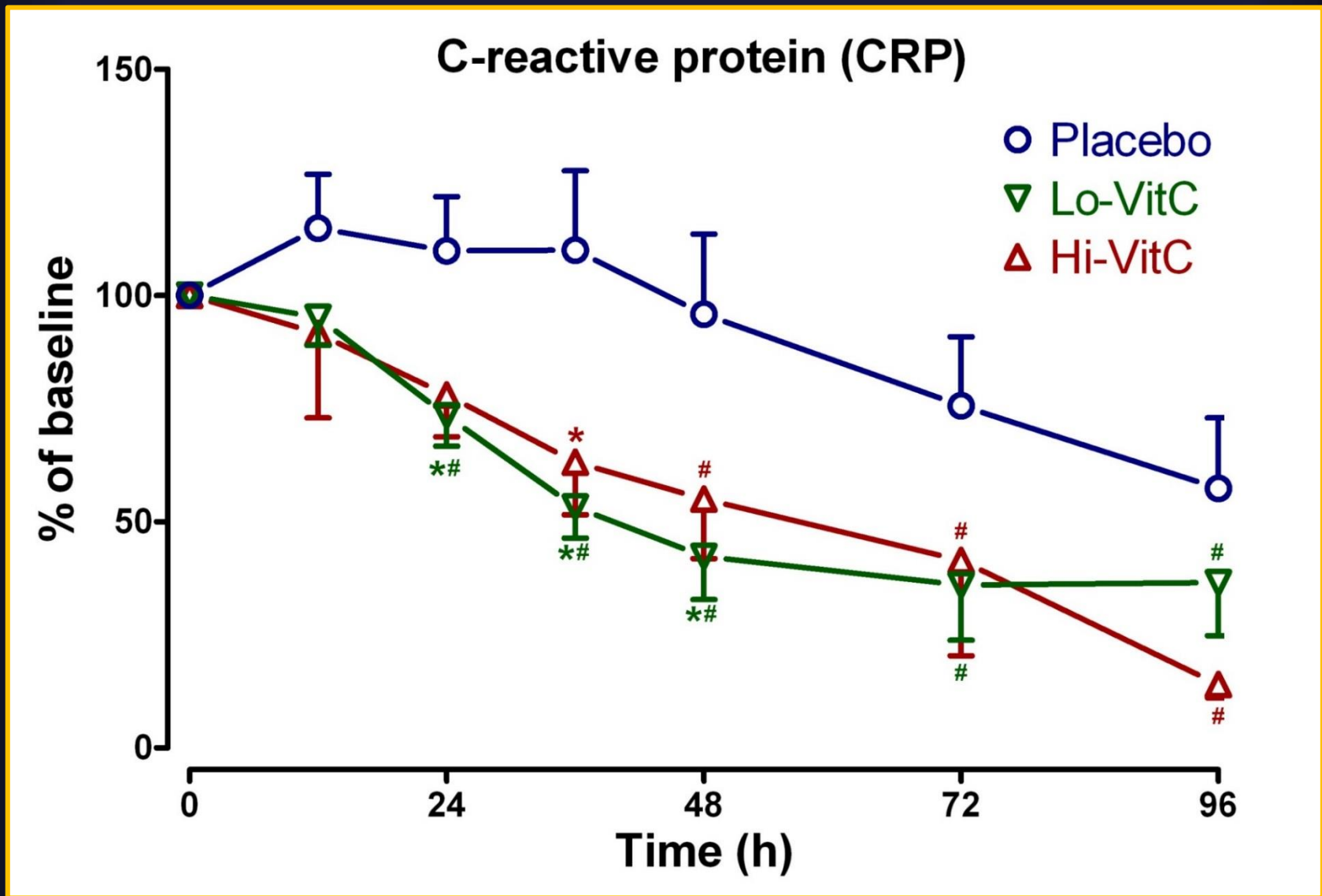


# Ascorbate Consumed In Sepsis

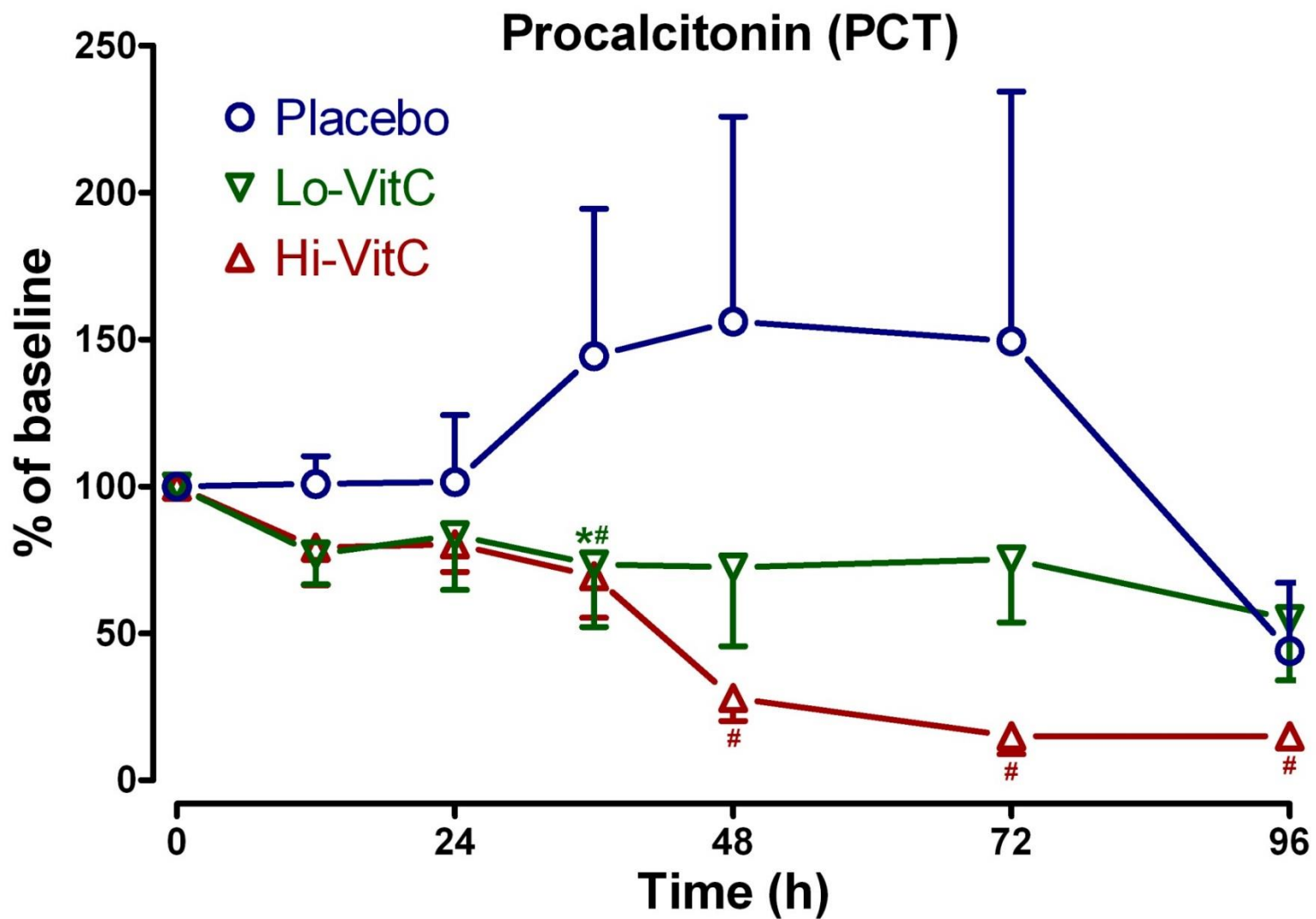
- By reduction of plasma free iron
- By the scavenging of aqueous free radicals
- By destruction of dehydroascorbic acid
- Destruction permits uncontrolled oxidant activity

# SOFA Scores

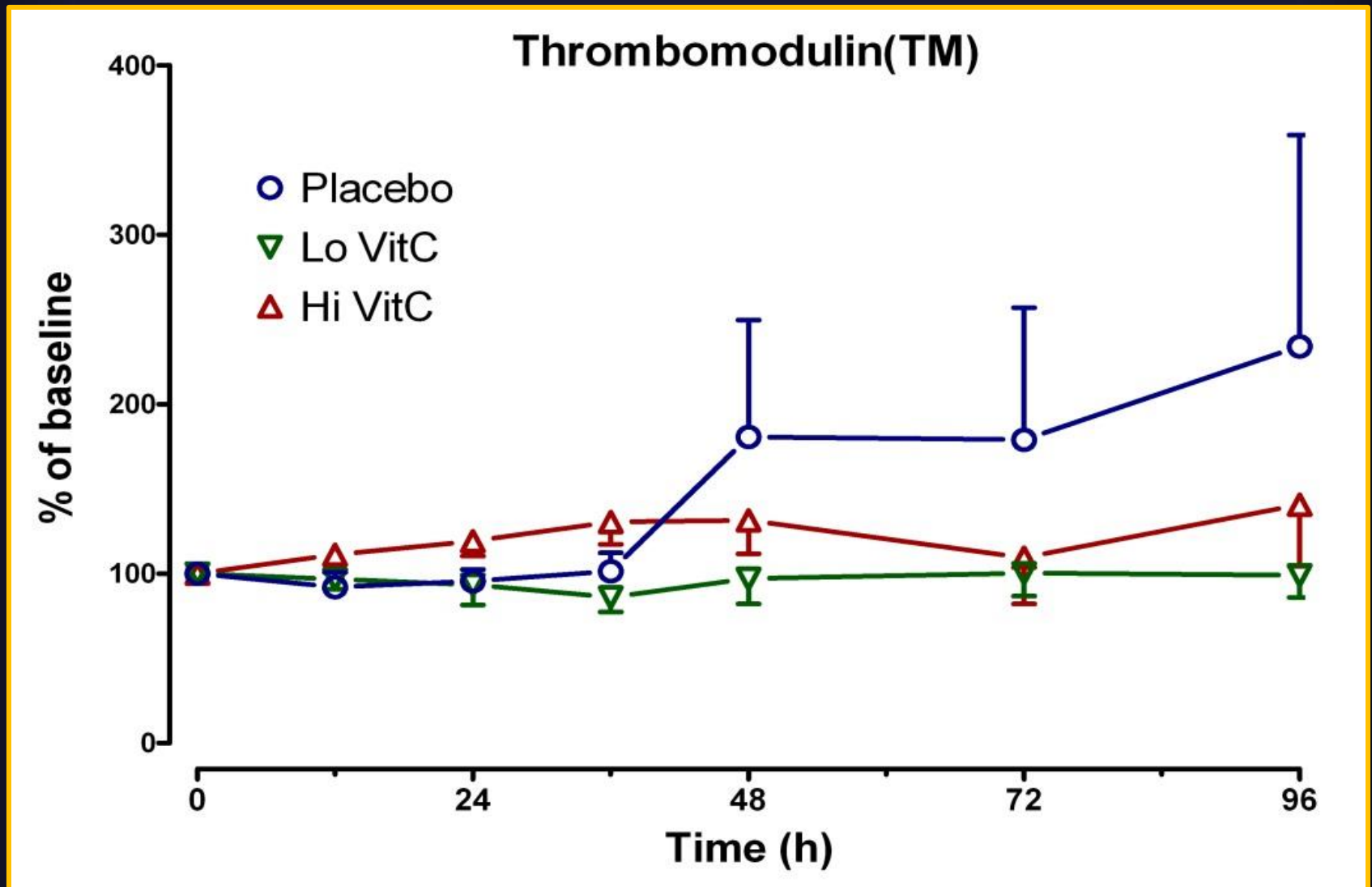












# Intravenous Vitamin C

- Safe
- Mortality reduced
- Multiple organ failure significantly reduced
- Blood markers inflammation and vascular injury significantly attenuated

