

Pathophysiology of sepsis and principles of management

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Sepsis...tell me who are you?



Hippocrate
- 460 - 470

σῆψις
“Putrefaction”

“Blood rot and
fever”

Avicennes
980 -1037

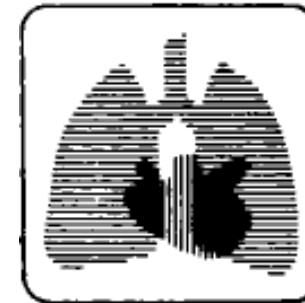


Schottmuller
1914

“**Pathogenic germs** invading the
bloodstream from an infectious
source and causing symptoms”

Sepsis: “SIRS + Infection”
Septic shock: Sepsis + Vasopressors

1992- 2001
ACCP/SCCM
SCCM/ESICM/ACCP/ATS/SIS



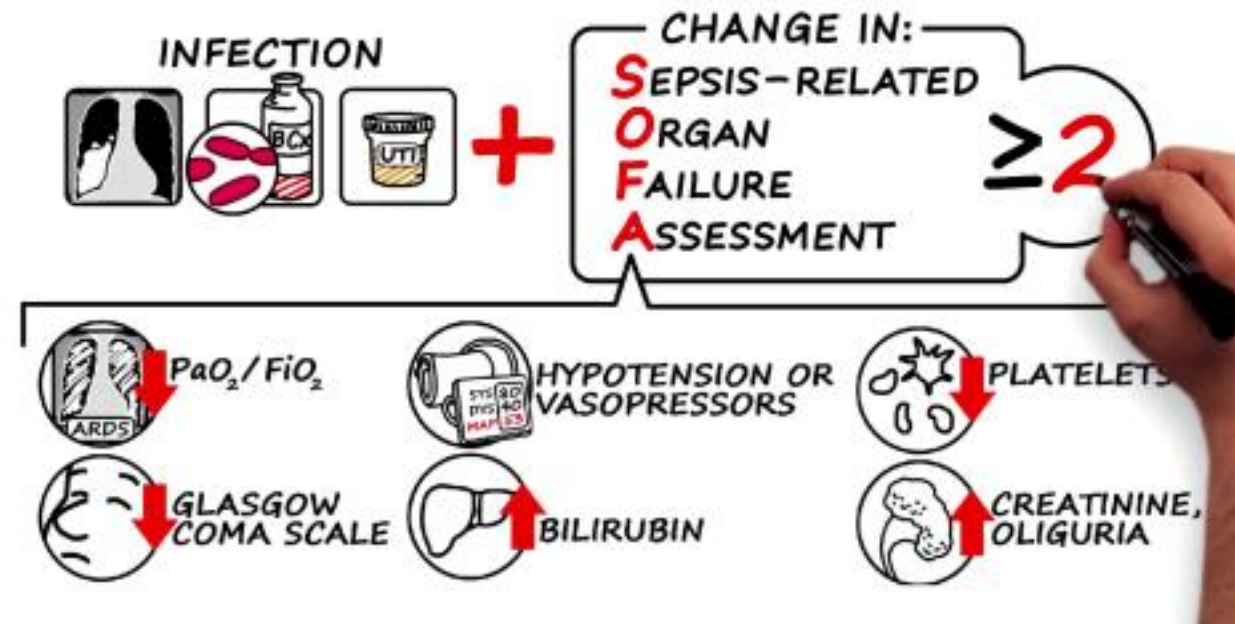
SEPSIS-3

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

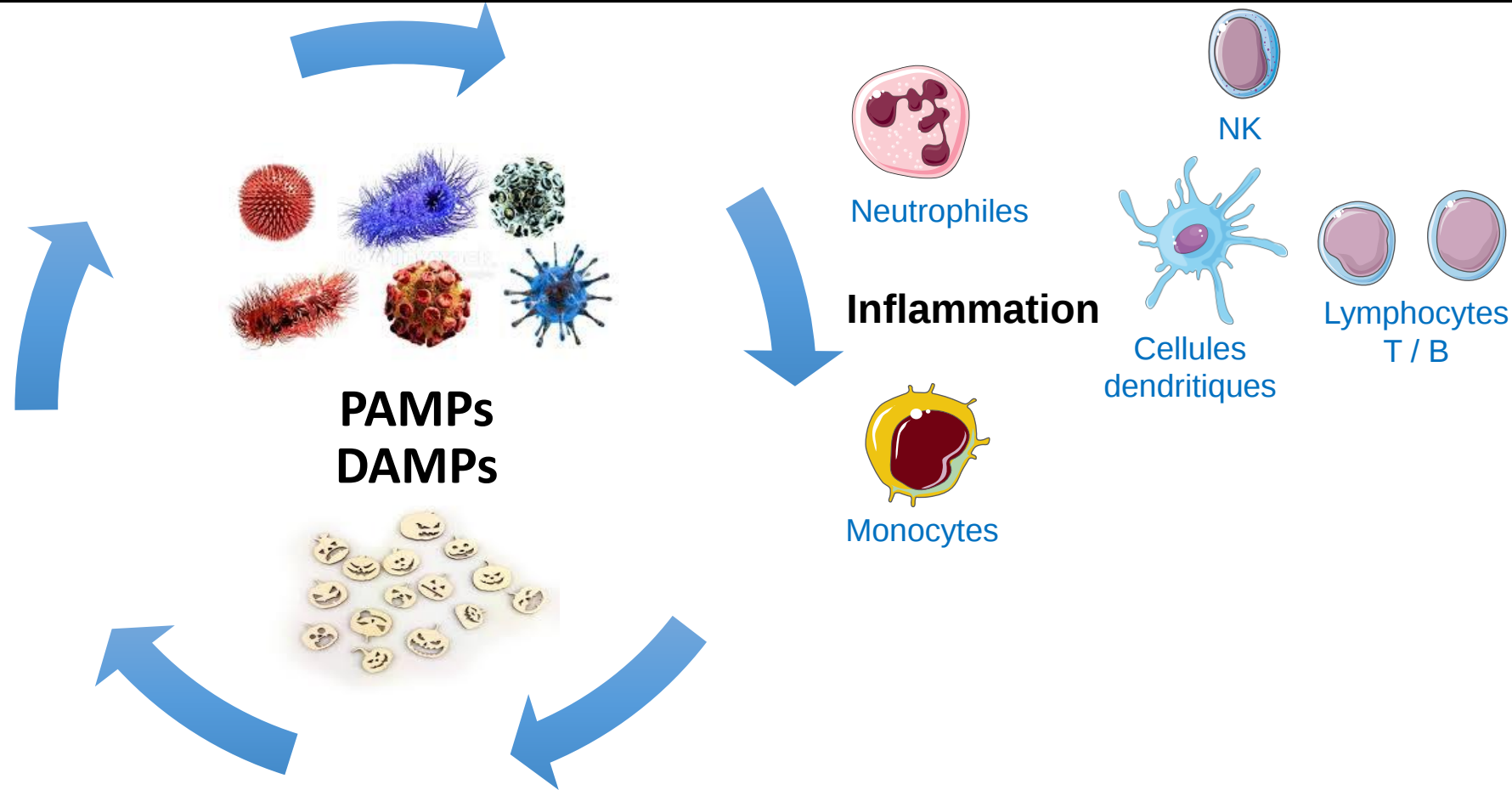
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

SEPSIS:

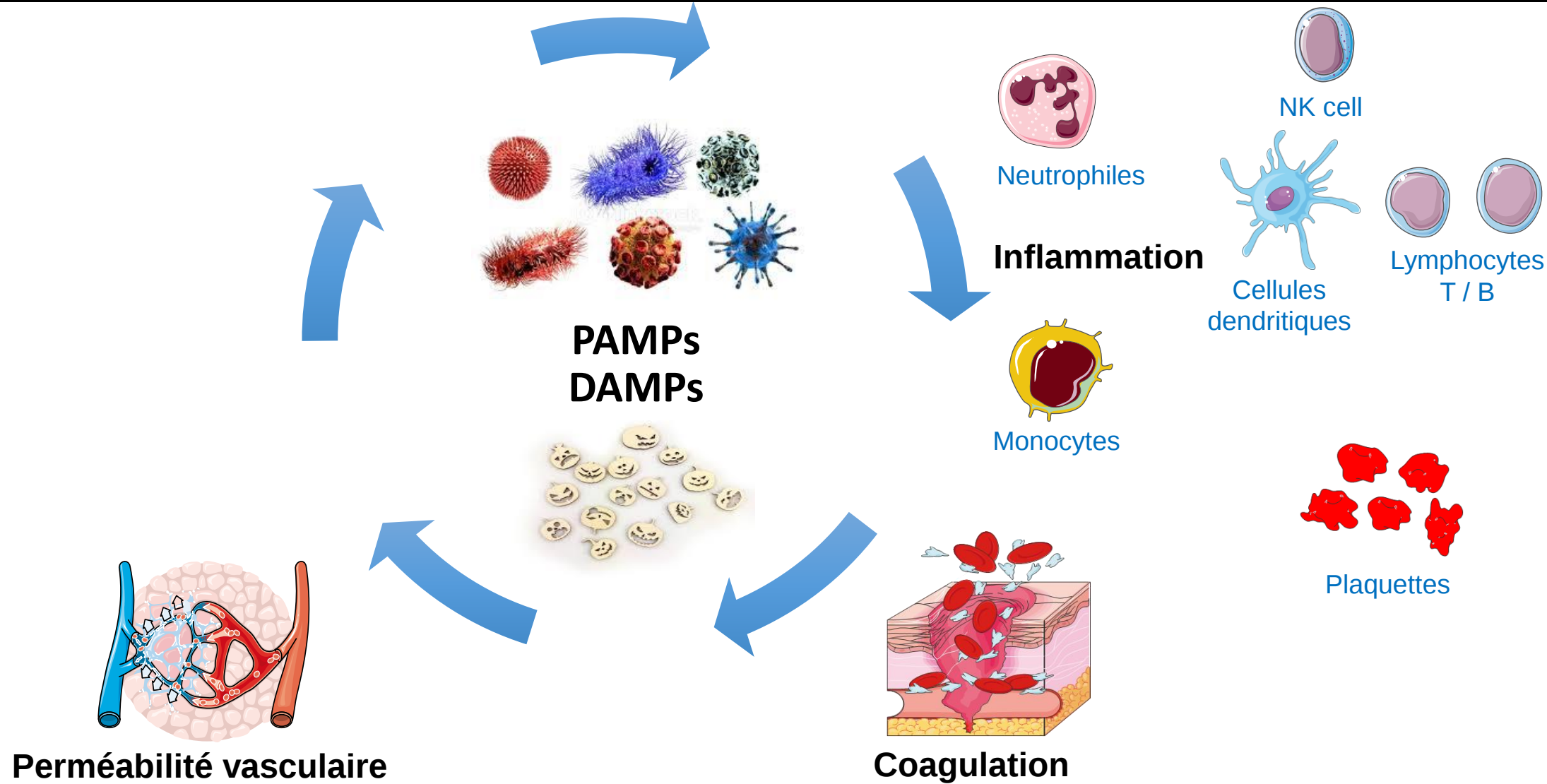
Life-threatening *organ dysfunction* due to a *dysregulated host response* to infection



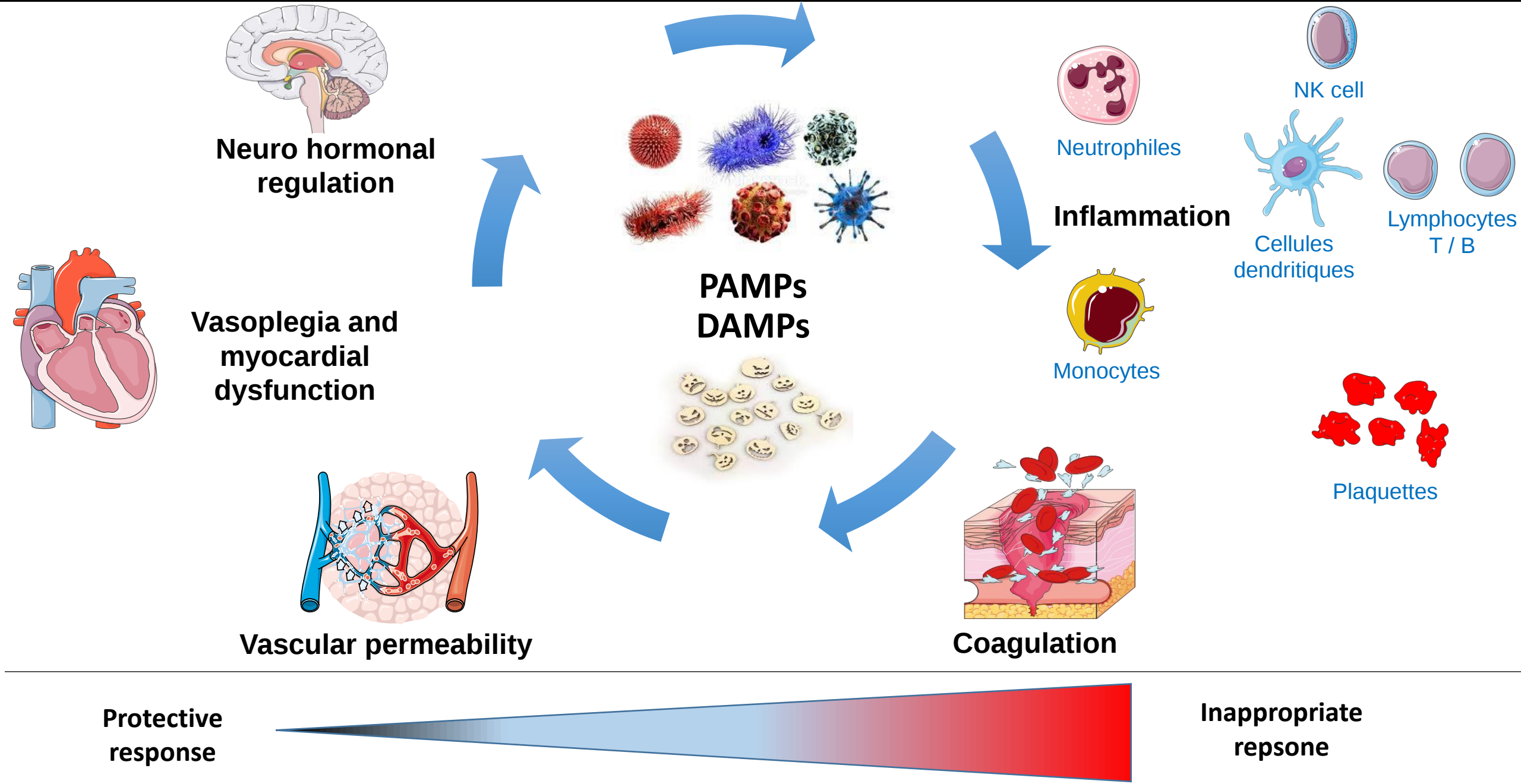
Host response



Host response?



Dysregulated host response?