# Plasma Vitamin C Augmentation

## Human Studies

- Lowered Incidence of ARDS and MOF in surgically critically ill
- Lowered capillary leak in patients with 50% full thickness burns
- Vit C + selenium + n-acetyl cysteine + Vit E lowered ARDS mortality by 50%

(Published in abstract only)

Nathens et al. Ann Surg. 2002, 236 (6): 814-822, PMID: 12454520.

Tanaka et al. Arch Surg. 2000, 135 (3): 326-331, PMID: 9041919.

Sawyer et al. Crit Care Med. 1989, 17: S153

## Acute Respiratory Distress Syndrome: E. Coli Sepsis



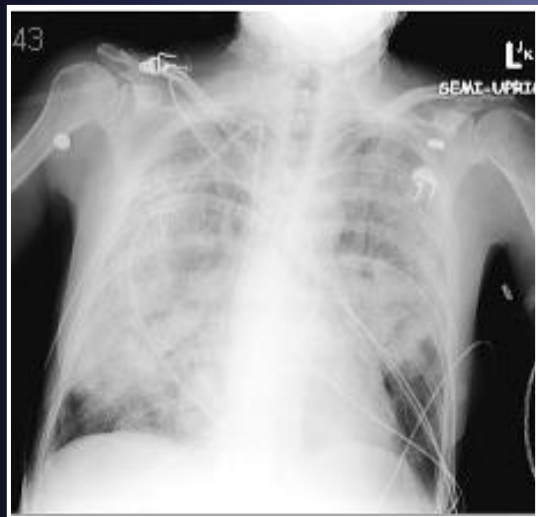
Baseline



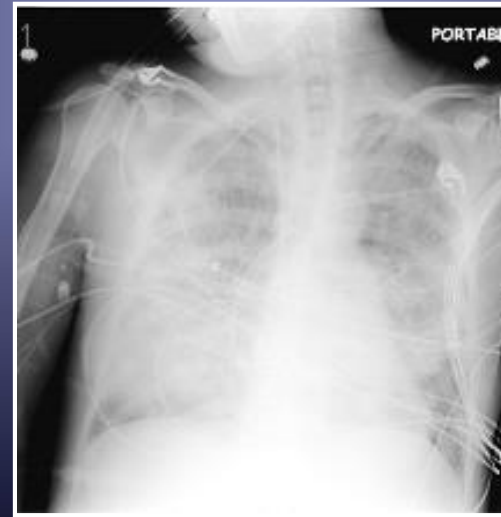
Day 2



Day 3 AM



Day 3 PM



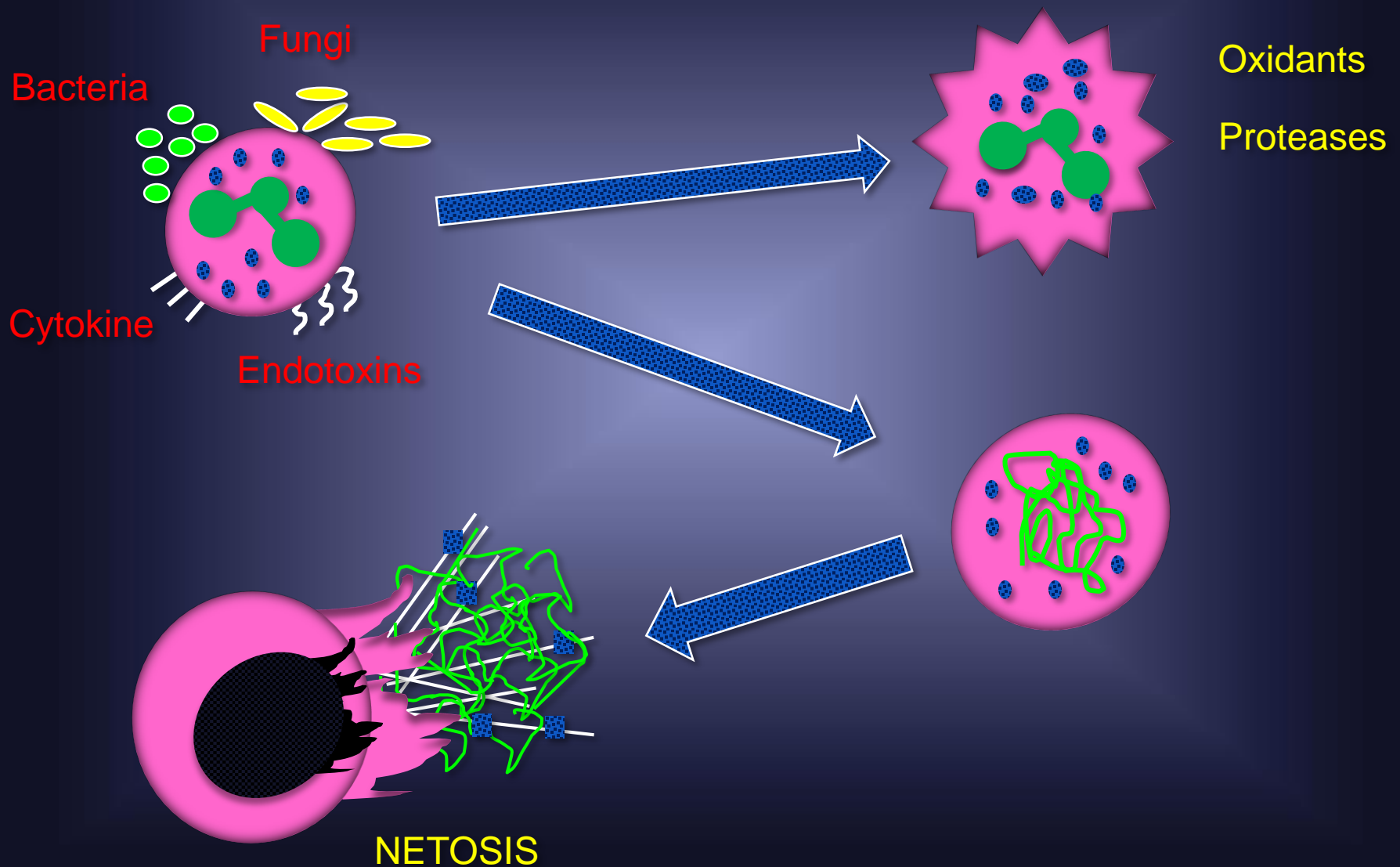
Day 3

Intubation/Mechanical Ventilation



Day 21

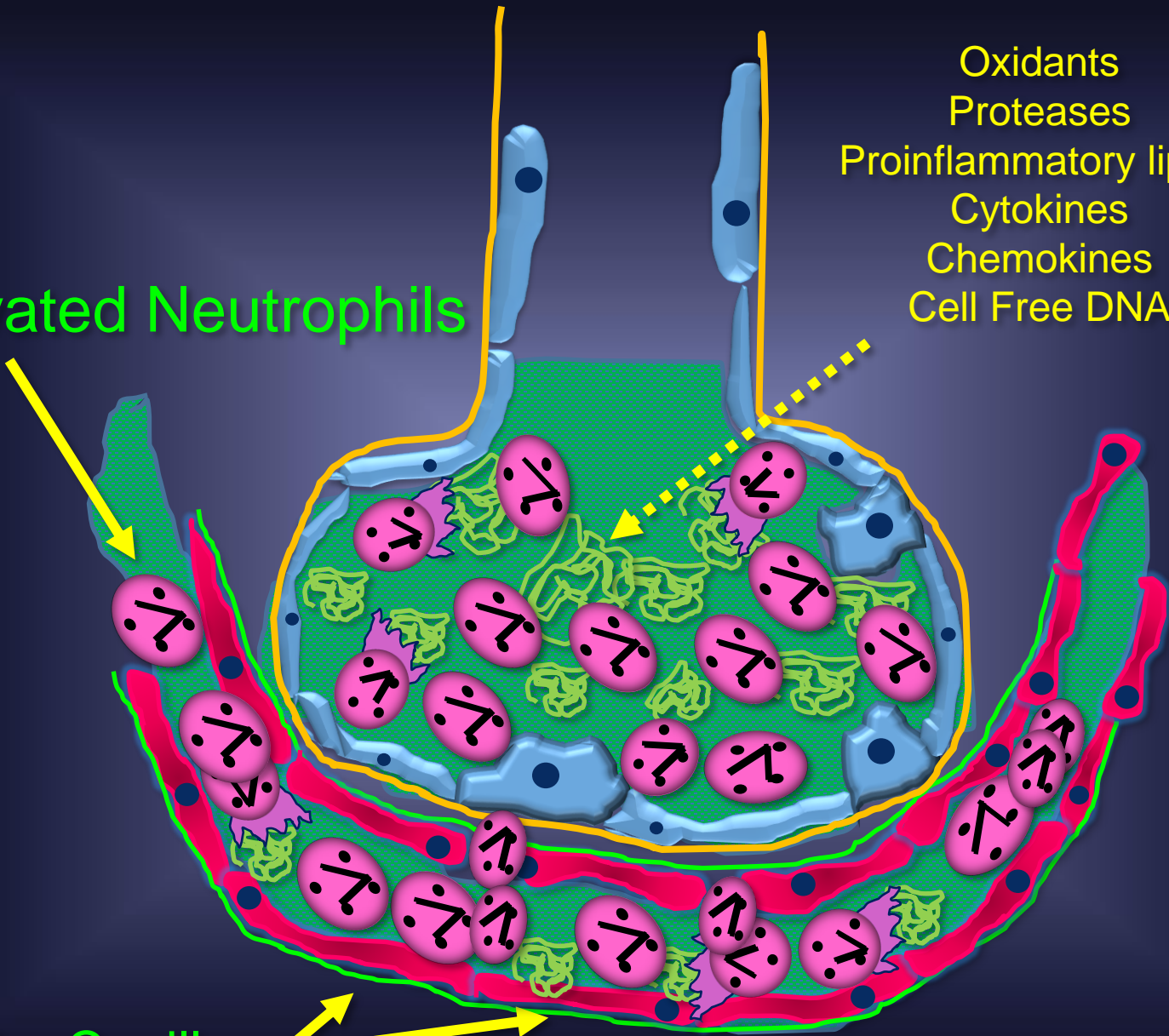
# Neutrophil Activation – NET Formation



Activated Neutrophils

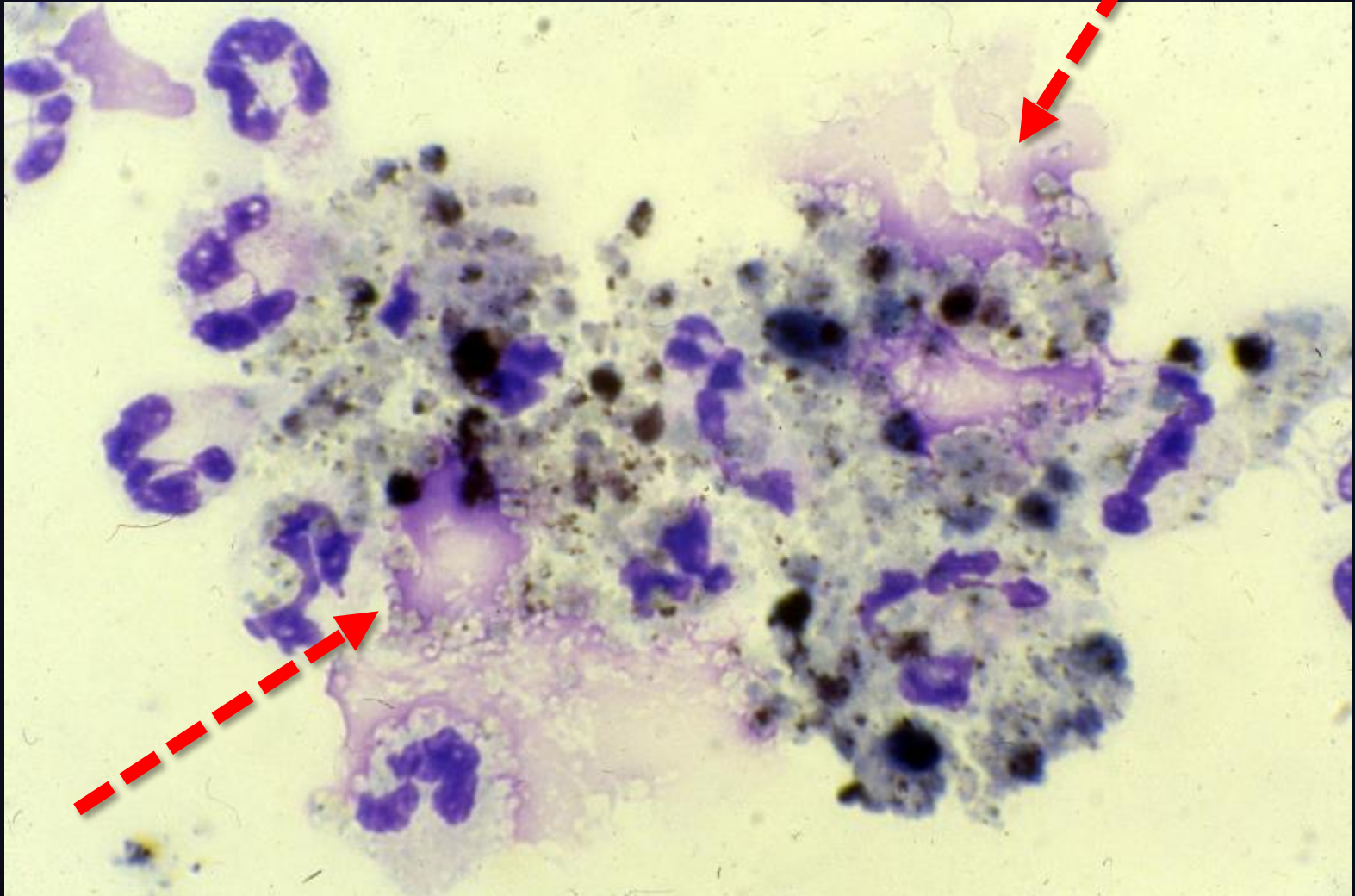
Oxidants  
Proteases  
Proinflammatory lipids  
Cytokines  
Chemokines  
Cell Free DNA

Alveolar Capillary





# ARDS Bronchoalveolar Lavage Cytology

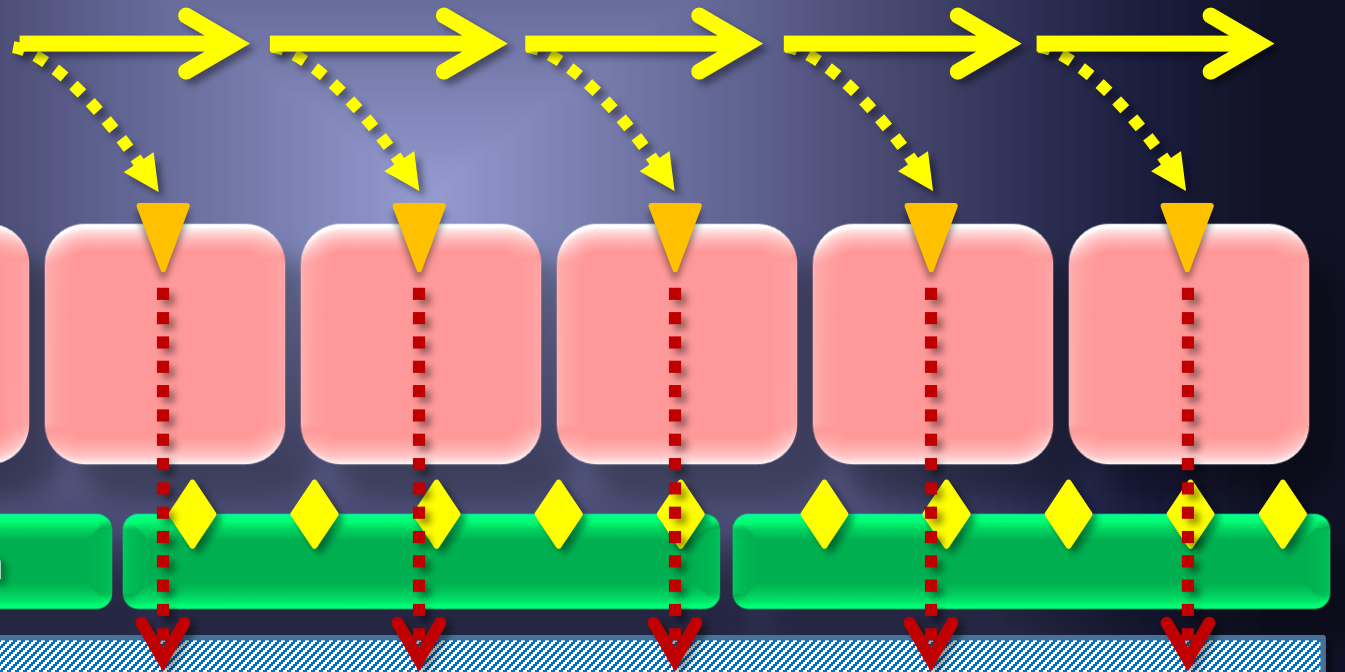


Vascular Endothelium

Vitamin C

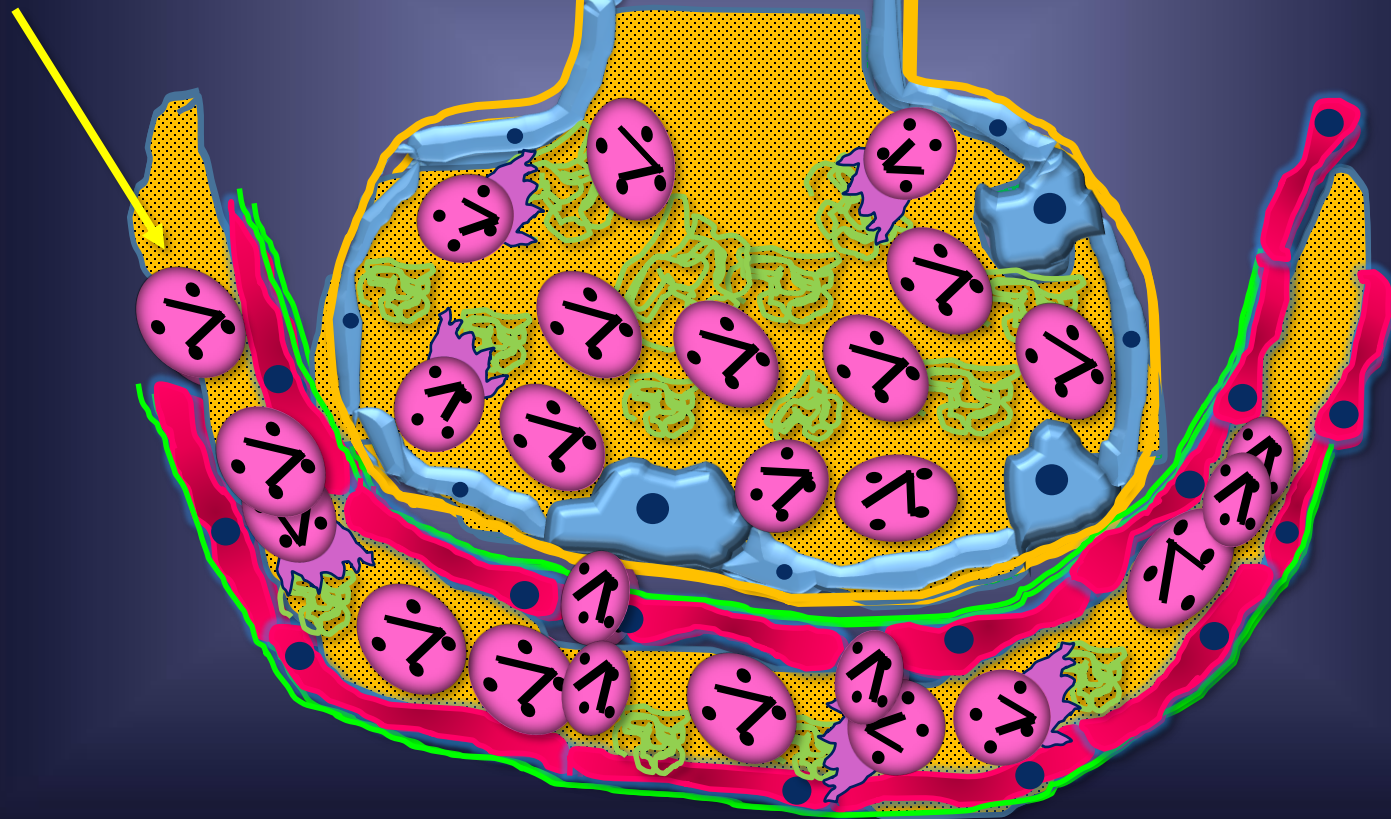
Alveolar Epithelium

Alveolar Space





Vitamin C Infusion



# UM1 Program

## (Novel Therapies of Lung Diseases)

- Phase II multi-center trial – proof of concept
- Randomized, double blinded, placebo-controlled
- Employ “*physiological*” and “*chemical measures*” of efficacy rather than mortality
- Data collected on well-characterized subjects
- Common drug with low toxicity
- Immuno-modulating therapy for ALI

# Vitamin C Infusion for Treatment In Sepsis-Induced Acute Lung Injury

## CITRIS-ALI

Assess Efficacy

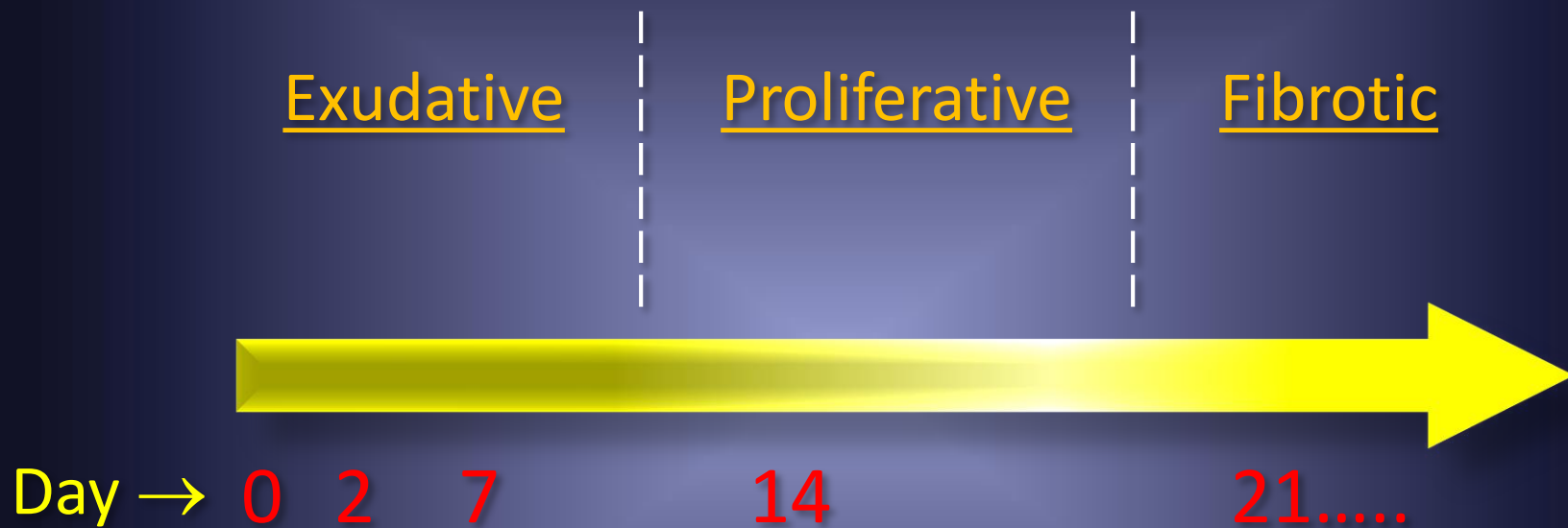