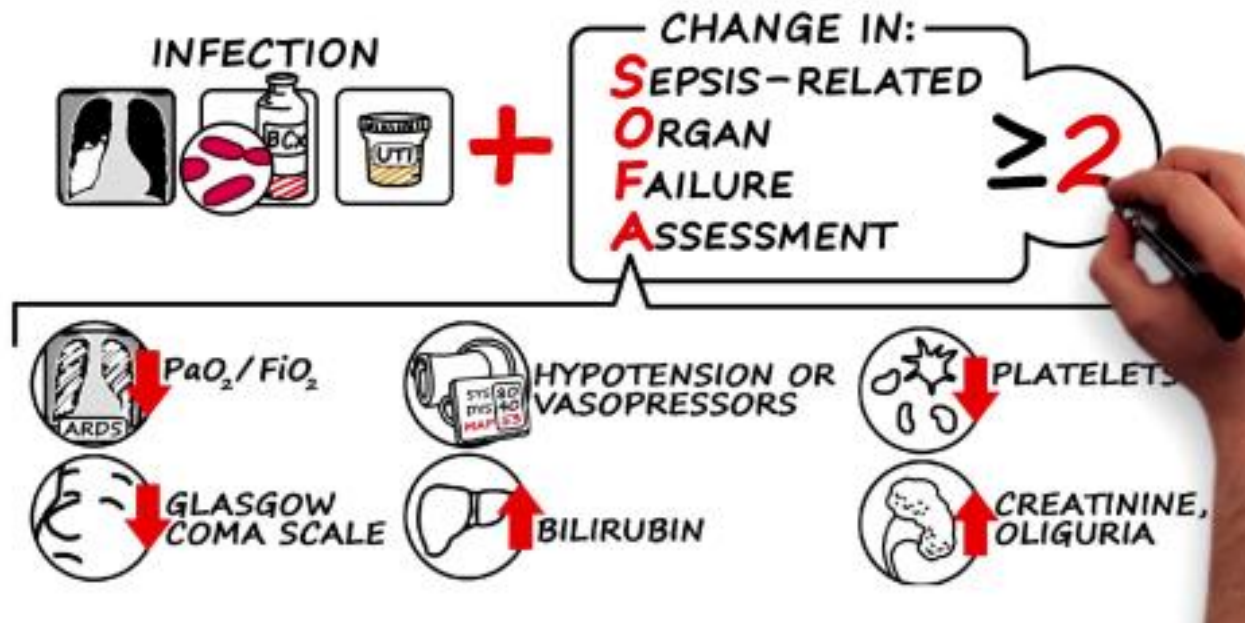
SEPSIS-3

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

SEPSIS:

Life-threatening *organ dysfunction* due to a *dysregulated host response* to infection



Septic shock:

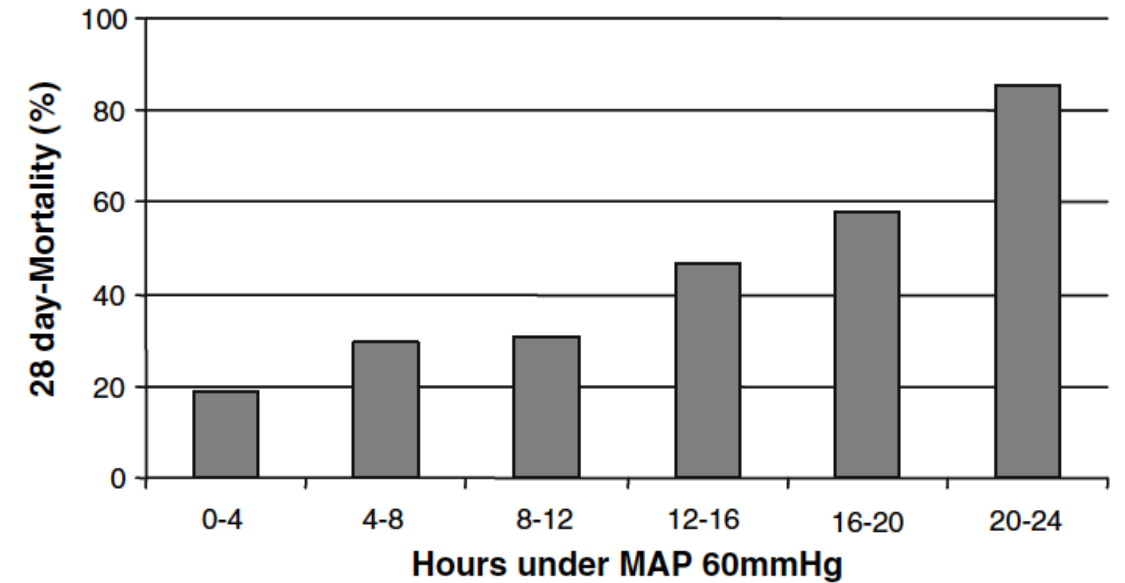
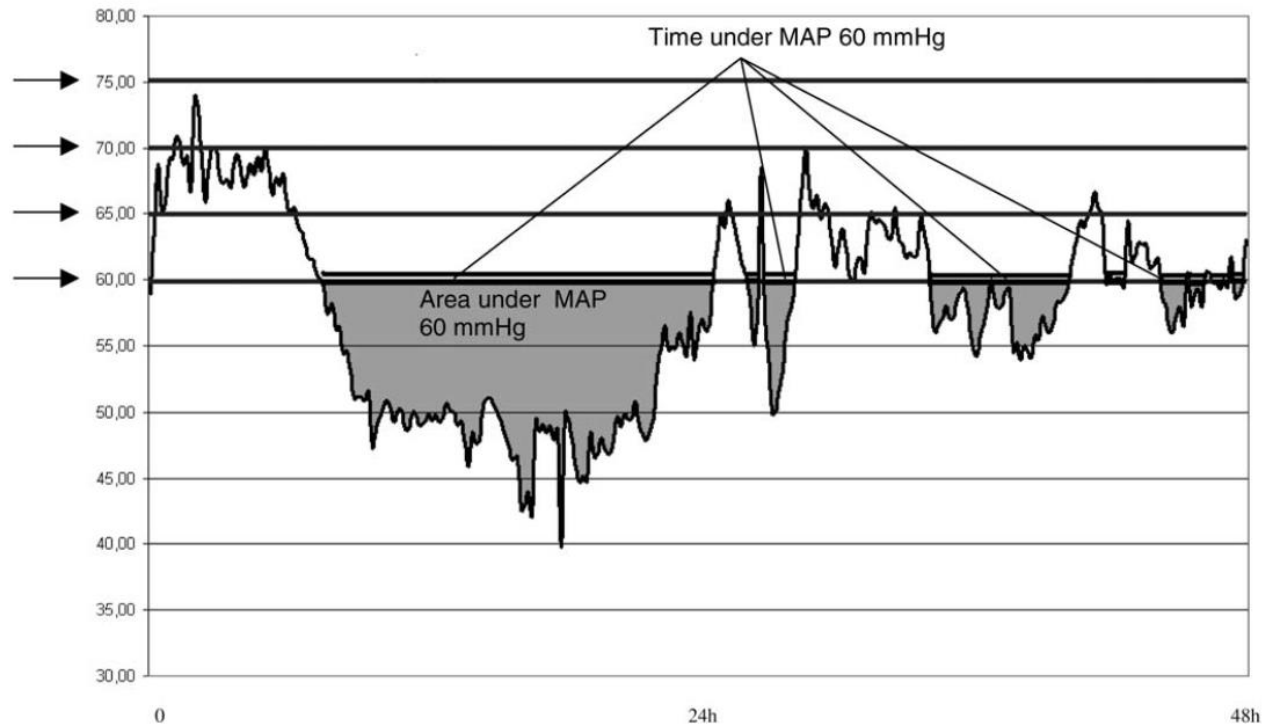
Sepsis +

Vasopressors +

Lactate $\geq 2\text{mmol/L}$

Mechanisms of organ dysfunction?

Hypotension



<i>n</i> = 190	SOFA		Max. lactate	
	r^2	<i>P</i> value	r^2	<i>P</i> value
HBPTI of SAP	0.267	0.009*	0.210	<0.001*
HBPTI of MAP	0.268	0.012*	0.196	<0.001*
HBPTI of MPP	0.233	0.013*	0.207	<0.001*

Mechanisms of organ dysfunction: hypotension ?

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JOURNAL *of* **MEDICINE**

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High versus Low Blood-Pressure Target in Patients with Septic Shock

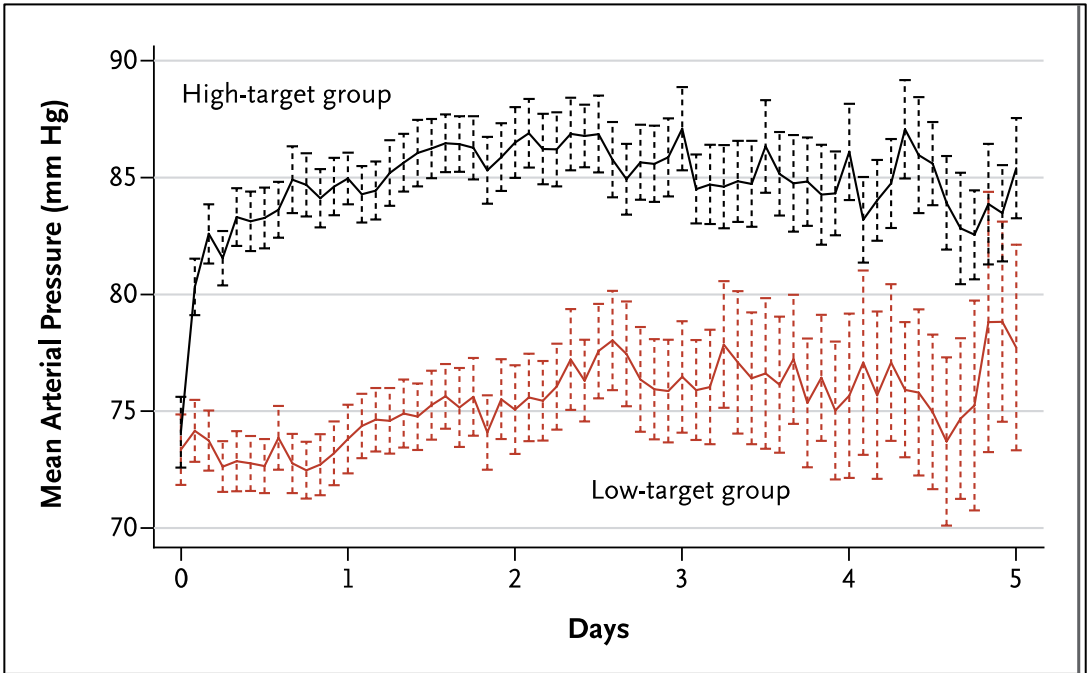


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

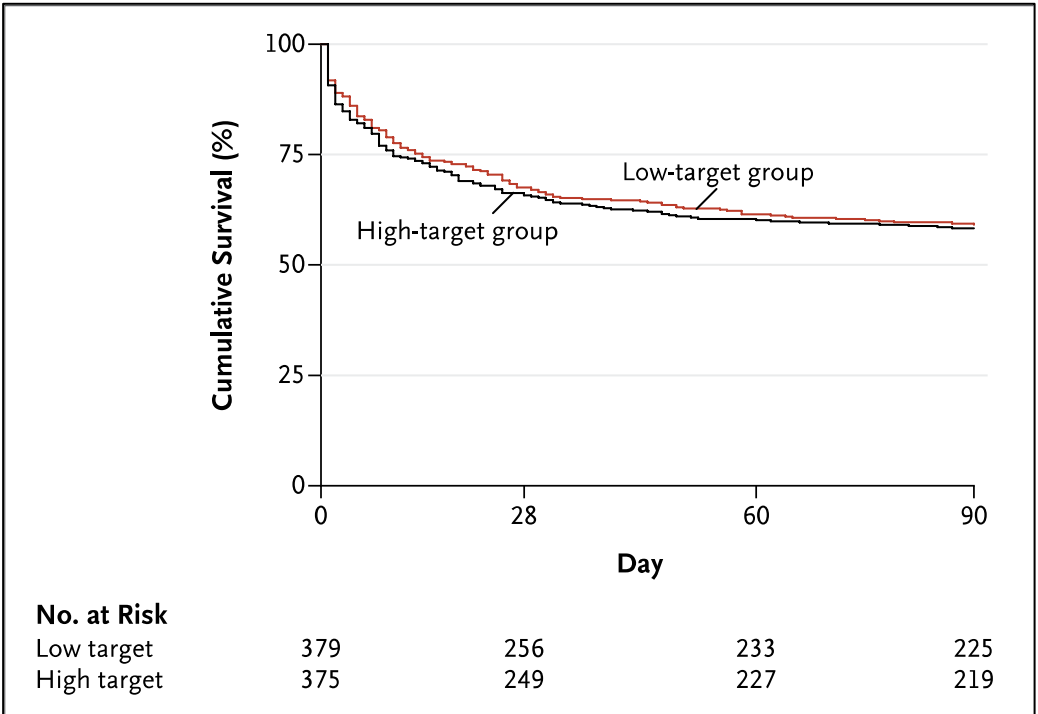
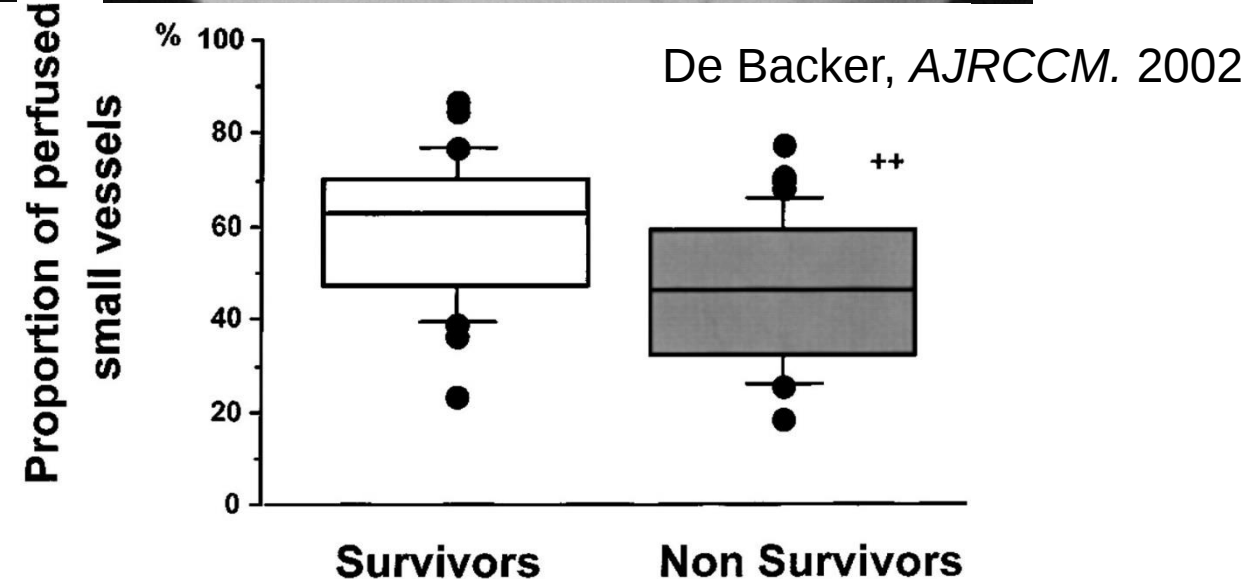
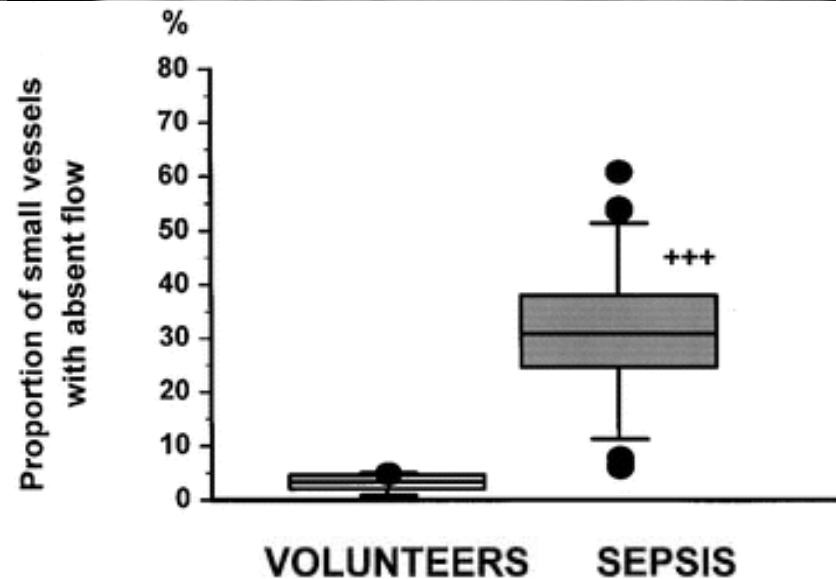
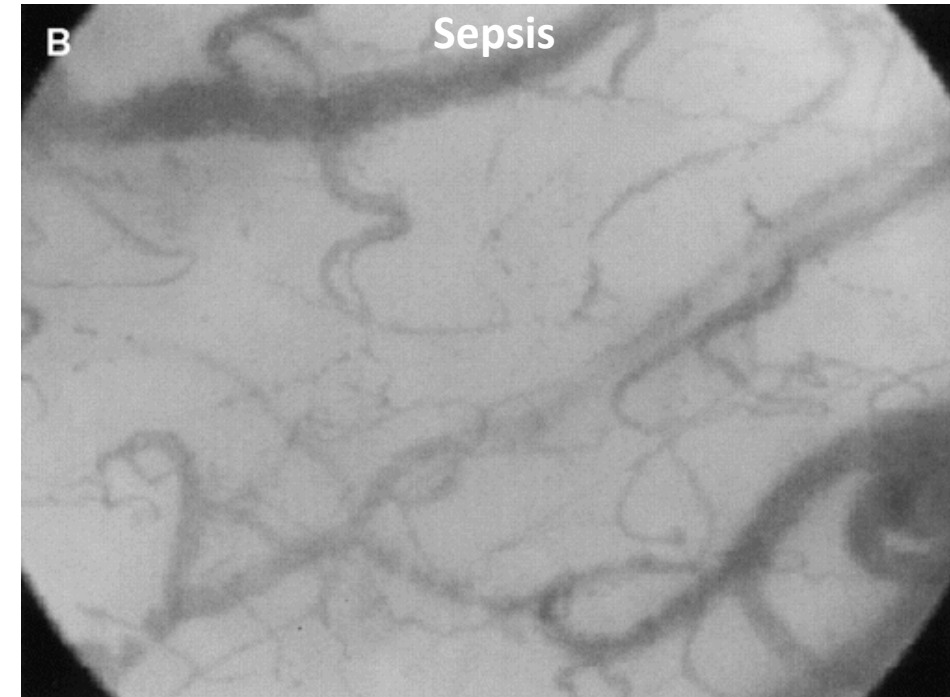
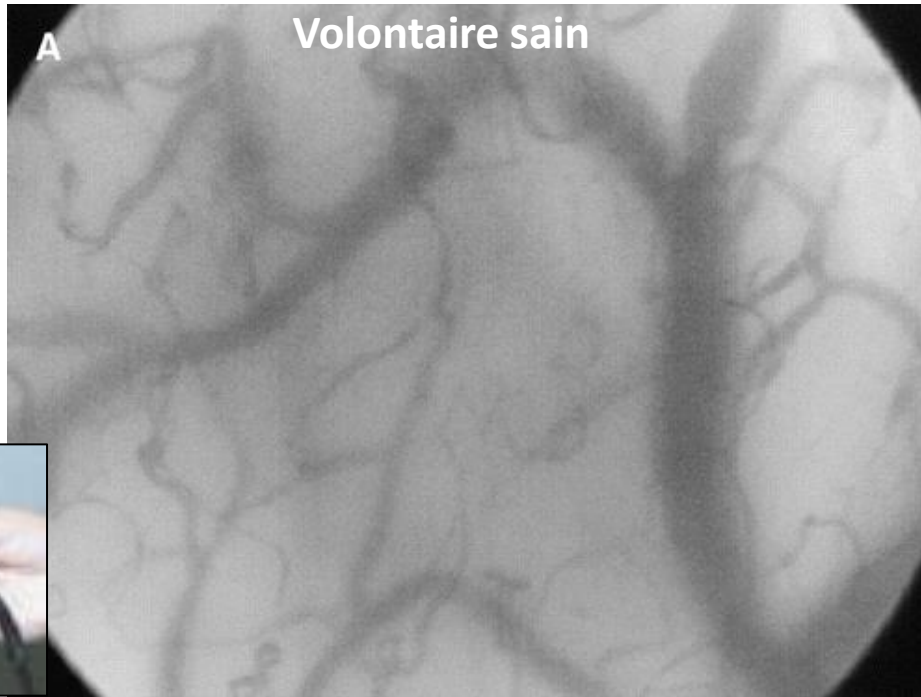


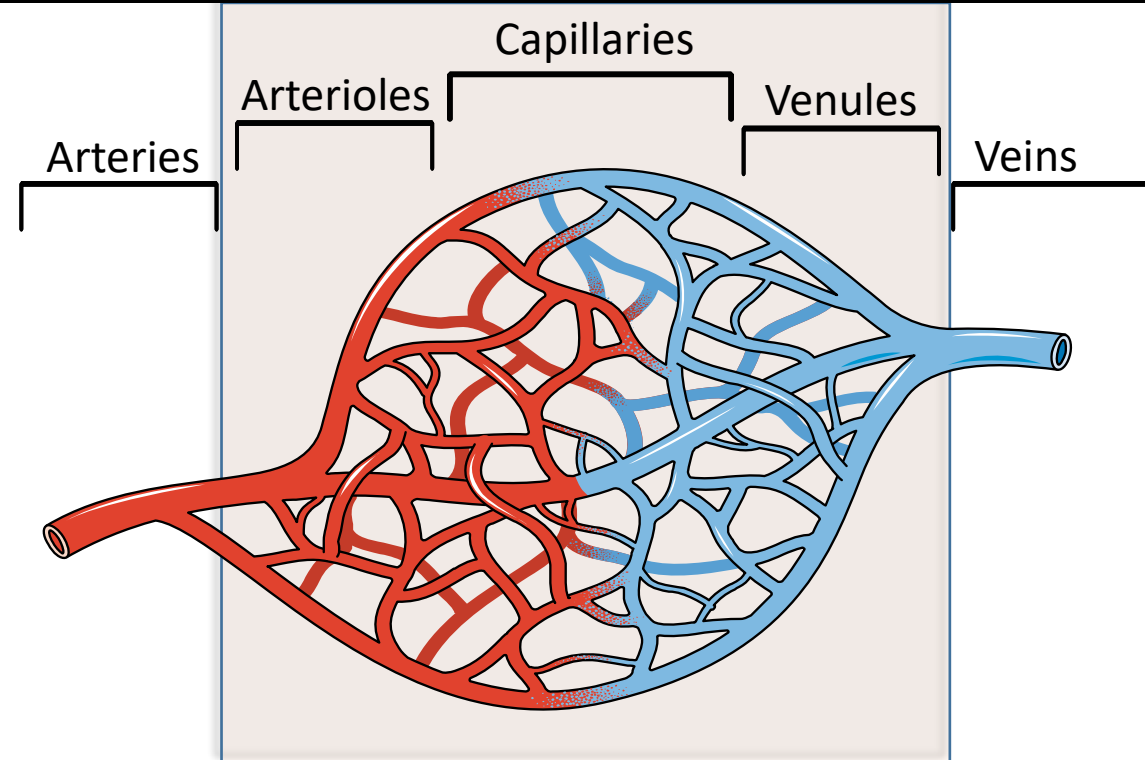
Figure 3. Kaplan–Meier Curves for Cumulative Survival.

Mechanisms of organ dysfunction: microcirculation



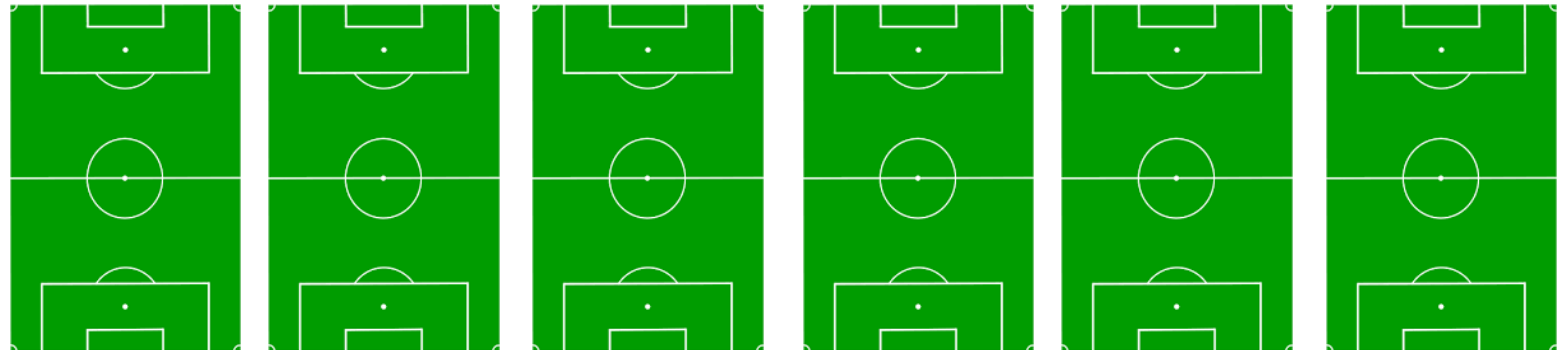
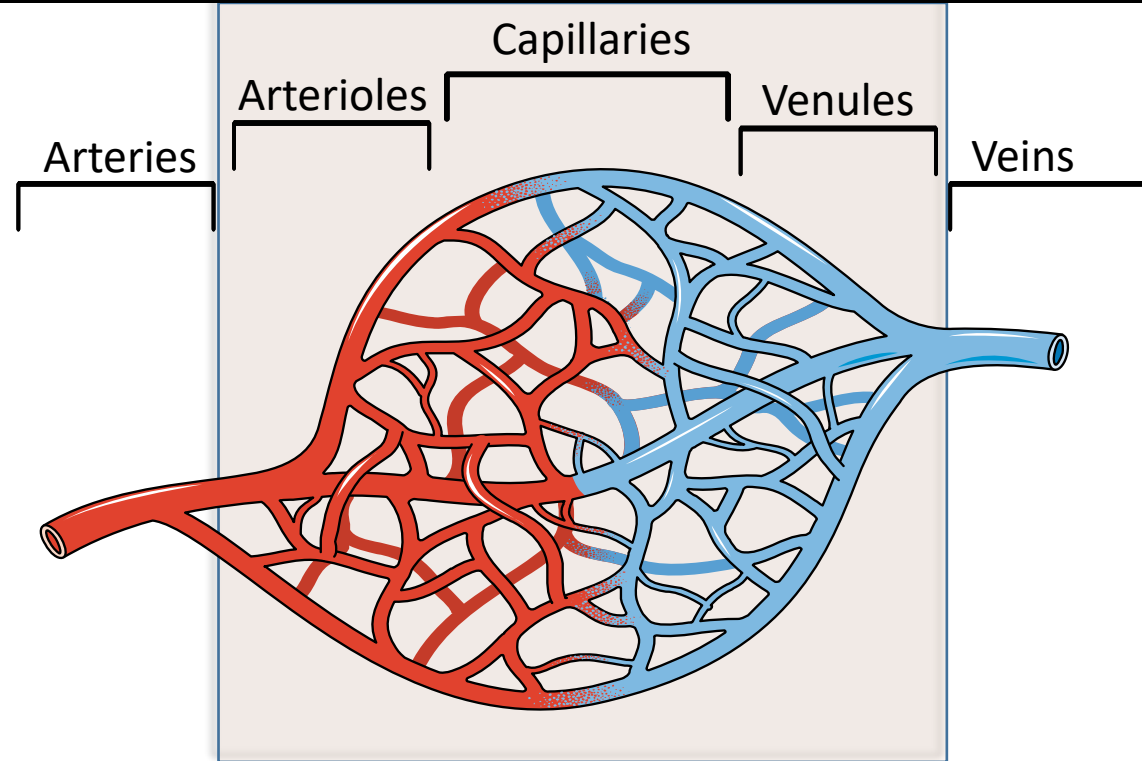
Microcirculation: Definition

- Vessels $< 100\mu\text{m}$:
Arterioles + capillaries + venules



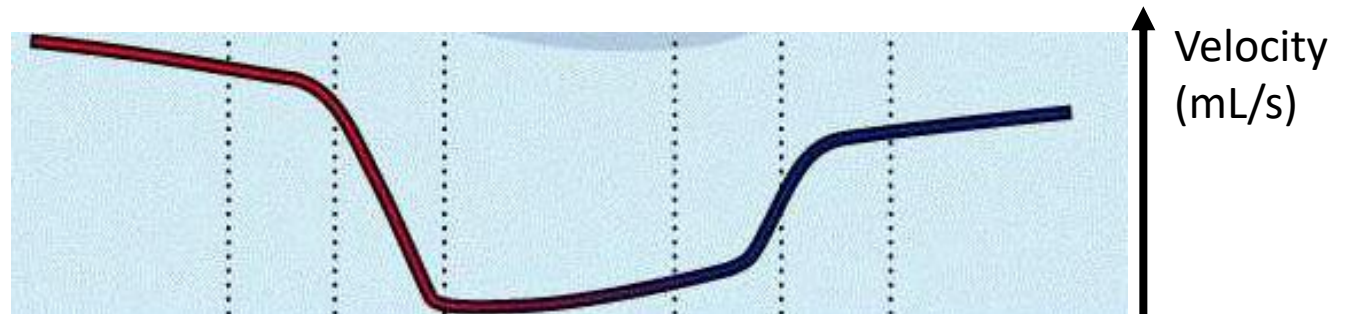
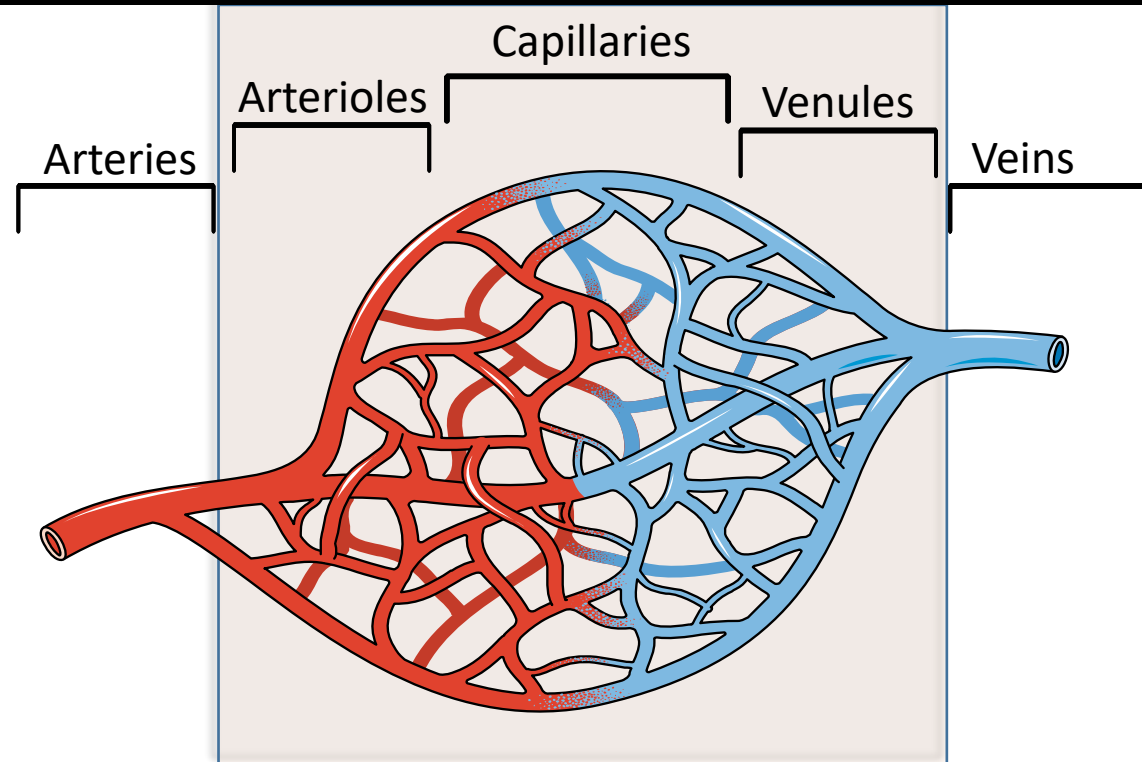
Microcirculation: Definition

- Vessels $< 100\mu\text{m}$:
Arterioles + capillaries + venules
- Surface $4000\text{--}7000\text{ m}^2$



Microcirculation: Definition

- Vessels $< 100\mu\text{m}$:
Arterioles + capillaries + venules
- Surface $4000\text{--}7000\text{ m}^2$
- Slow flow



Microcirculation: Definition

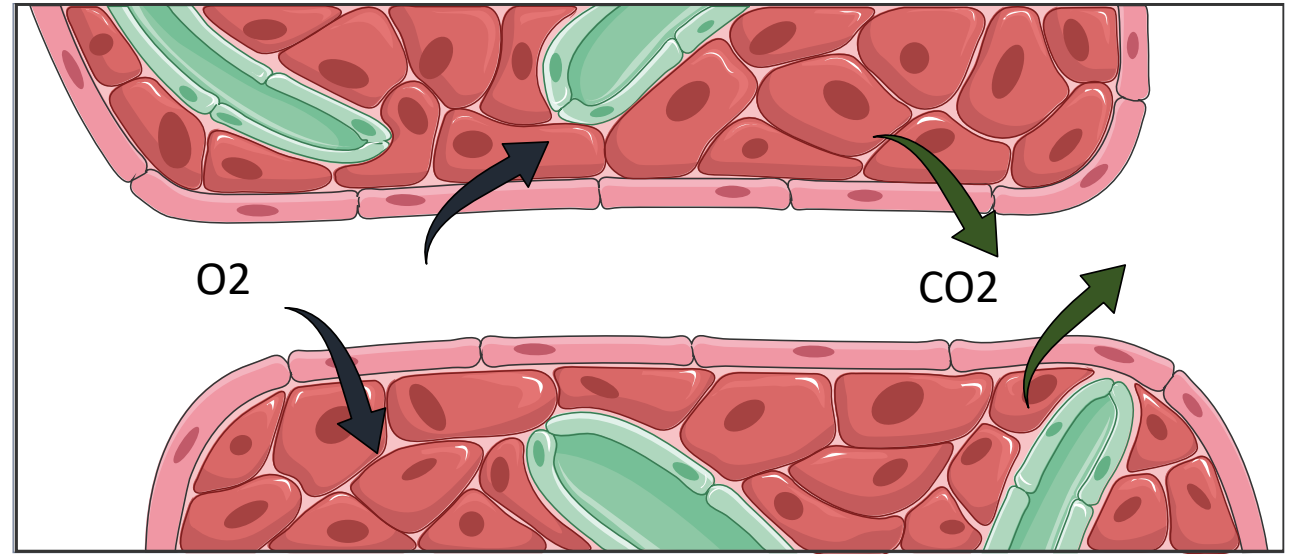
- Vessels $< 100\mu\text{m}$:
Arterioles + capillaries + venules