96-hour Vitamin C Infusion  
(200 mg/kg/24 Hours)  
Septic Acute Lung Injury

# CITRIS-ALI

- Multi-Center Trial
  - ❖ VCU
  - ❖ The Cleveland Clinic
  - ❖ The Medical College of Wisconsin
  - ❖ The University of Kentucky
  - ❖ Emory University (First Trial Year)
- Proposed 170 patients with sepsis-induced ARDS
- Trial completed (November 2017)

# Hypotheses

- Attenuate septic lung injury  
(oxygenation index and  $\dot{V}_E$  40)
- Attenuate sepsis-induced organ failure  
(SOFA Score)
- Attenuate injury biomarkers
  - ❖ Inflammation
  - ❖ Alveolar Epithelial Injury
  - ❖ Fibrinolysis
  - ❖ Vascular Injury
  - ❖ Barrier Function



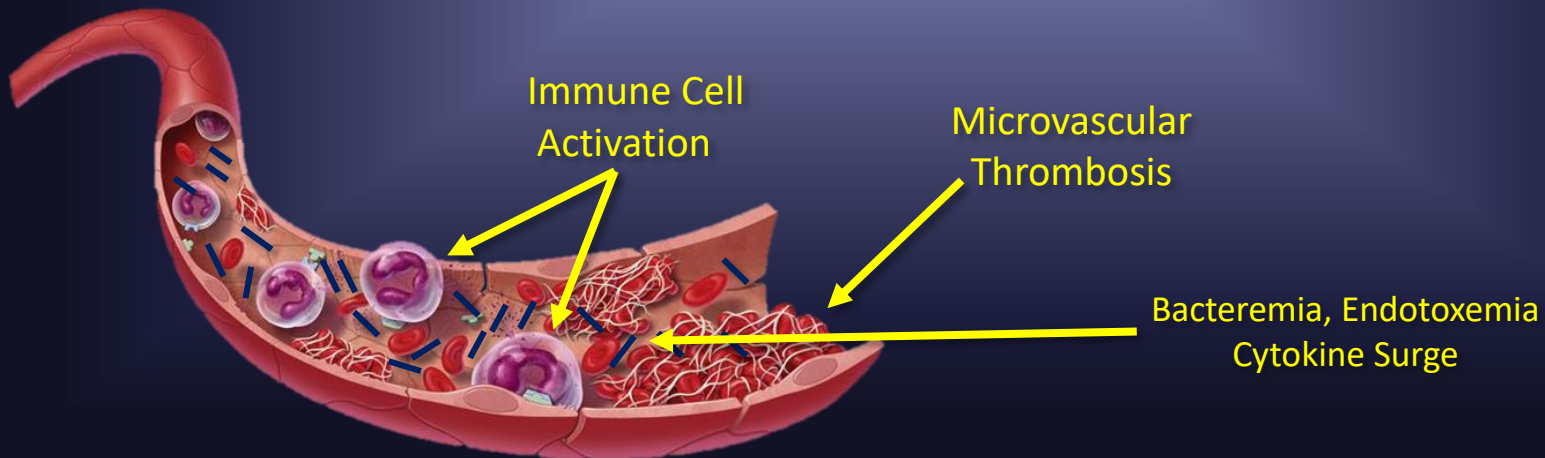
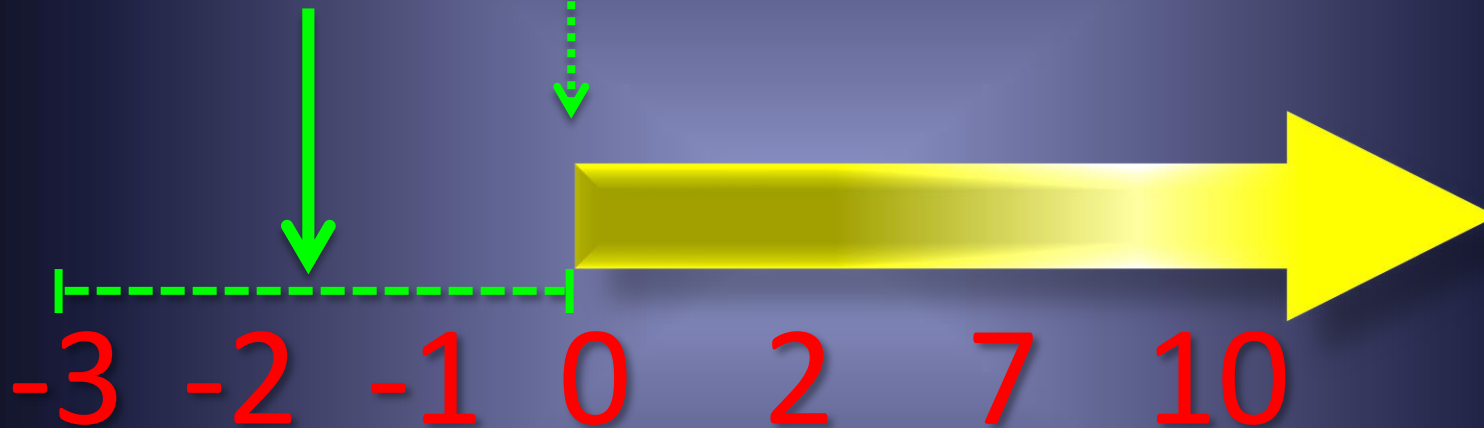
“Phases” of ARDS