- Surface $4000\text{--}7000\text{ m}^2$

- Slow flow



Exchange function



Microcirculation homeostasis

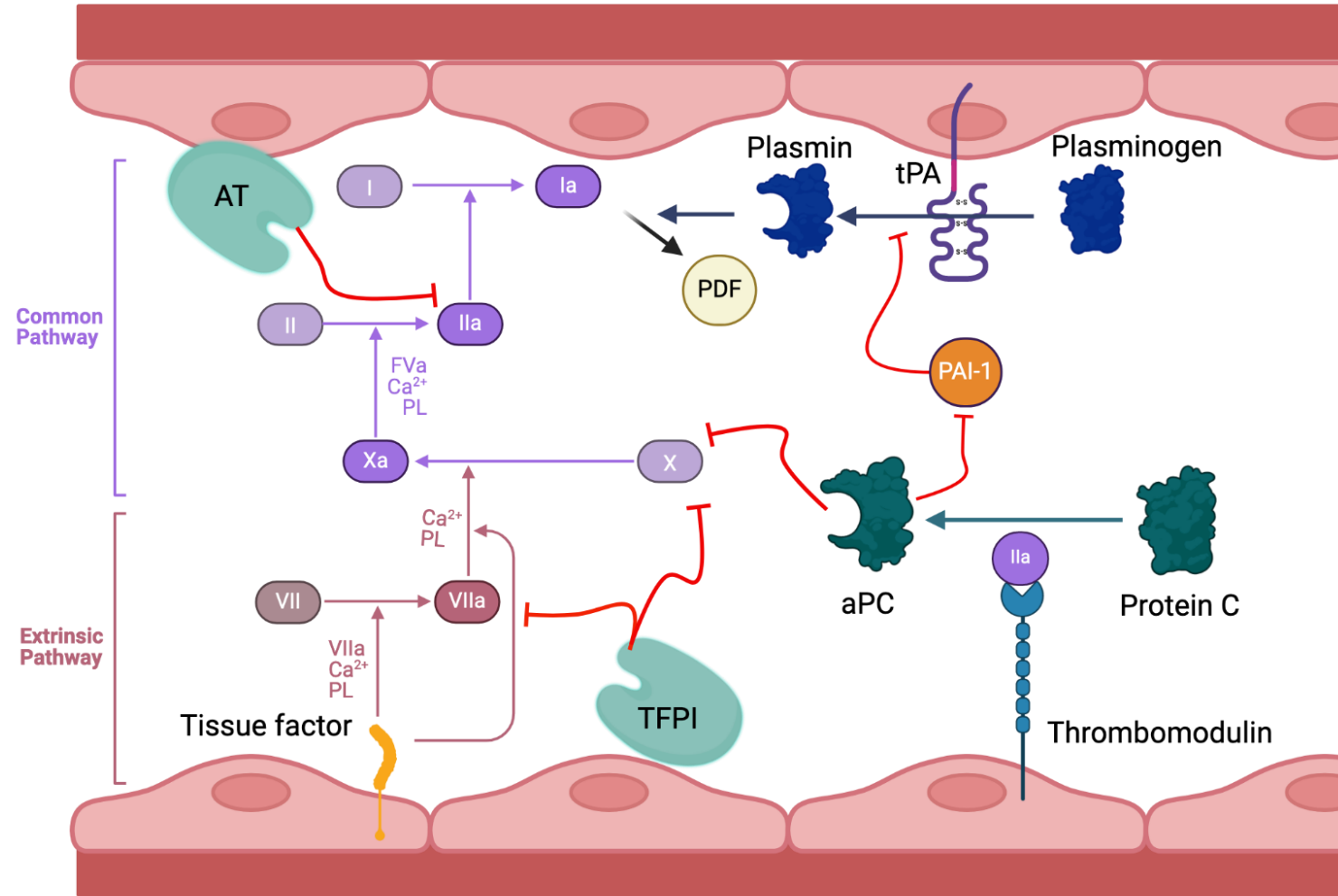
- Vessels < 100µm:
Arterioles + capillaries + venules

- Surface 4000–7000 m²

- Slow flow

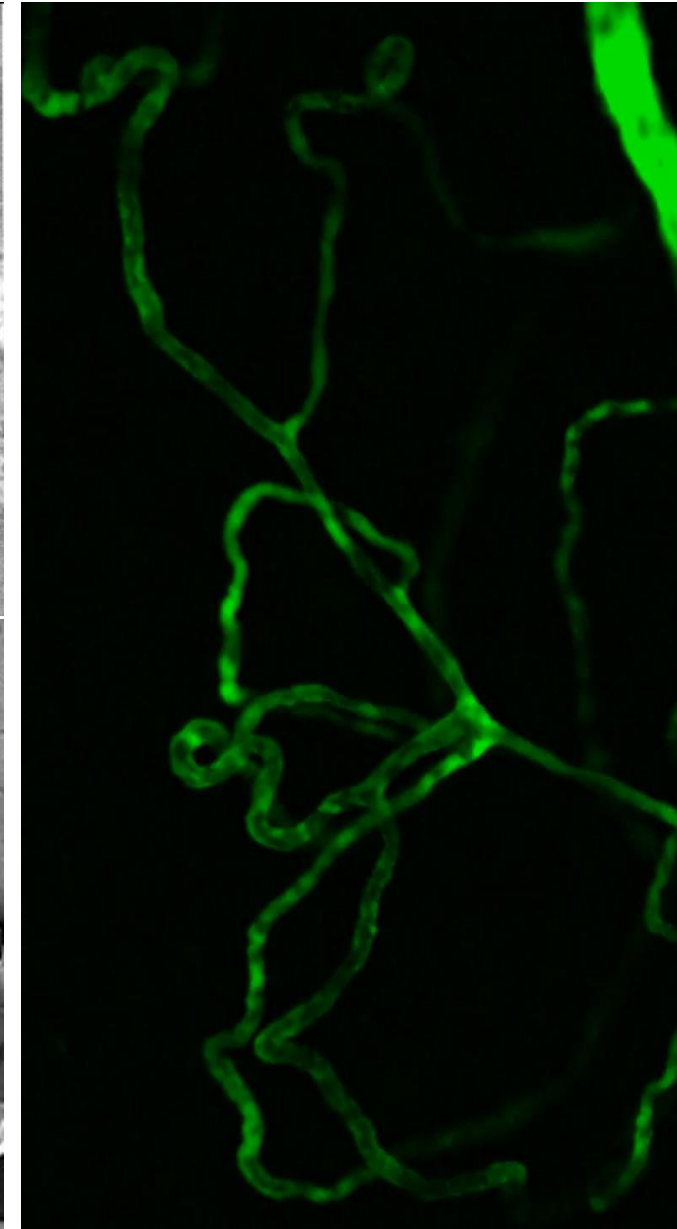
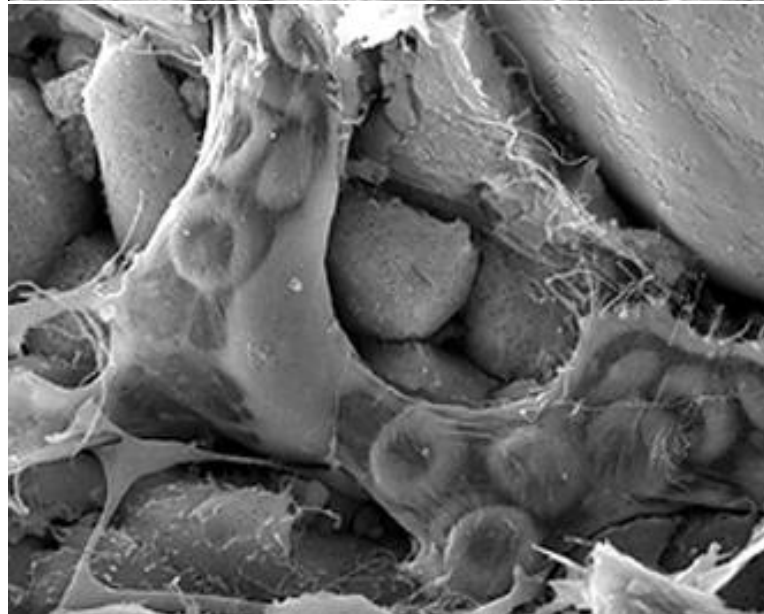
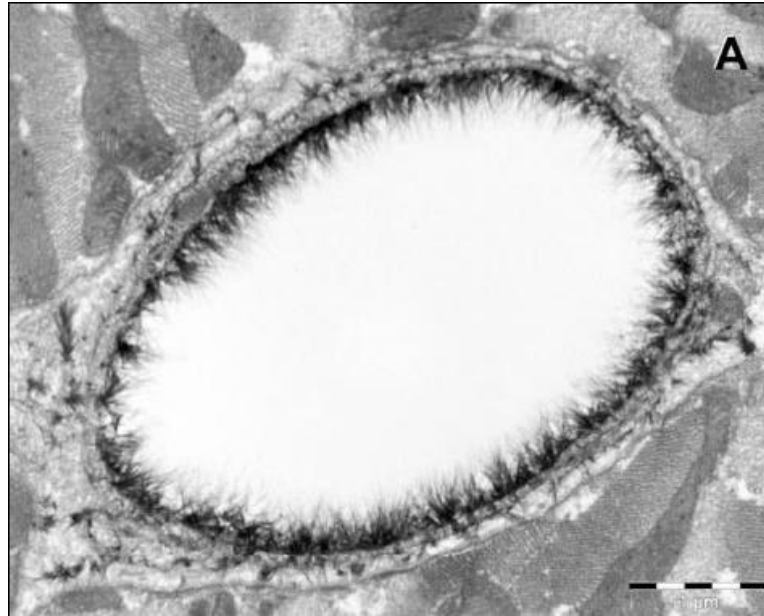
} Exchange function

- Microvascular endothelium homeostasis:
 - Anticoagulation



Microcirculation homeostasis

- Vessels $< 100\mu\text{m}$:
Arterioles + capillaries + venules
 - Surface $4000\text{--}7000\text{ m}^2$
 - Slow flow
- } Exchange function
- Microvascular endothelium homeostasis:
 - Anticoagulation
 - Rheology

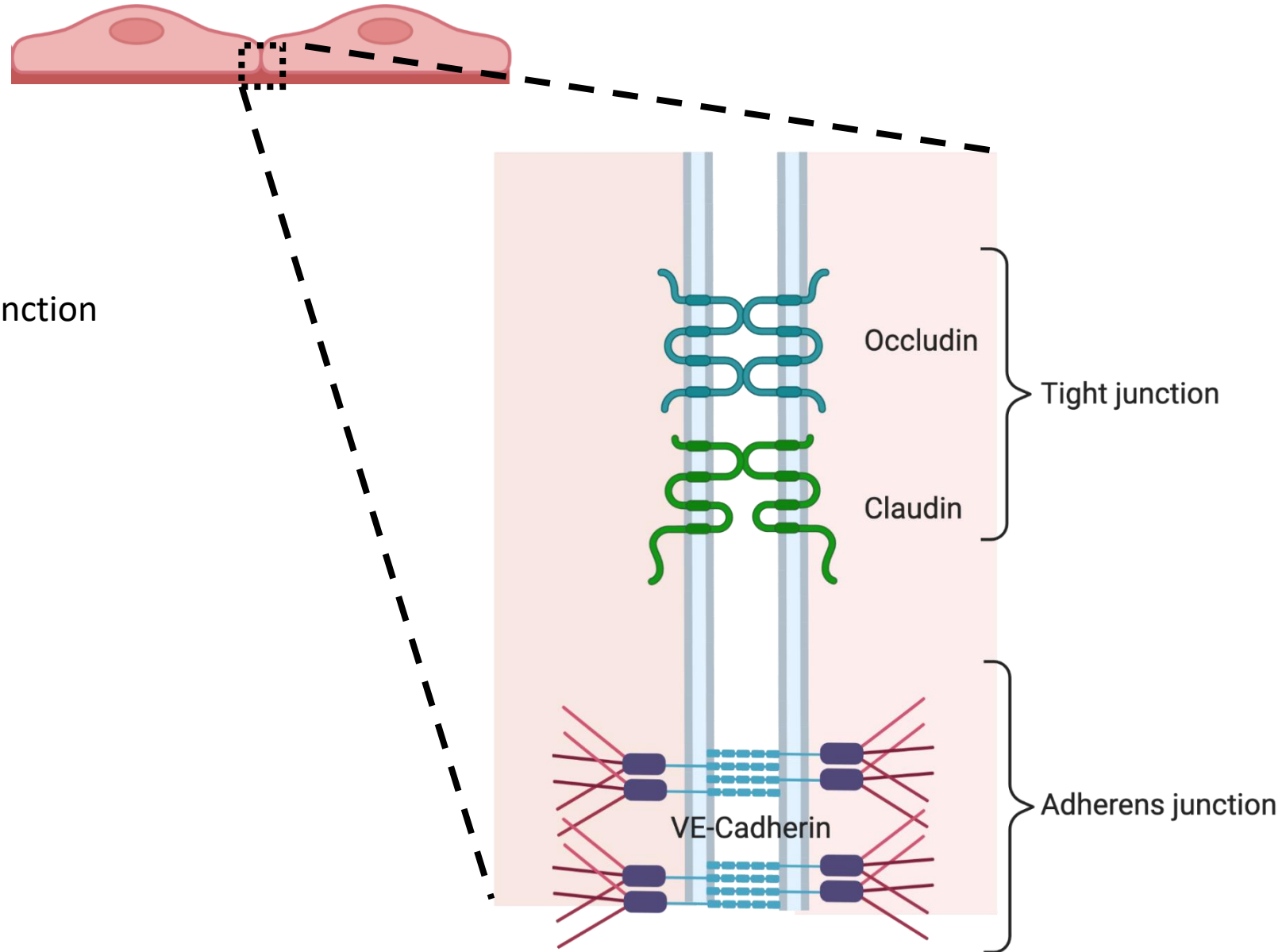


Microcirculation homeostasis

- Vessels < 100 μ m:
Arterioles + capillaries + venules

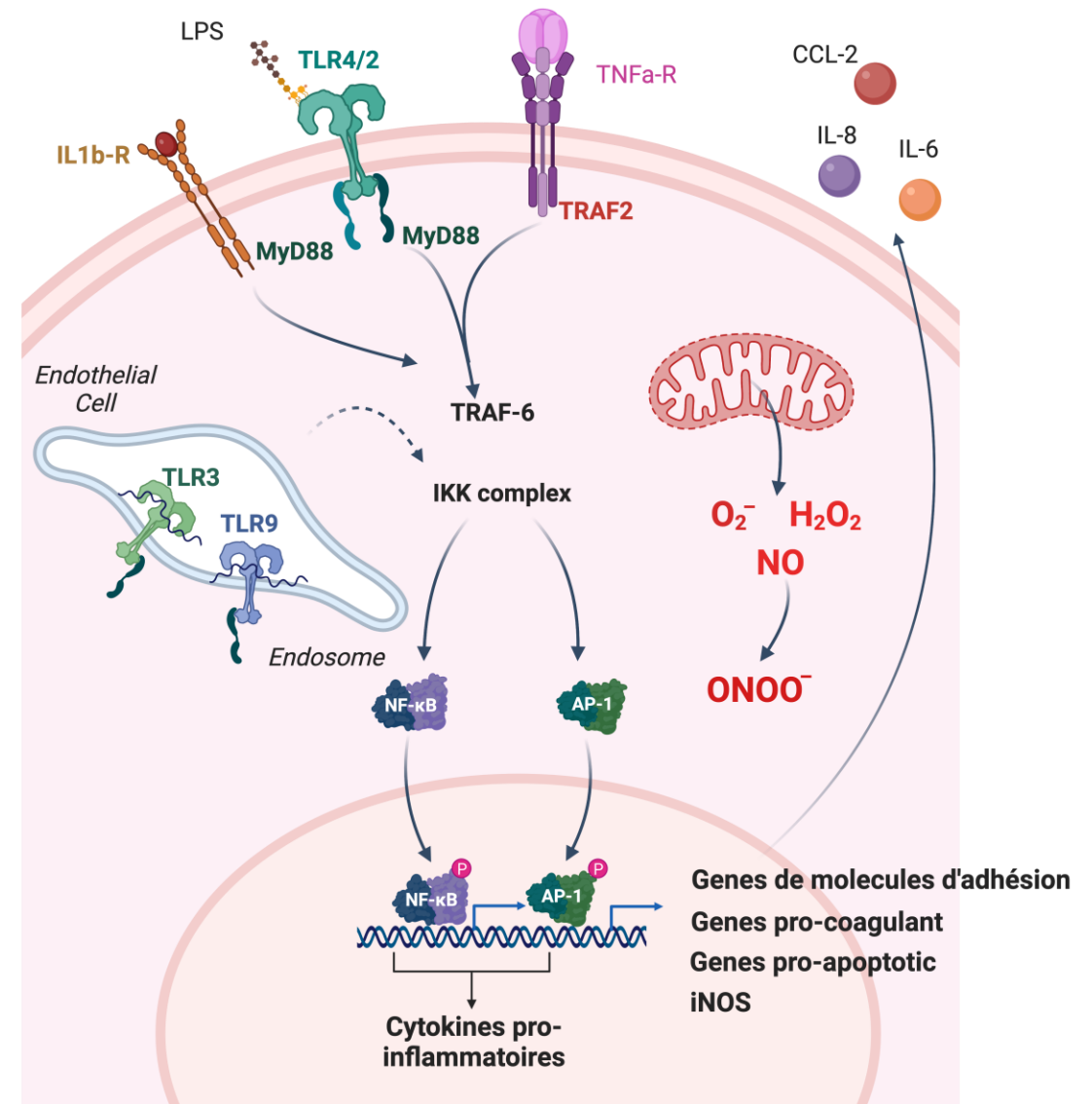
- Surface 4000–7000 m²
 - Slow flow
- } Exchange function

- Microvascular endothelium homeostasis:
 - Anticoagulation
 - Rheology
 - “Impermeability”



Microvascular endothelial cells are « innate immune cells »

- Multiple PAMPs/ DAMPs receptor:
 - TLRs / TREM-1...
 - IL-1 β R, TNF- α R, ...
 - Highly conserved
 - Redundance
- => non-specific response to inflammatory stimuli



Adapted from Joffre, AJRCCM. 2020

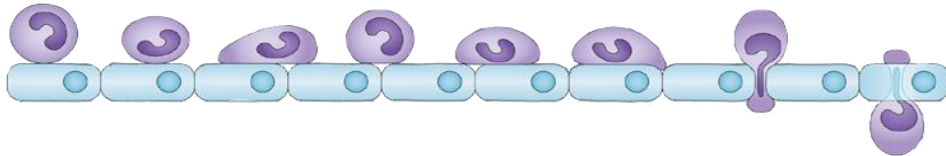
The regulator of leukocyte recruitment

- Adhesion molecules Up-regulation :

- Monocytes
- Neutrophils
- Platelets

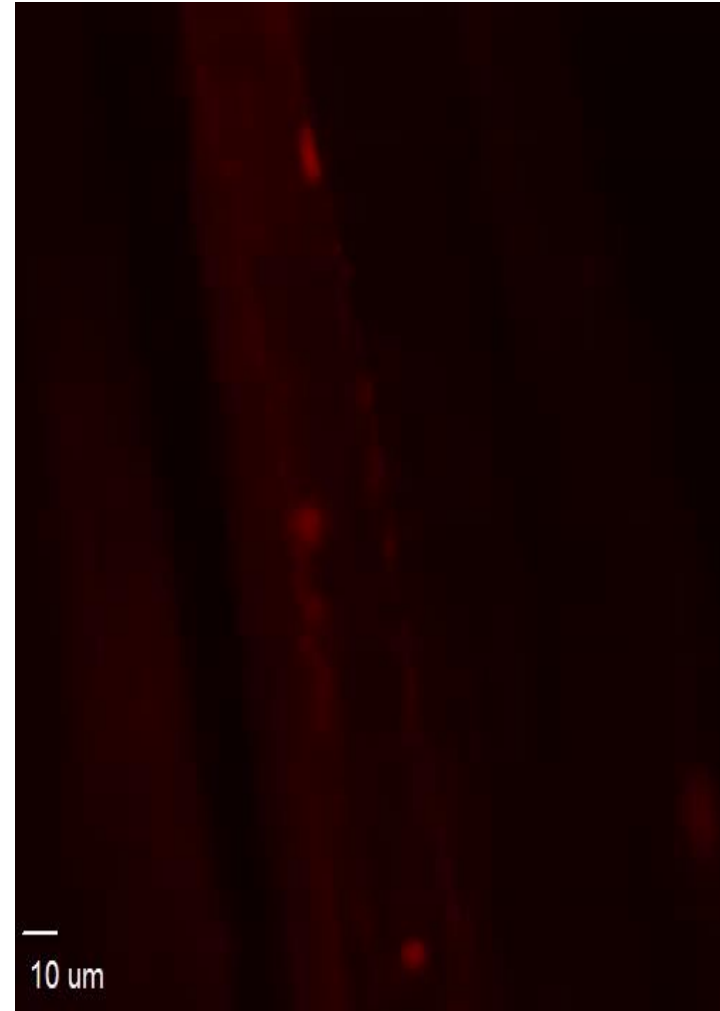


- Rolling – Adhesion
- Diapedesis- tissue infiltration

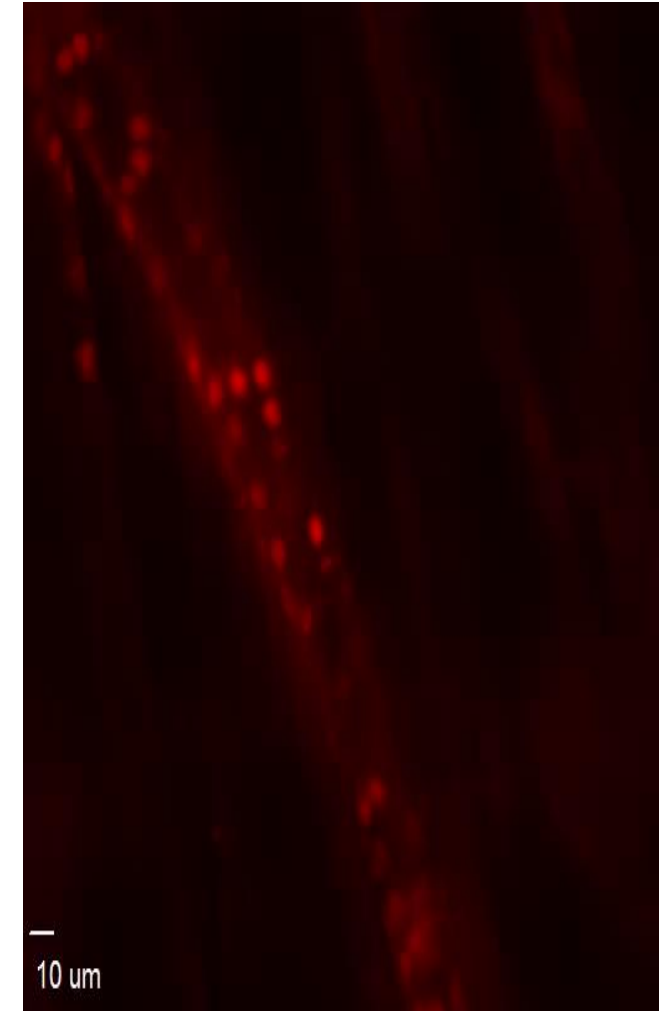


- Organ injury

Baseline



+ LPS

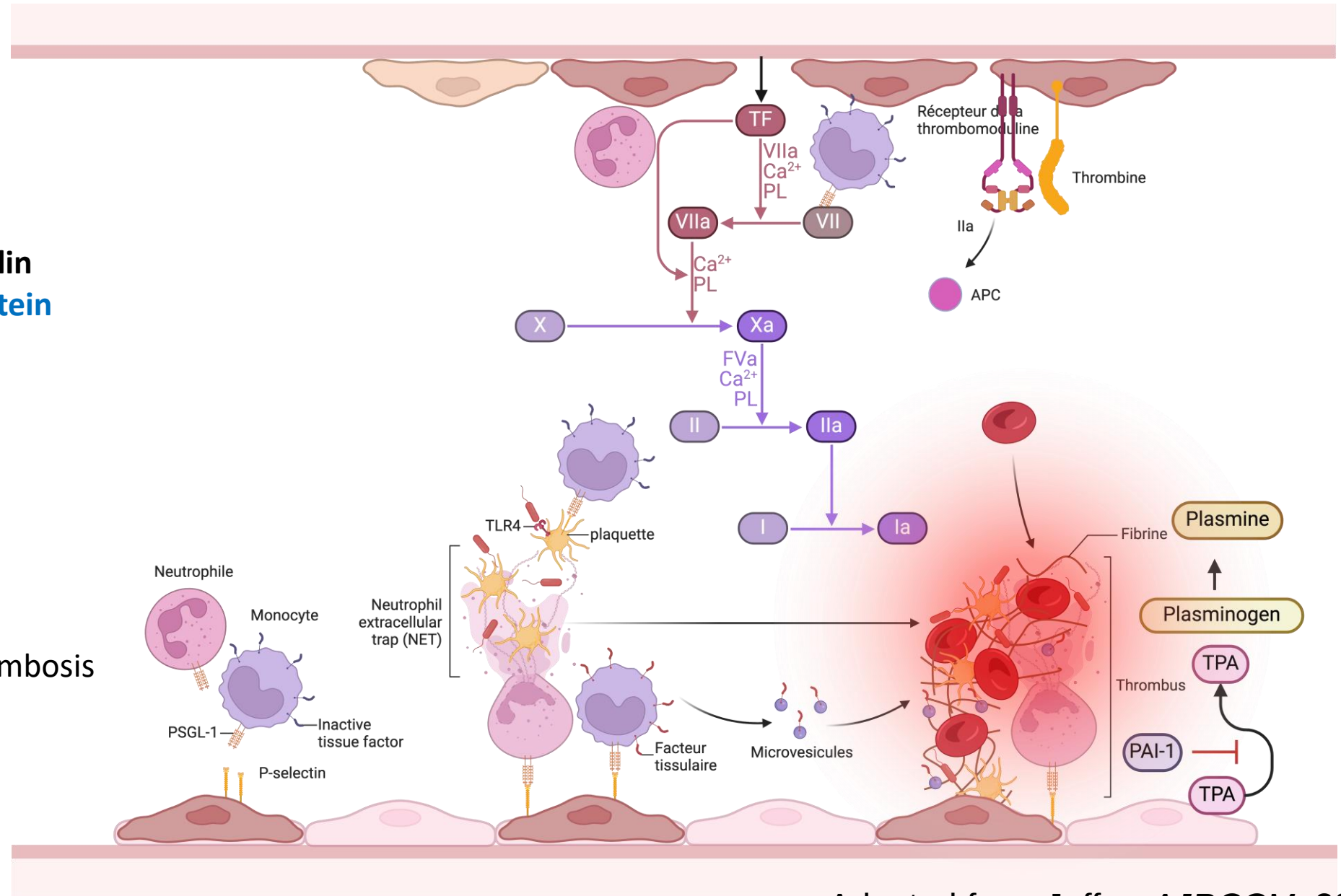


Courtesy of Dr. Nivoit- Pasteur

A switch towards a prothrombotic phenotype

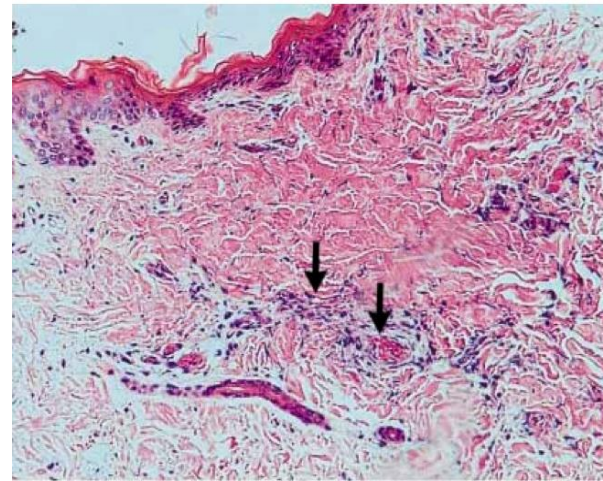
- **Pro coagulant:**
 - Tissue factor expression
 - Endothelial MP release
 - Decreased AT3
 - Decreased thrombomodulin
 - Decreased **activated C-protein**
- **Antifibrinolytic:**
 - PAI-1 overexpression

 Immunothrombosis

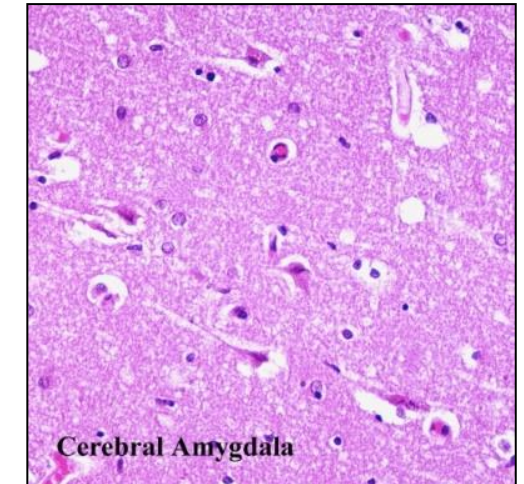


Adapted from Joffre, AJRCCM. 2020

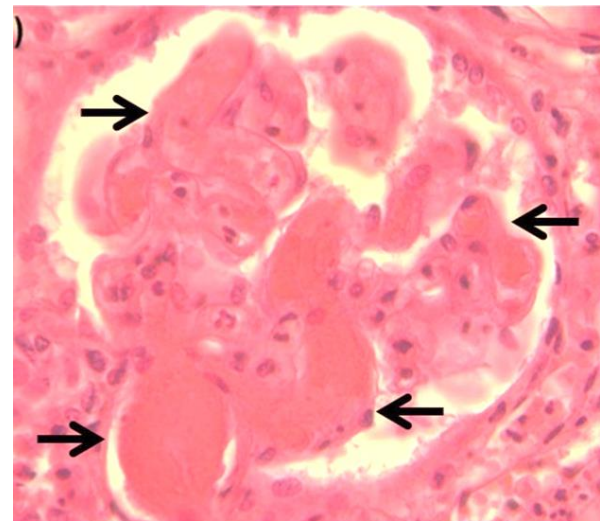
Immuno-thrombosis



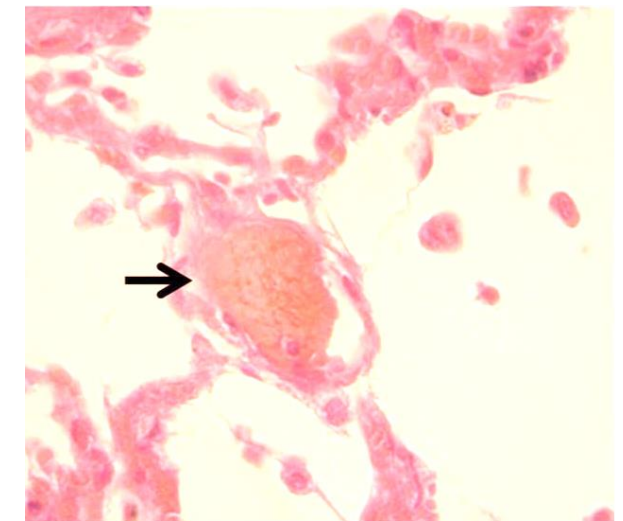
Skin



Brain



Kidney

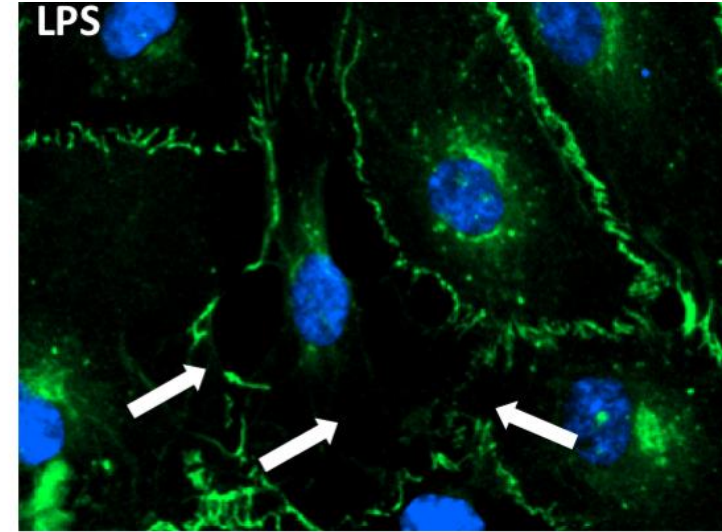
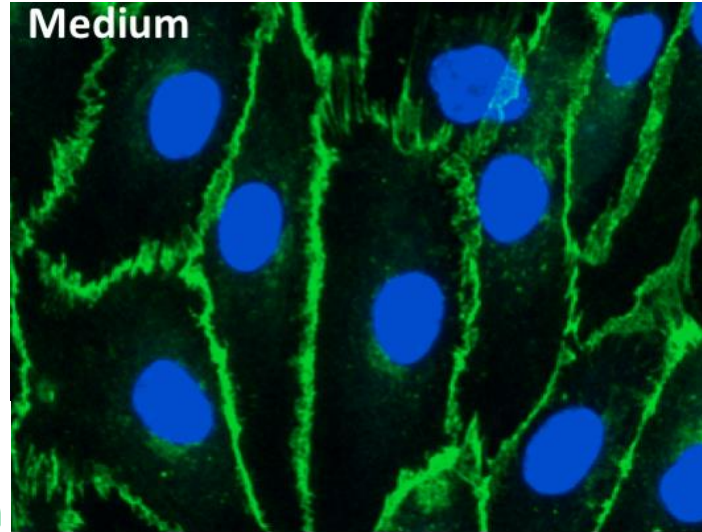