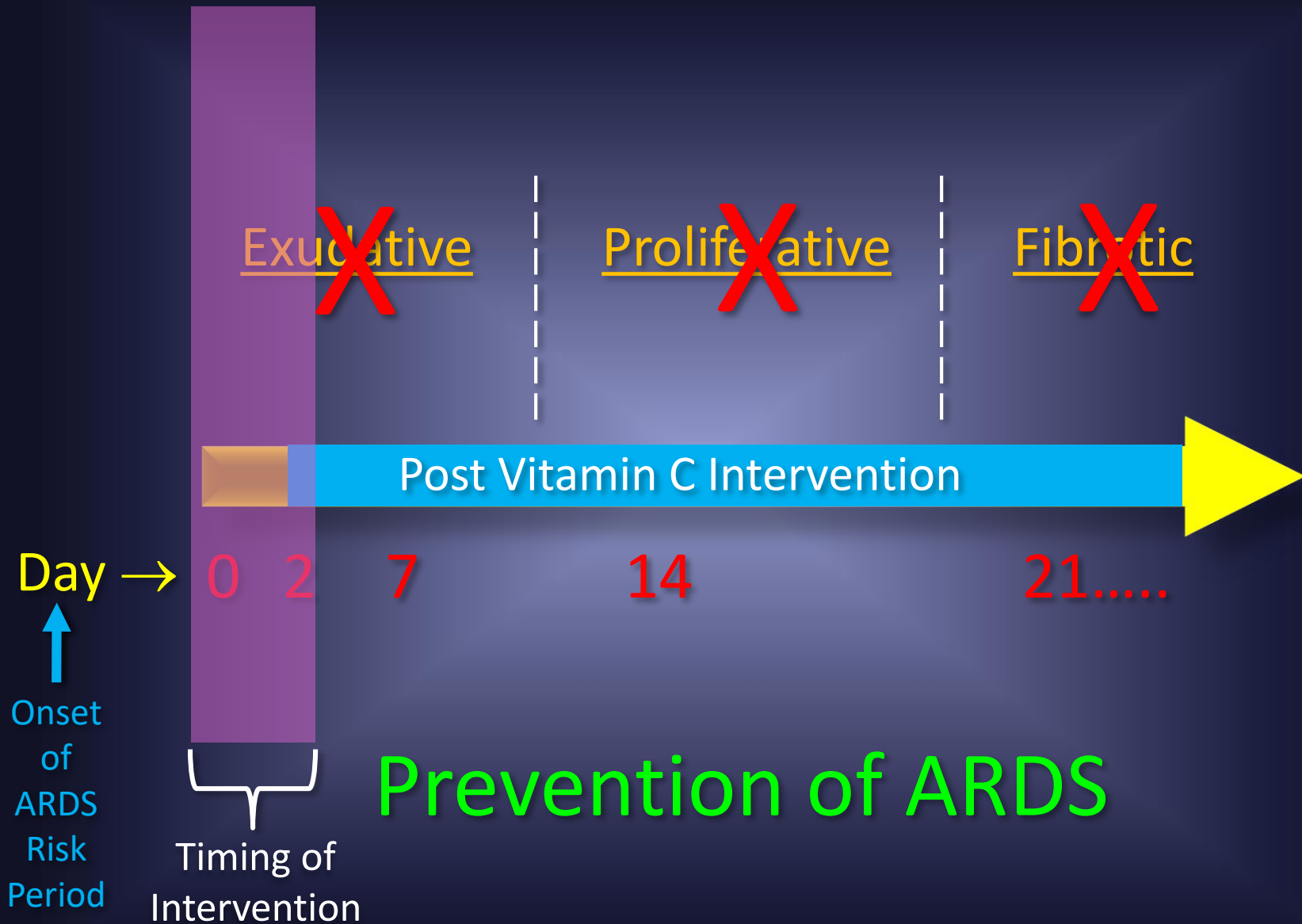
# Clinical Recognition of

## Sepsis Onset Organ Injury

(Risk Period)