Lung

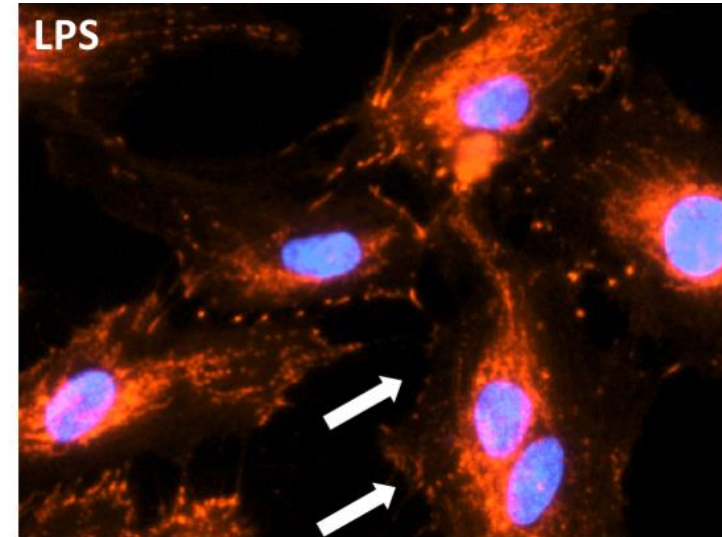
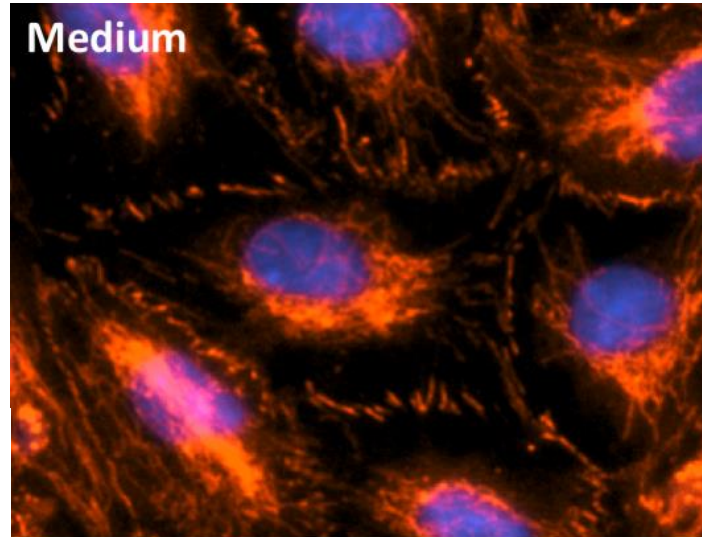
The substratum of endothelial « impermeability »

- PAMPs and DAMPs disrupt endothelial junctions

DAPI
VE-Cadherin



DAPI
ZO-1



The substratum of endothelial « impermeability »

- PAMPs and DAMPs disrupt endothelial junctions



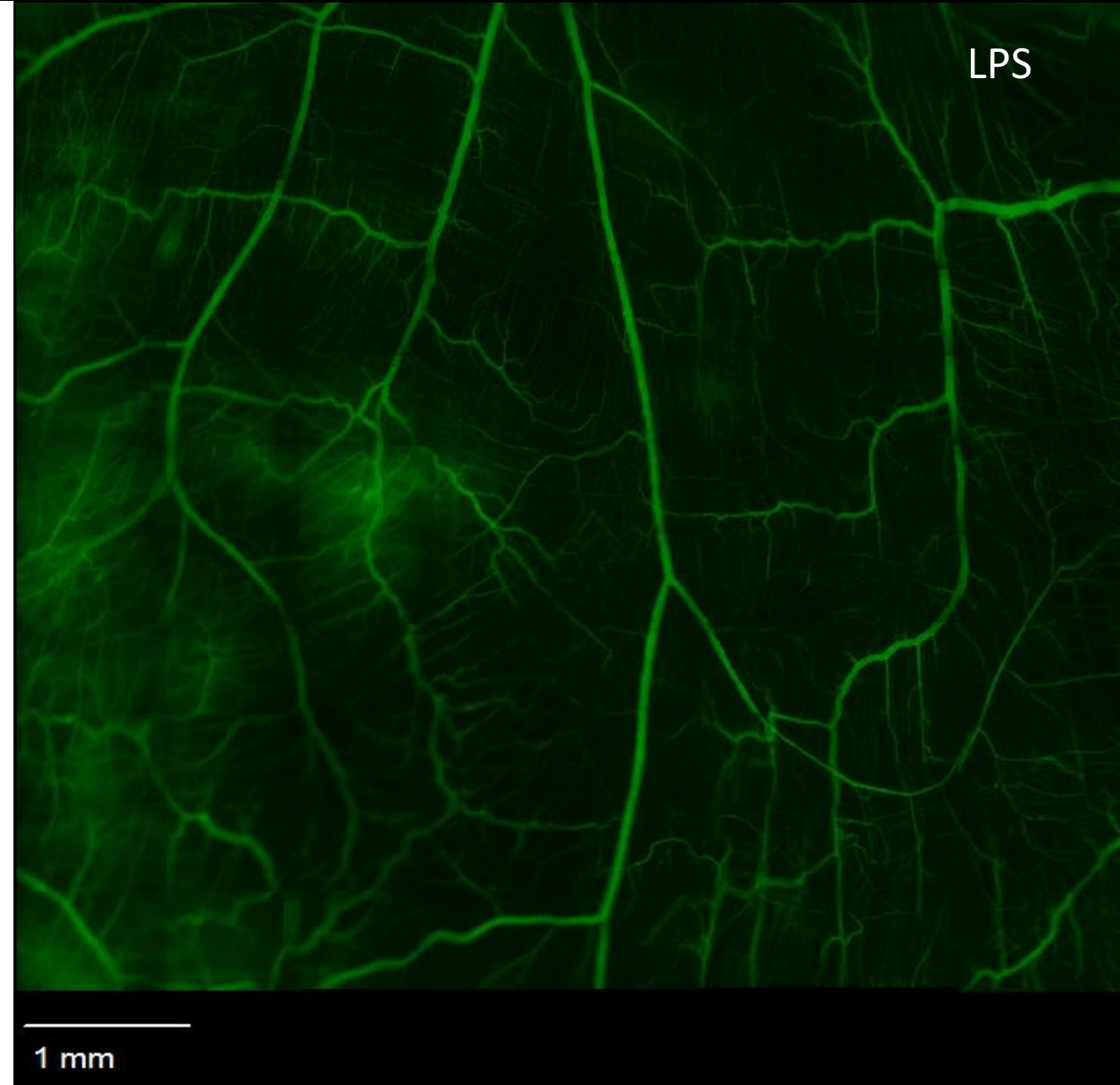
- Capillary leak:
Fluids + proteins (albumin)



- Lesional edema
- Ineffectiveness of fluid challenge
- Increased interstitial pressure



- Organ failure

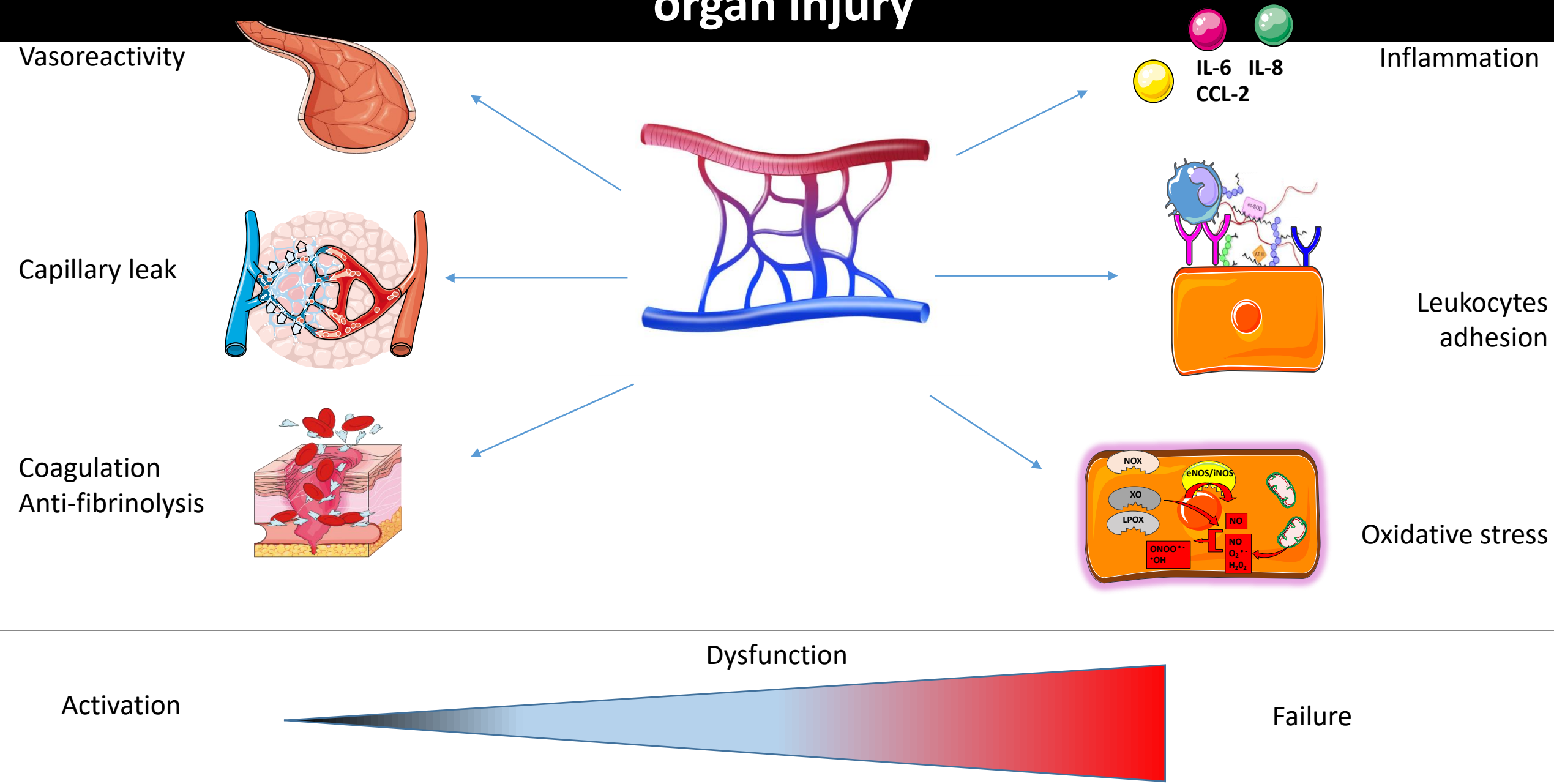


Courtesy of Dr. Nivoit- Pasteur

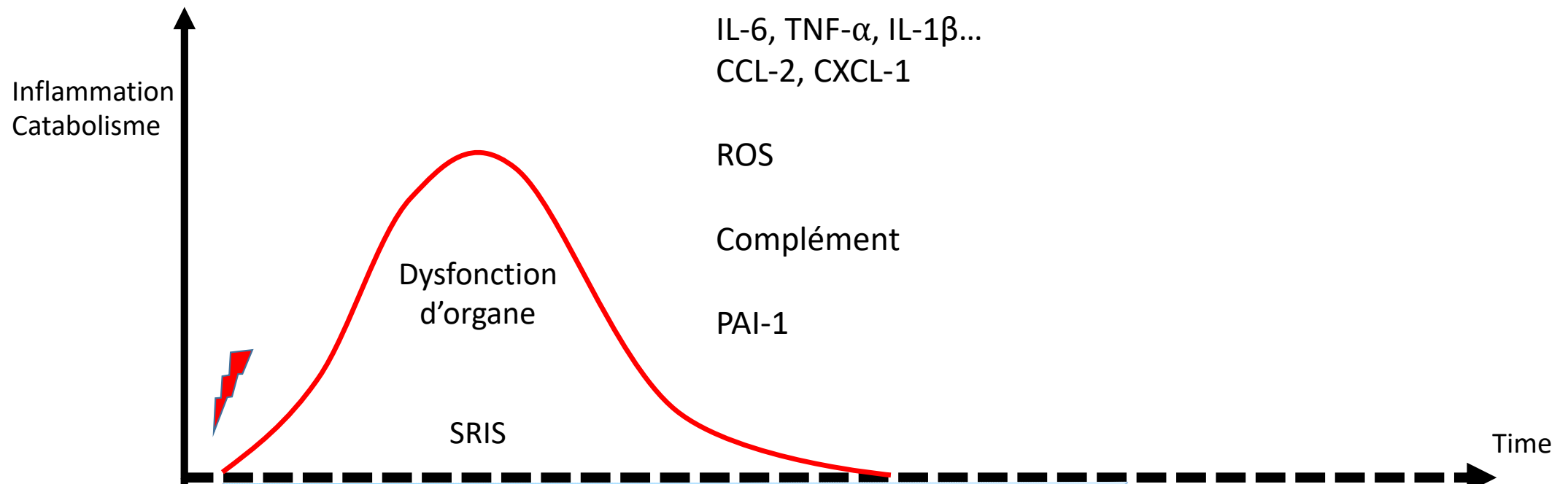
Capillary leak in early and late in septic shock



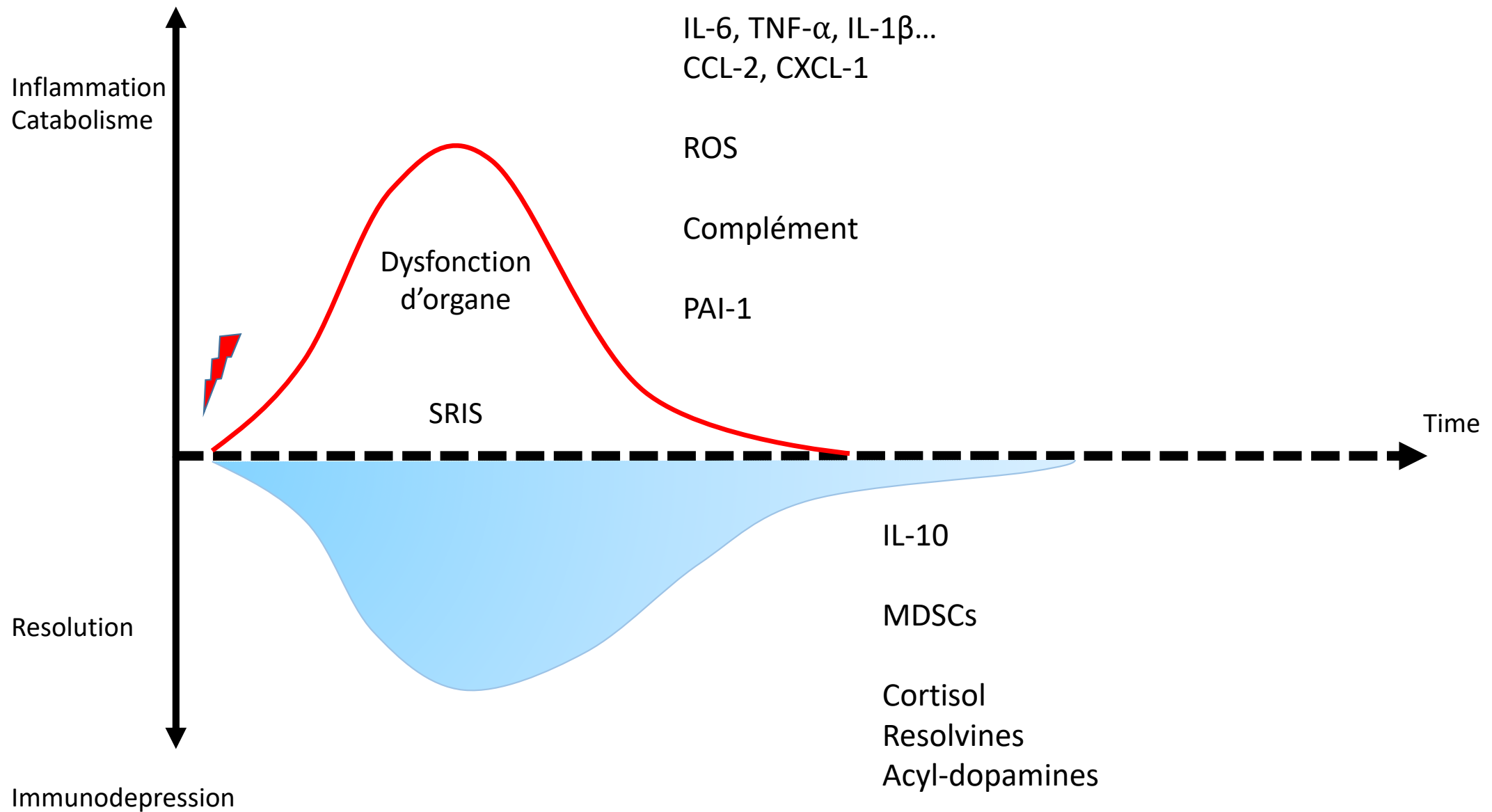
Microvascular endothelial response to infection is a major driver of organ injury



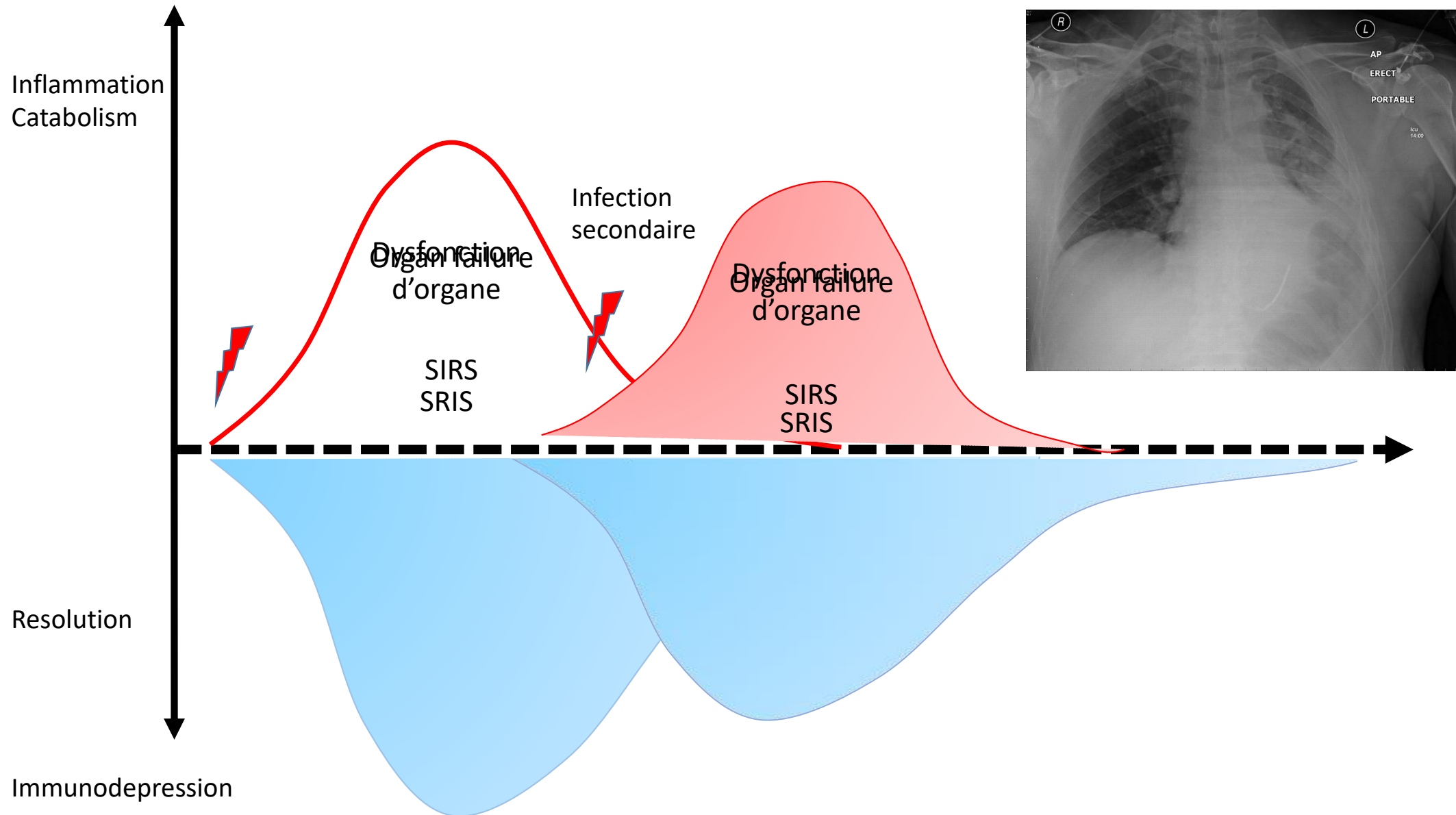
Mechanisms of organ dysfunction: Inflammation



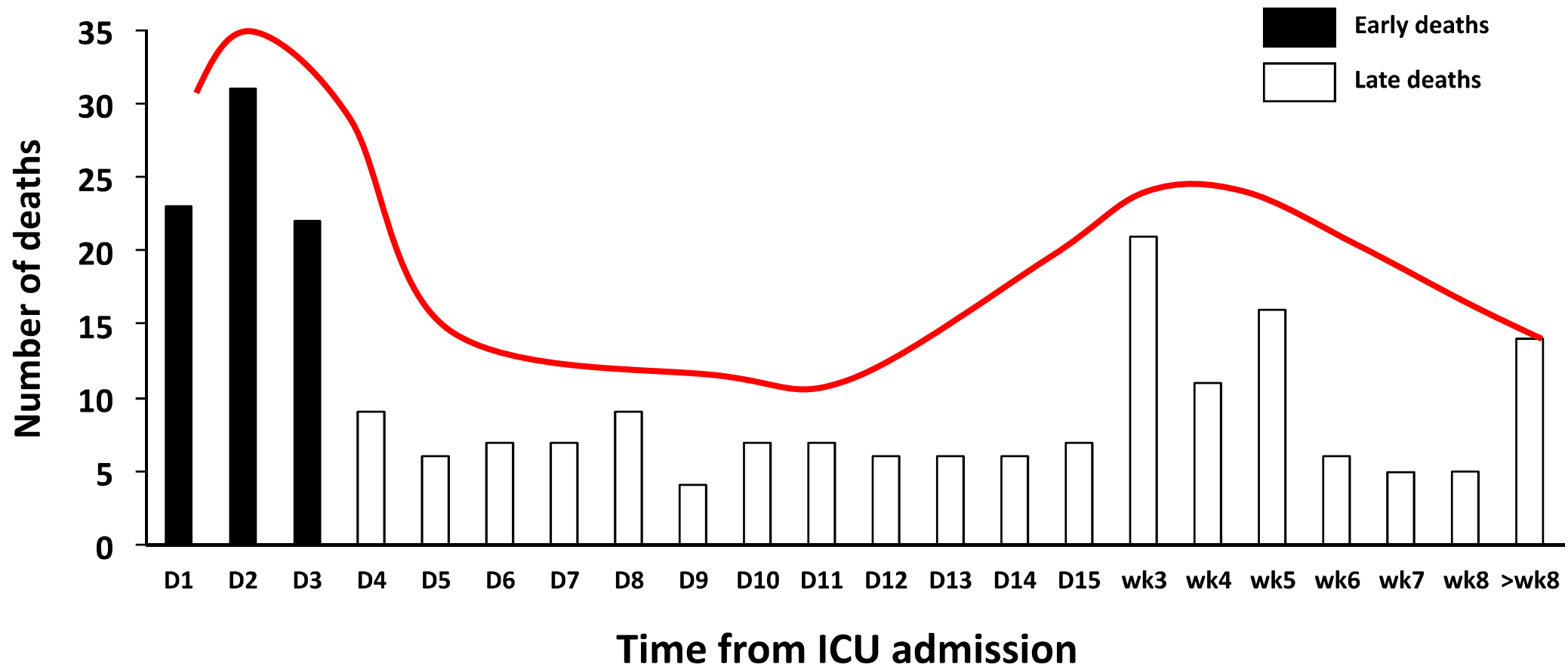
Inflammatory response dynamics



Inflammatory response dynamics



Inflammatory response dynamics



Physiopathology

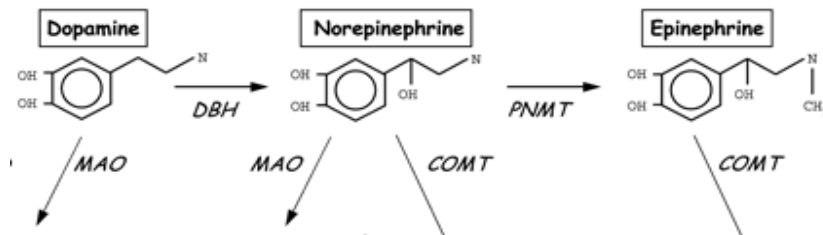


Bedside use



Cutting-edge sepsis resuscitation in 2025 !

Fluids + Vasopressors + Antibiotics



Sir Bernard Katz



Ulf von Euler



Julius Axelrod



Target 1: Kill germs and control the source



- Don't miss the diagnostic

- Hit early

- Hit large

- Think of source control

Rate of diagnostic errors and serious misdiagnosis

Sepsis	9.5% (8.2-20.8)
Spinal abscess	62.1% (54.6-69.2)
Meningitis/encephalitis	25.6% (20.8-30.8)
Endocarditis	25.5% (21.7-29.6)
Pneumonia	9.5% (2.3-14.3)

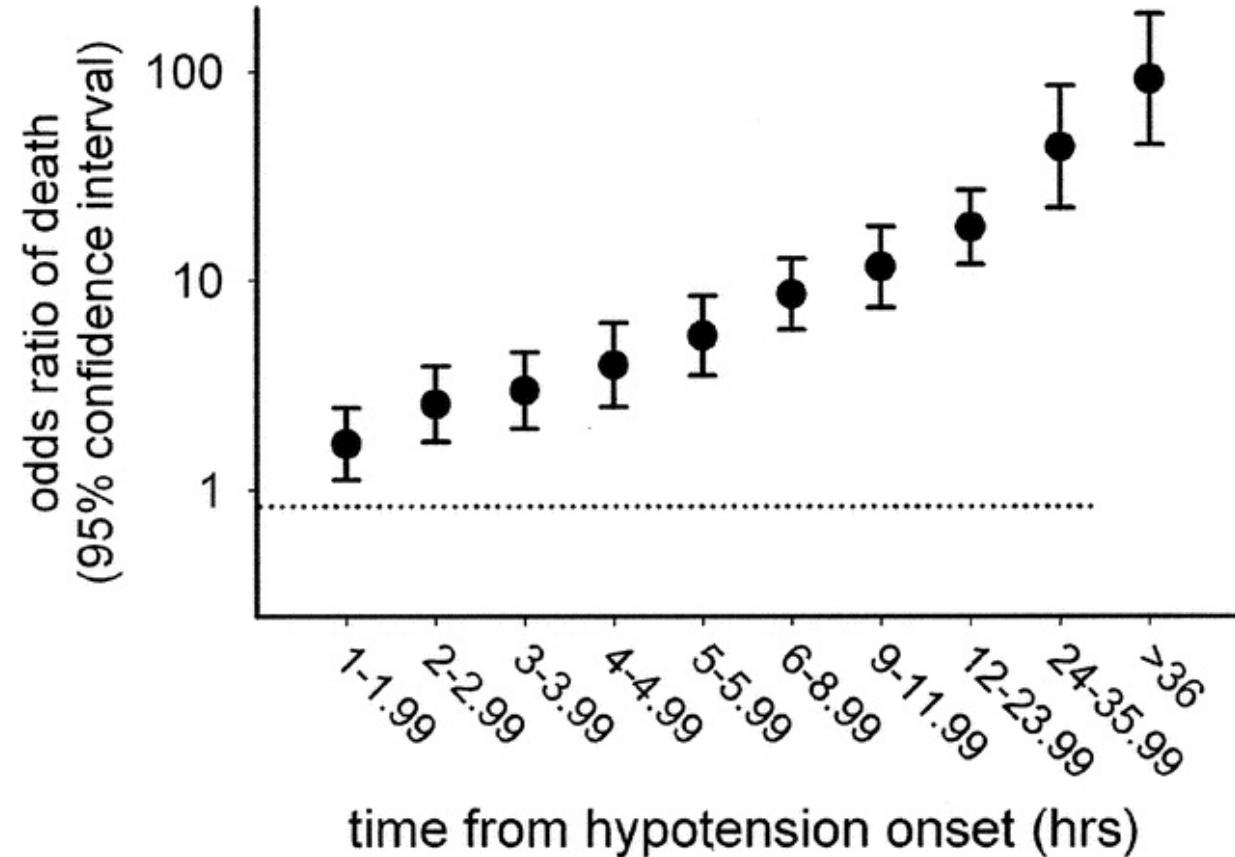
→ Serious harms in 16-55%

Newman-Toker, *Diagnosis*. 2021

Target 1: Kill germs and control the source



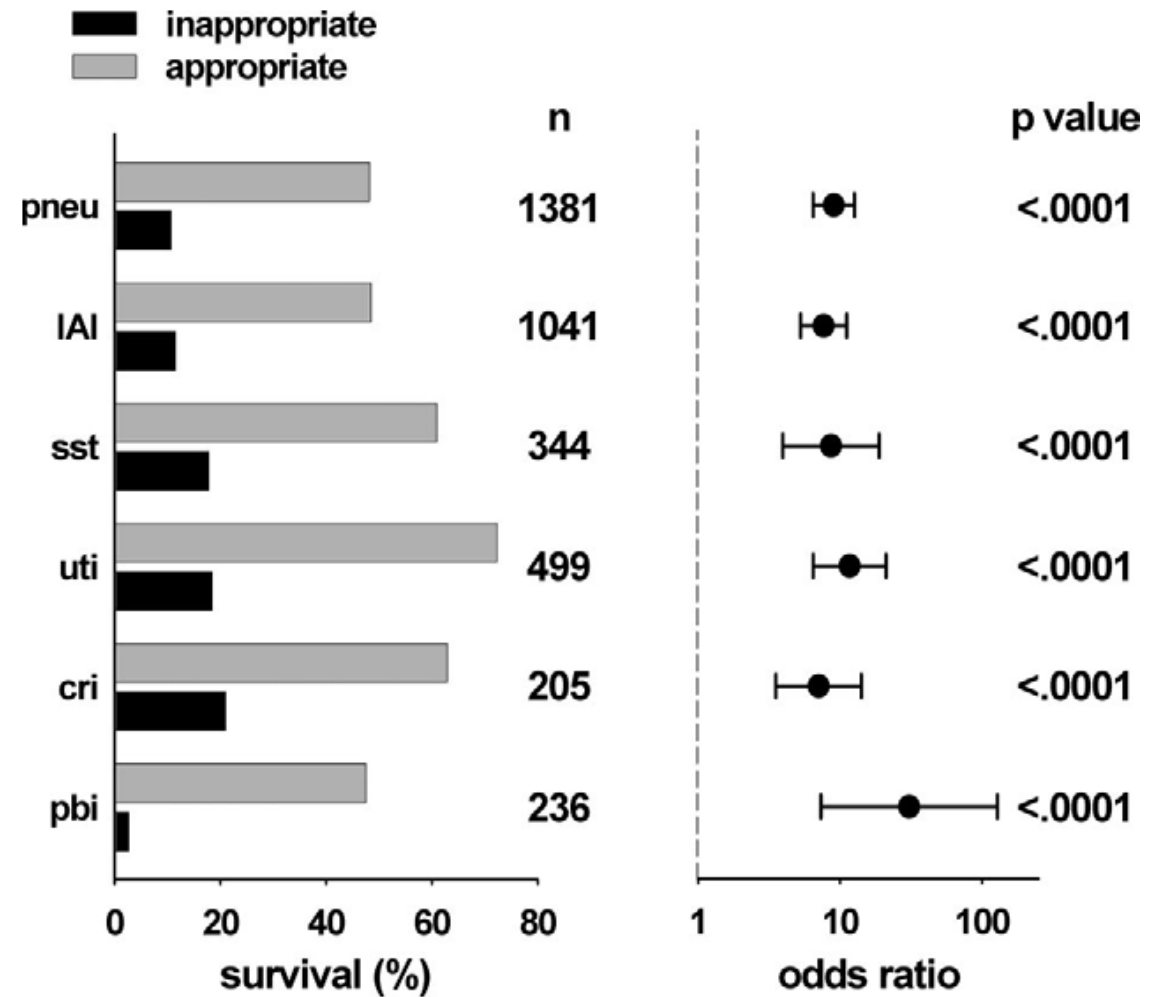
- Don't miss the diagnostic
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Target 1: Kill germs and control the source