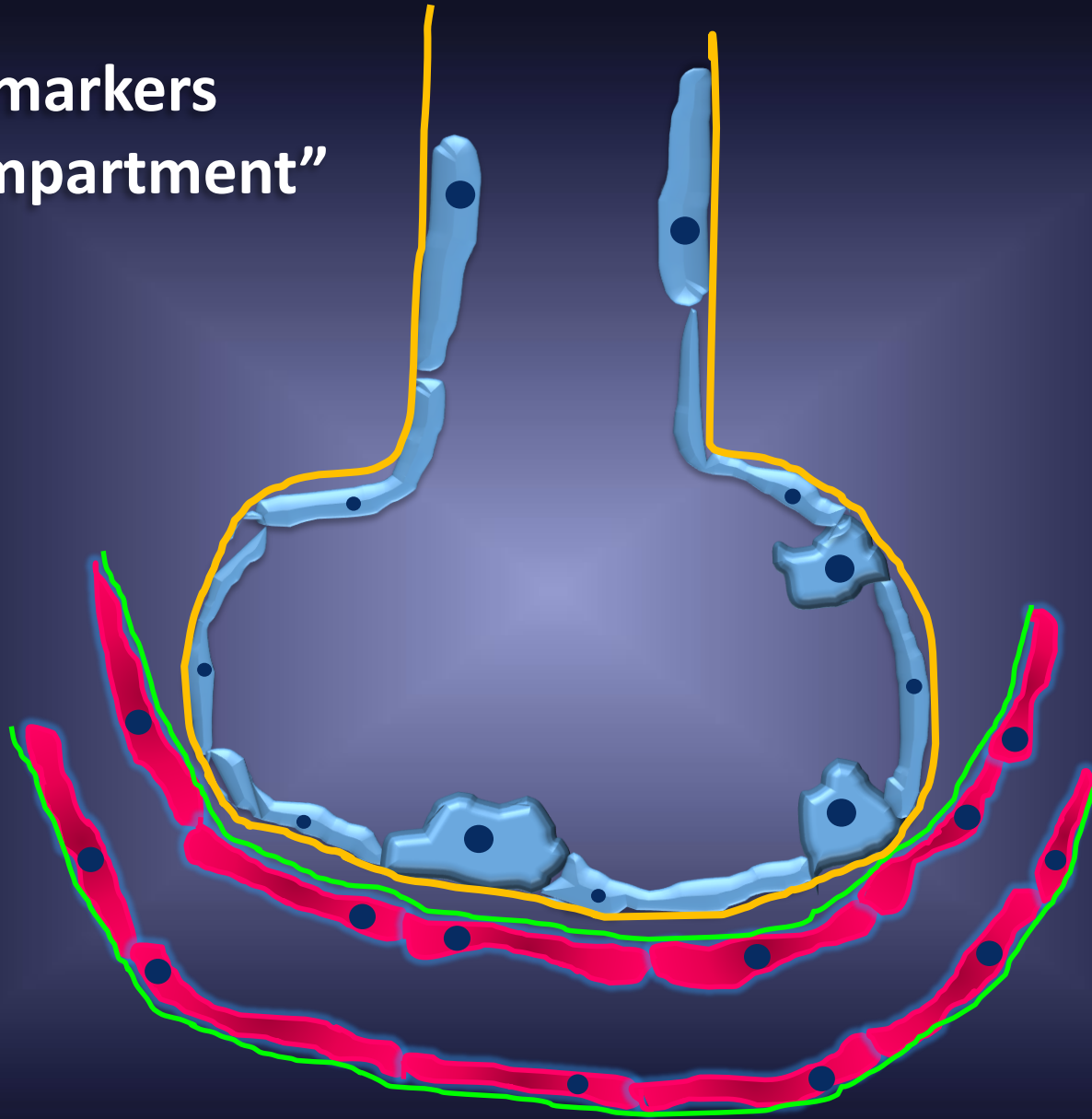
Days





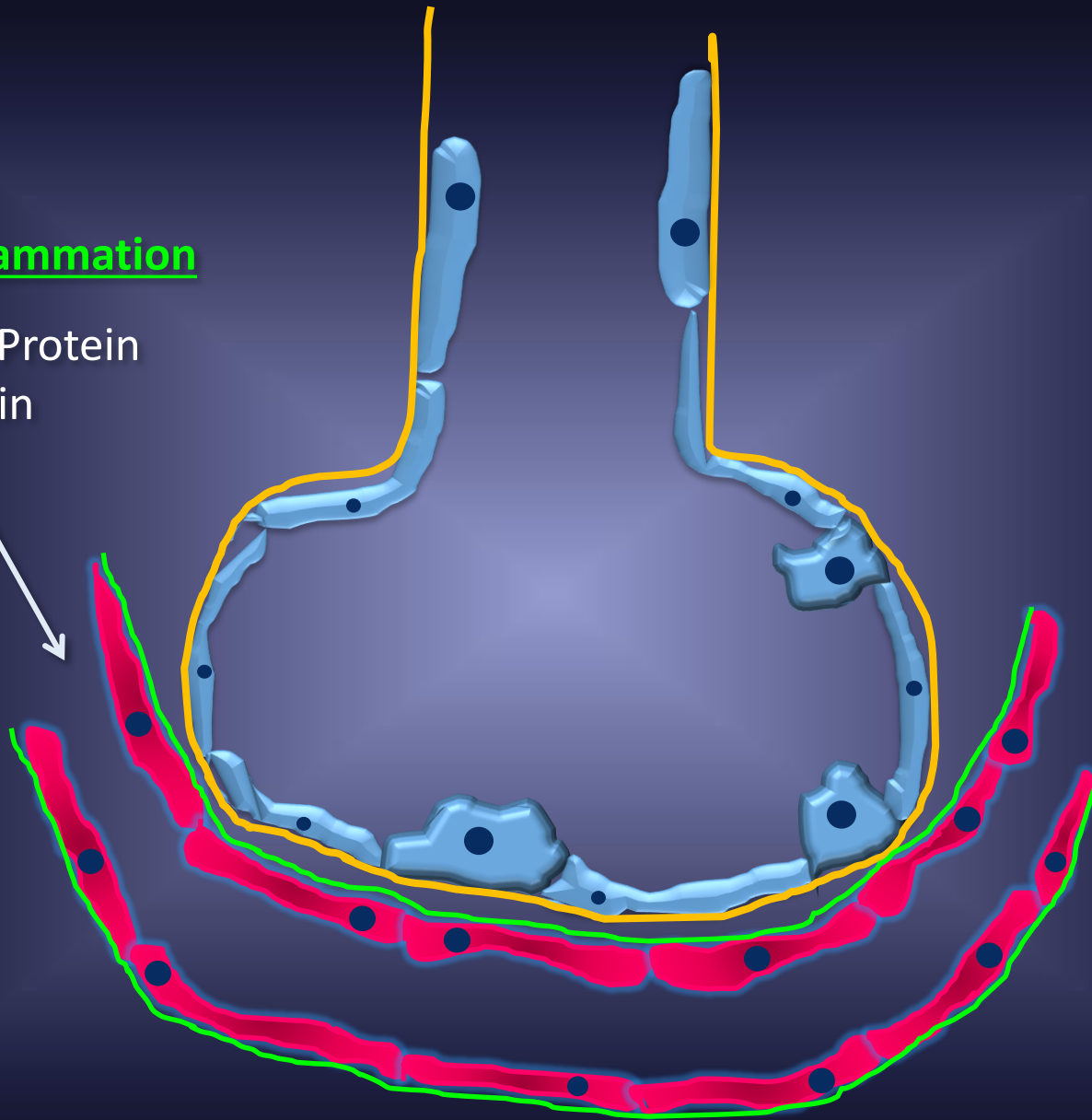


# Biomarkers By “Compartment”



## Systemic Inflammation

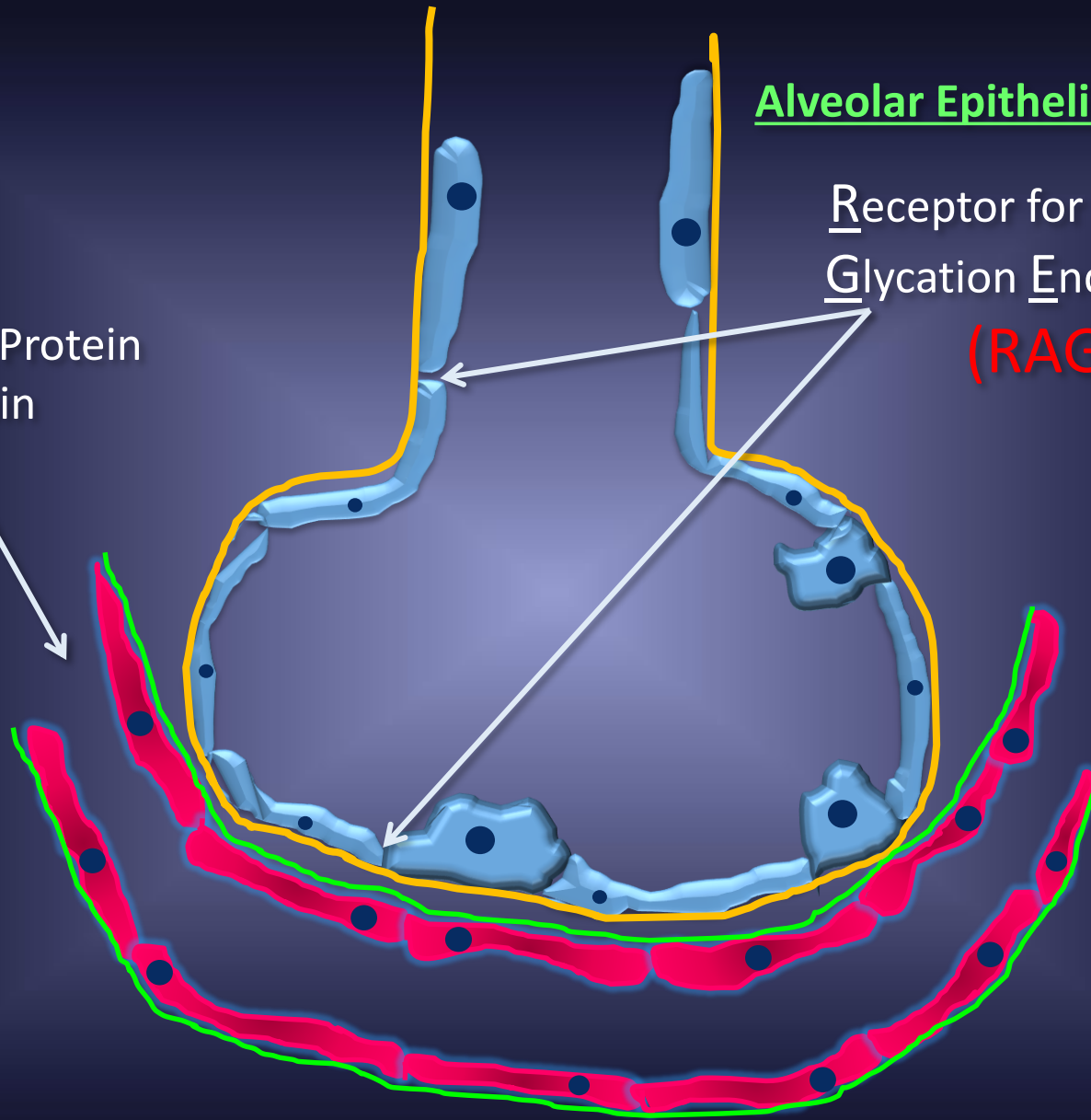
C-Reactive Protein  
Procalcitonin



## Alveolar Epithelial Injury

Receptor for Advanced  
Glycation End Products  
(RAGE)

C-Reactive Protein  
Procalcitonin

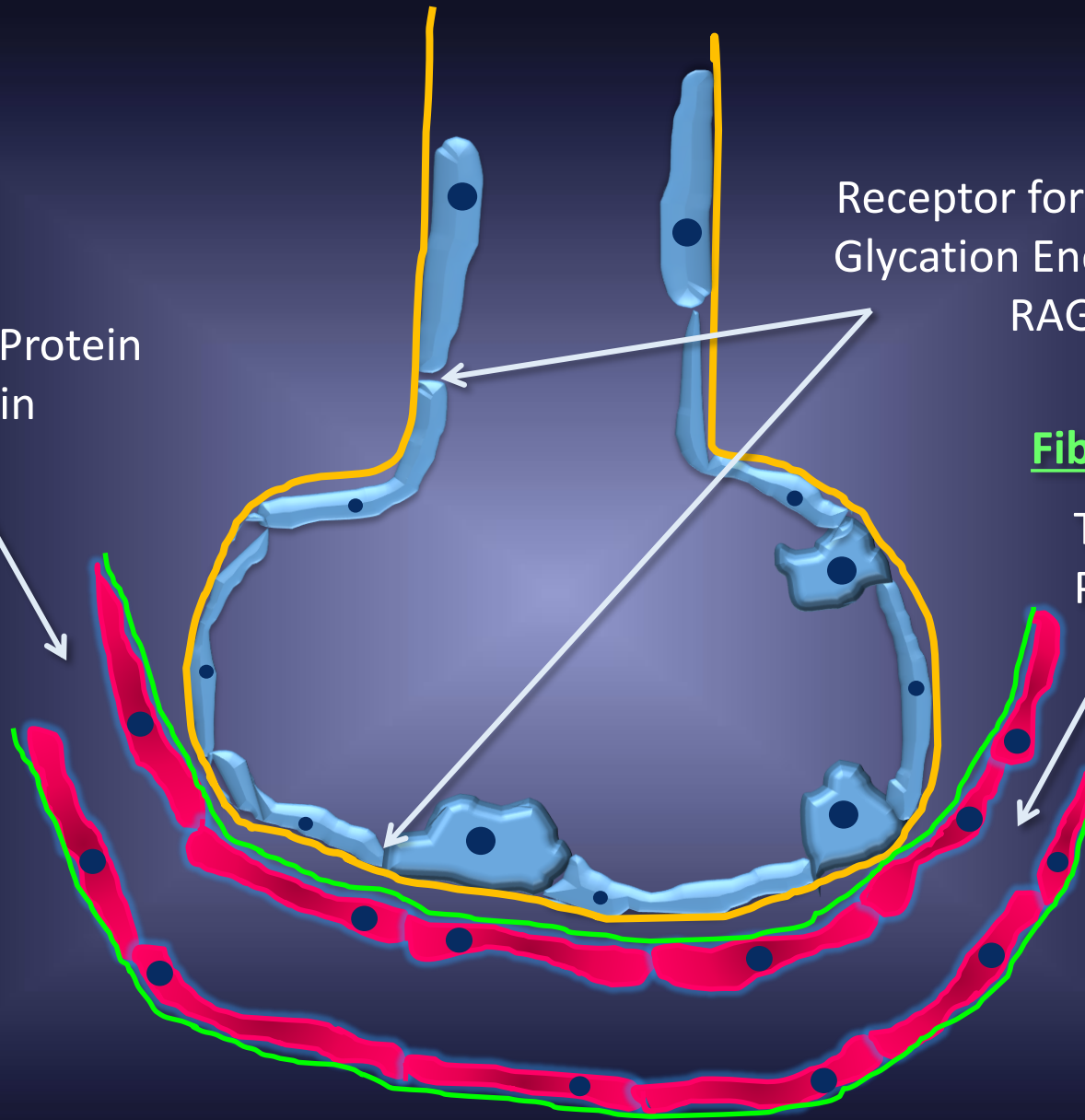


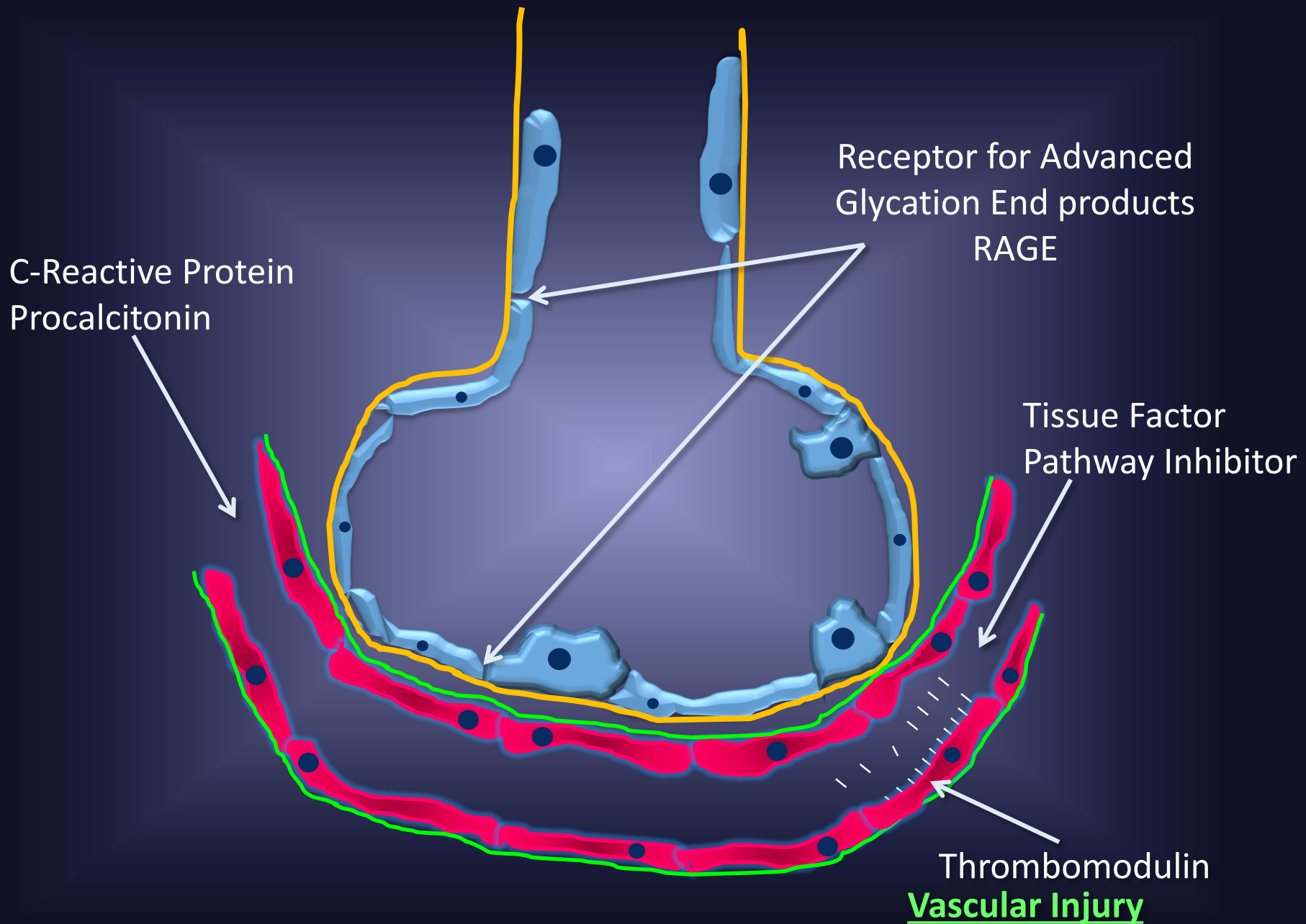
C-Reactive Protein  
Procalcitonin

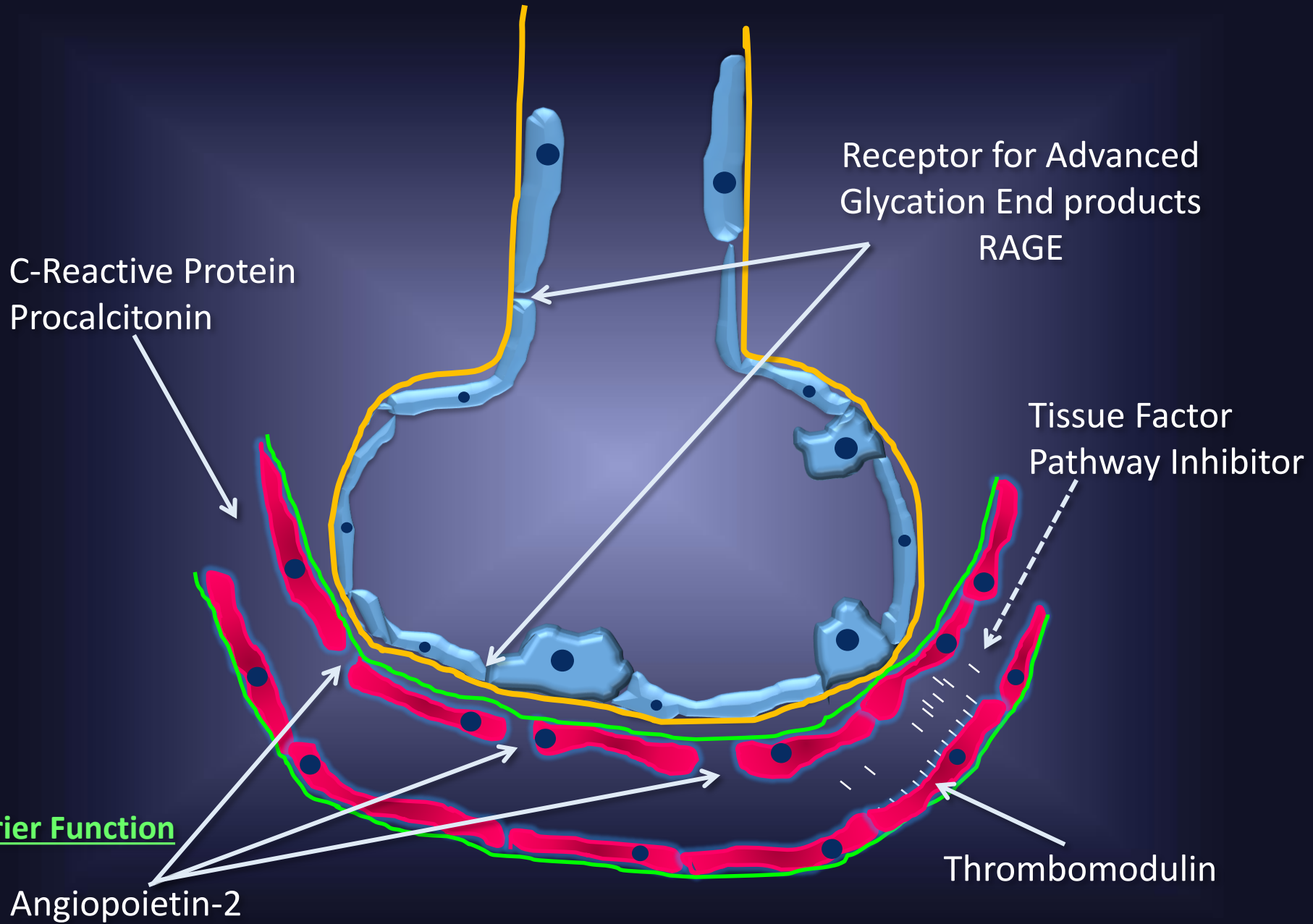
Receptor for Advanced  
Glycation End products  
RAGE

Fibrinolysis

Tissue Factor  
Pathway Inhibitor

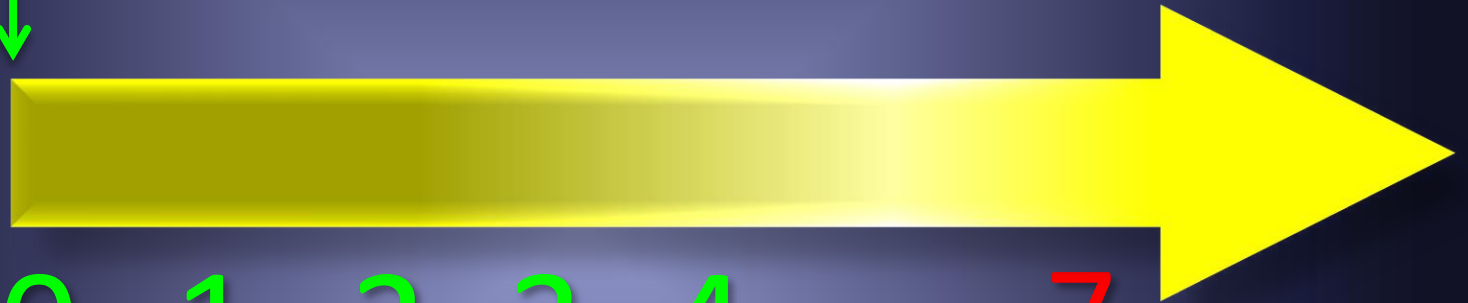








# ONSET LUNG INJURY



-1 0 1 2 3 4 ..... 7



Active Treatment

200 mg/kg/day

50 mg/kg/Every 6 hours

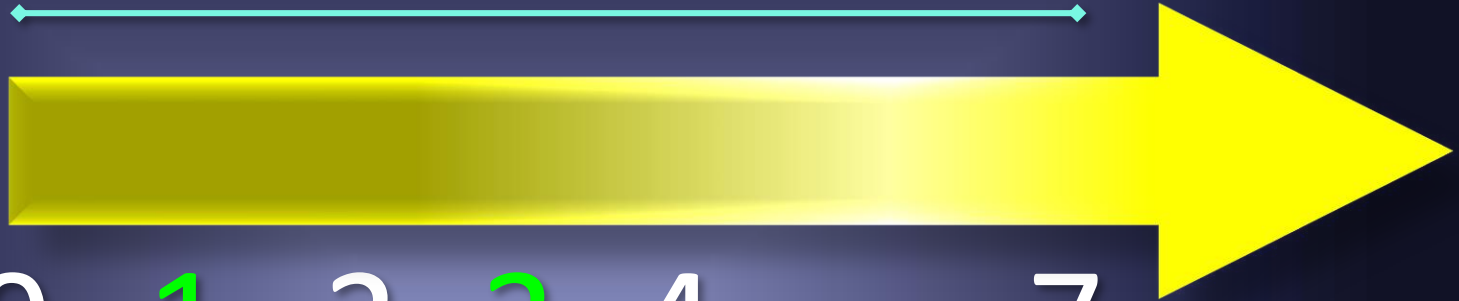
4 days

# Assessment Schedule



- SOFA Score
- Plasma Ascorbate
- Biomarkers

# Physiological Assessment



-1 0 1 2 3 4 .... 7

Oxygenation Index

$\dot{V}_E - 40$

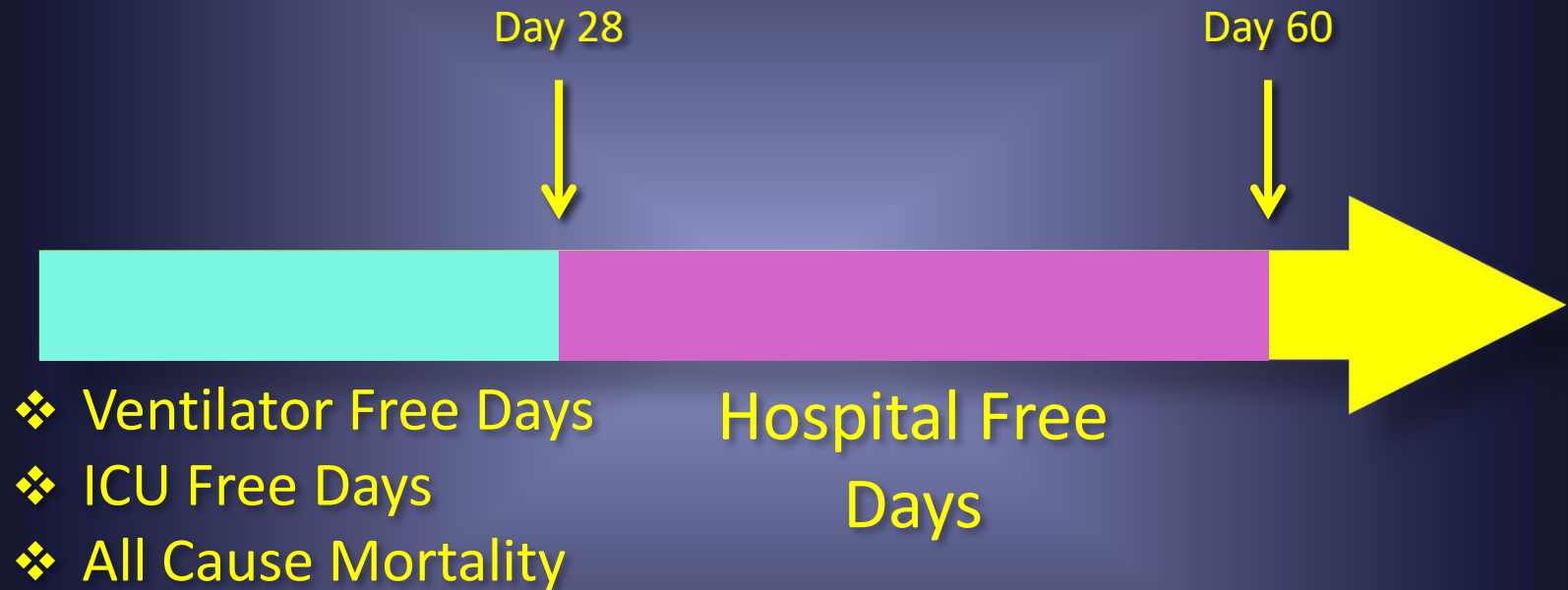
$$OI = \frac{\text{Mean Airway Pressure} \times F_i O_2}{P_a O_2}$$

$$\dot{V}_E - 40 = \frac{\dot{V}_E}{\text{Weight (KG)}} \times \frac{PaCO_2}{40}$$

# “Responder Phenotype”

- ↓ C-Reactive Protein and Procalcitonin
- ↓ RAGE
- ↑ Tissue Factor Pathway Inhibitor
- ↓ Serum-free Thrombomodulin
- ↓ Angiopoietin-2

# Epidemiological Assessment (Secondary Outcomes)





Day 1



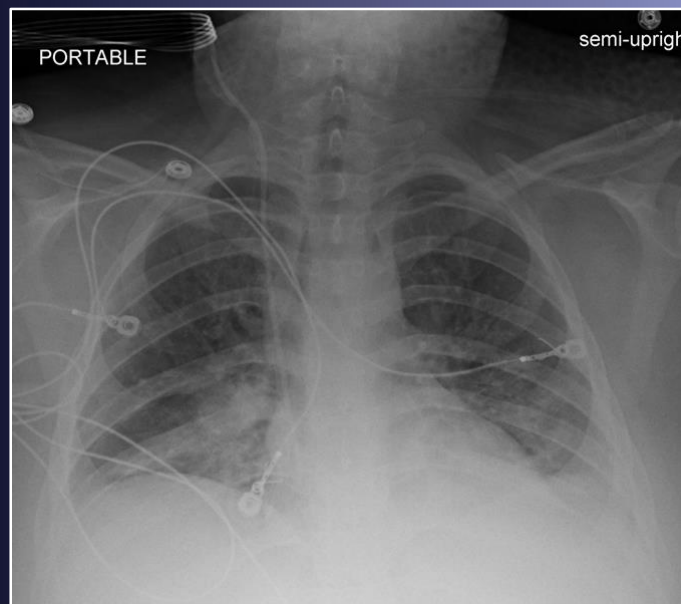
Day 2



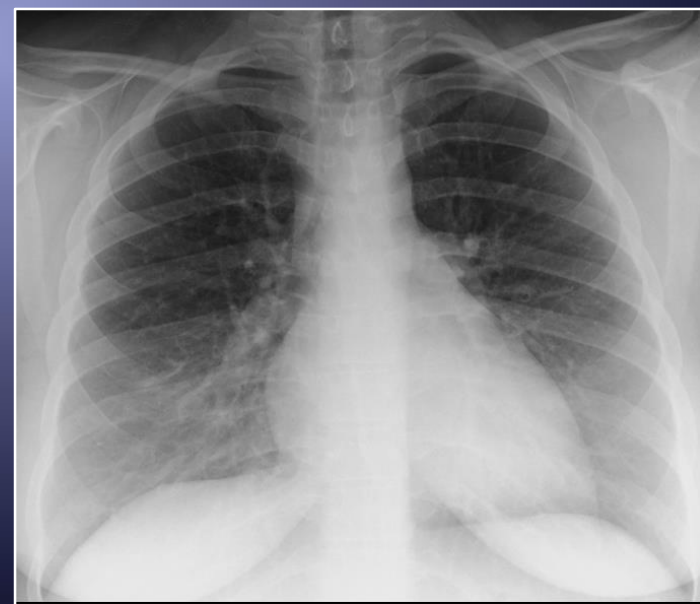
Day 2

**Vit C Infusion Started**

Day 4



Day 7

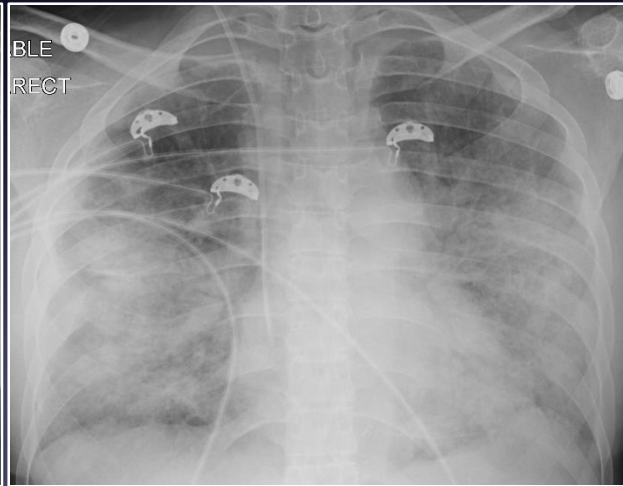


Day 13

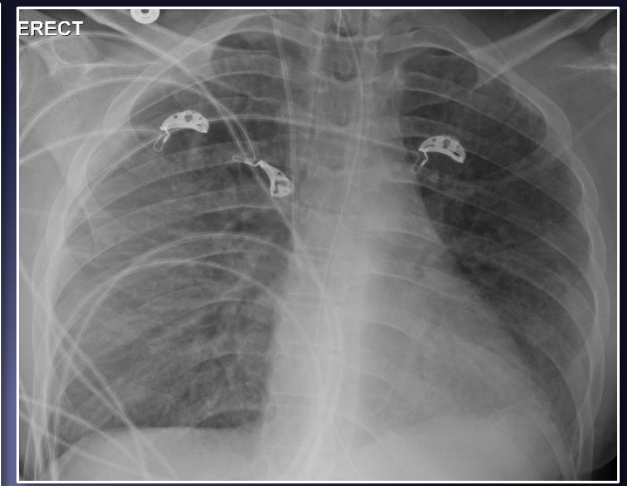




Baseline



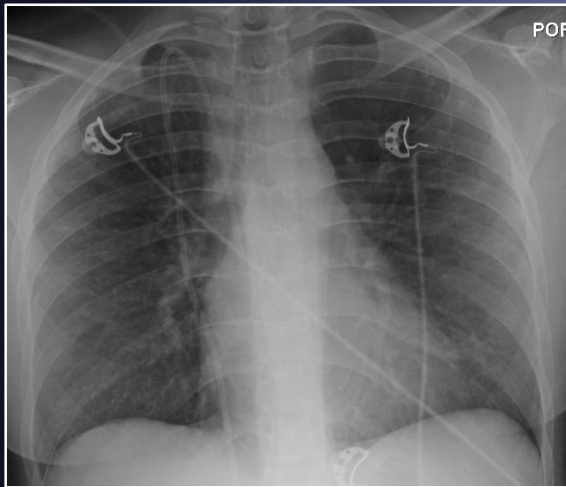
Day 2



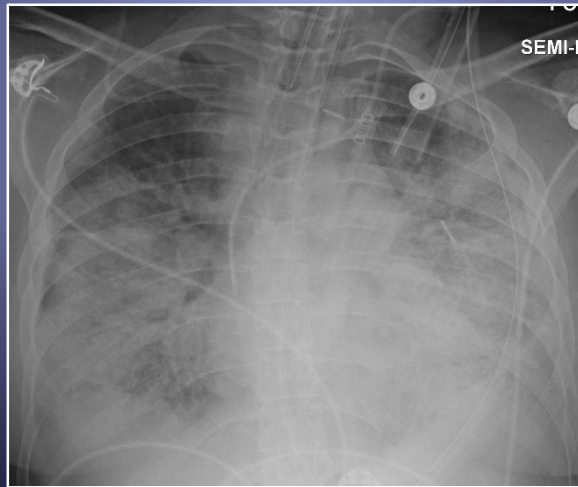
Day 7

Day 4

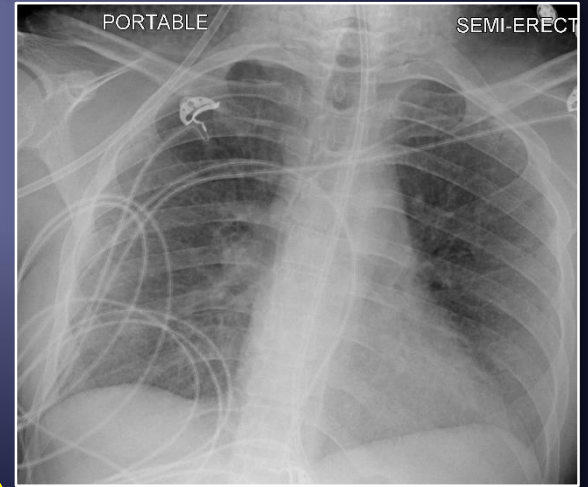
Vit C Infusion Started



Baseline



Day 4



Day 10

Day 4

Vit C Infusion Started

INFECTION

Bacteremia

Fungemia

Viremia

Sepsis

Severe Sepsis

Septic Shock

Systemic Inflammatory Response Syndrome

Burn

Trauma

Pancreatitis

Vitamin C

Vitamin C