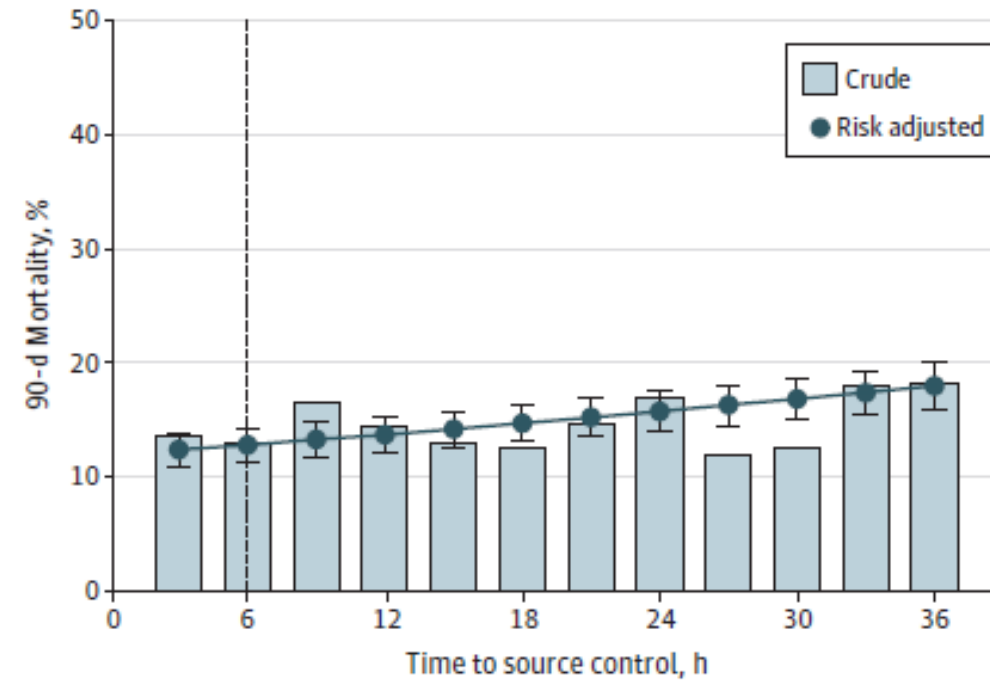
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Target 1: Kill germs and control the source



- Don't miss the diagnostic
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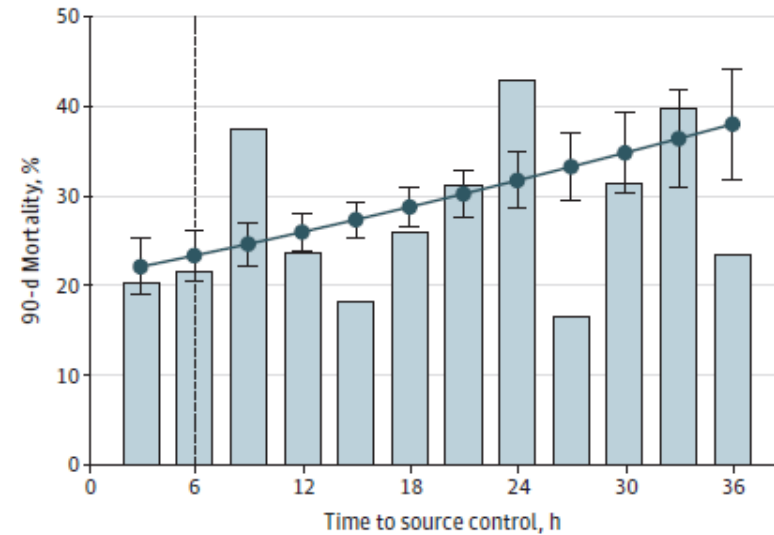


Target 1: Kill germs and control the source

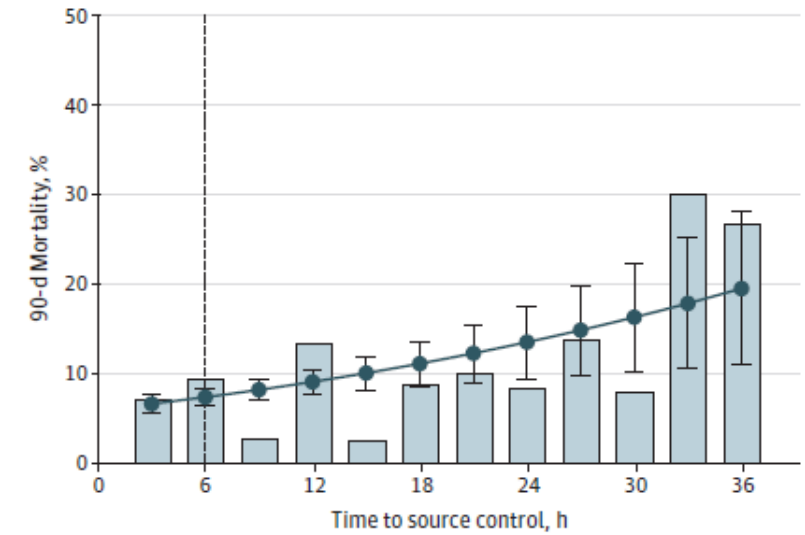


- Don't miss the diagnostic
- Hit early
- Hit Big
- Think of source control

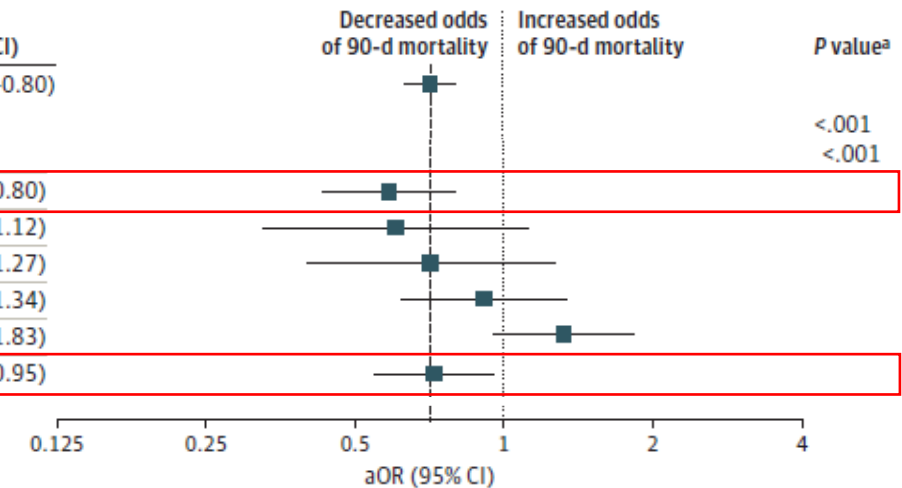
B Exploratory laparotomy^a (n=680)



E Soft tissue debridement (n=704)



Prespecified group	Early source control, No. (%)	Subgroup, No.	aOR (95% CI)
Overall	1315 (26.5)	4962	0.71 (0.63-0.80)
Age, y			
Anatomic site			
Gastrointestinal and abdominal	482 (35.1)	1372	0.59 (0.43-0.80)
Hepatopancreatobiliary	87 (9.9)	883	0.61 (0.33-1.12)
Thoracic	139 (40.1)	347	0.71 (0.40-1.27)
Urologic and gynecologic	127 (17.8)	714	0.91 (0.62-1.34)
Orthopedic and cranial	129 (20.9)	616	1.33 (0.96-1.83)
Soft tissue	351 (34.1)	1030	0.72 (0.55-0.95)

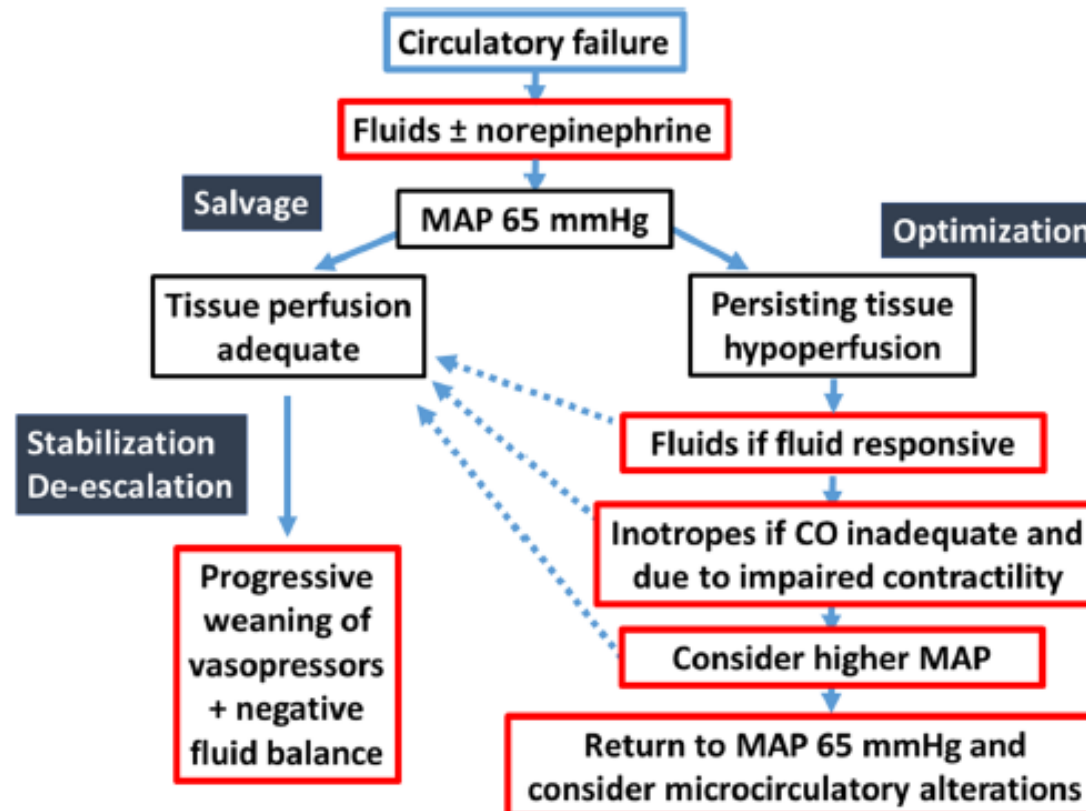


- Personalized PPGT ?



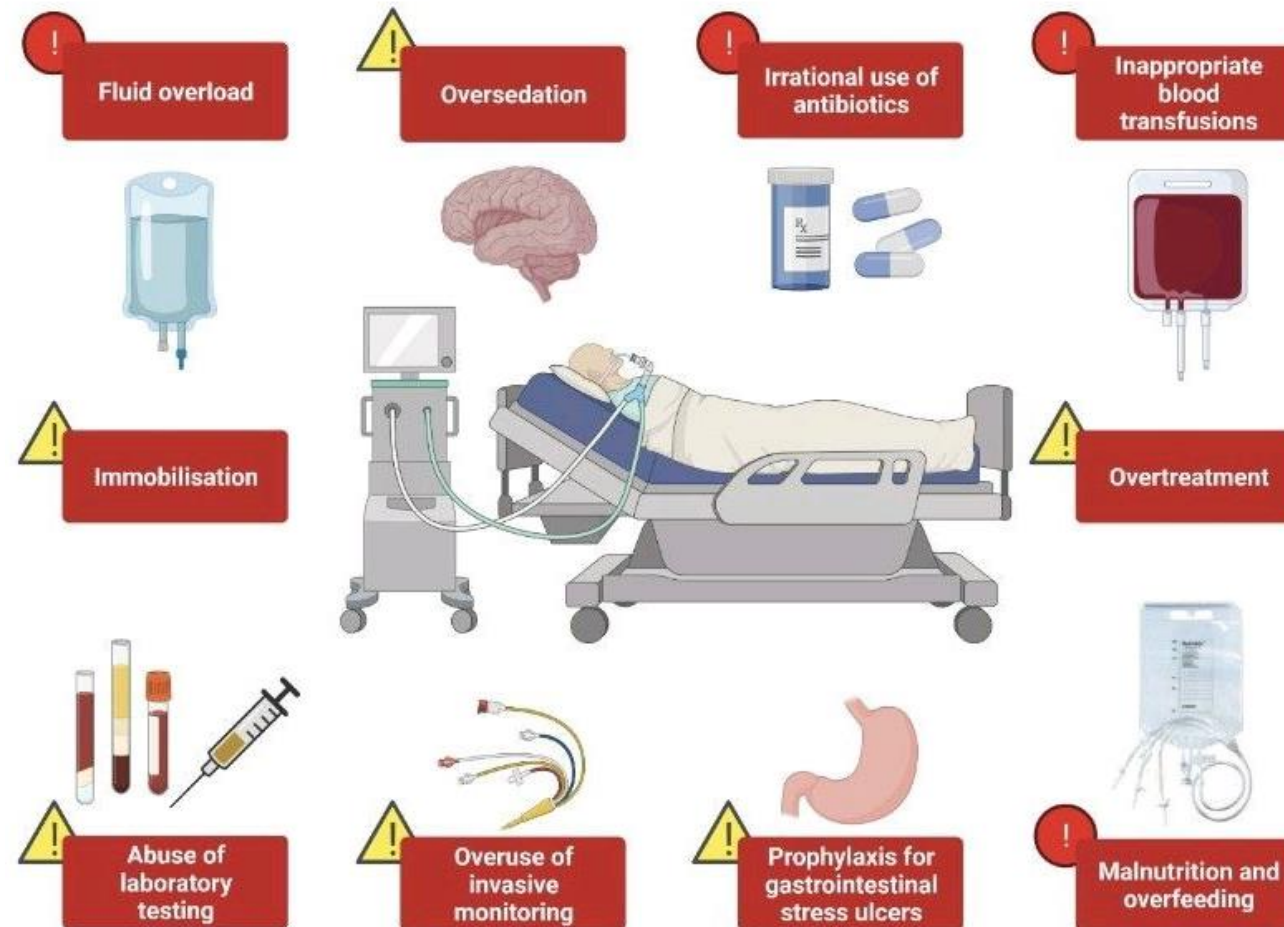
8

Surviving sepsis campaign, *ICM*. 2022



Target 2: Prevent organ dysfunction

- Be fast: golden hours
- Multiparametric evaluation: including perfusion parameters !
- Personalized PPGT
- Be accurate: de-escalation/avoid over resuscitation



What's should we do next ?

Be smarter !

- Best triage for inclusion in clinical trials
- Meaningful readouts in RCTs
- Open data sharing platform

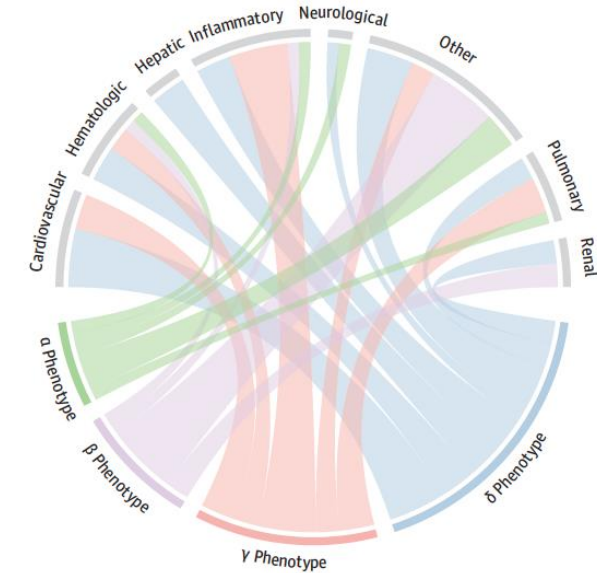
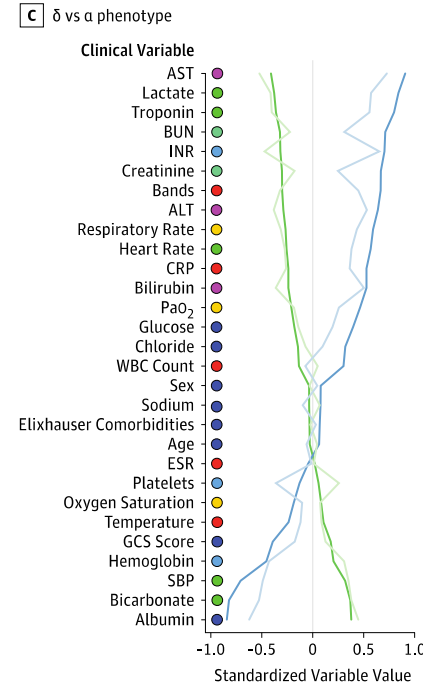


Table 2. Characteristics of the 4 Phenotypes (continued)

Characteristic ^a	Total	Phenotype			
		α	β	γ	δ
Outcomes					
Mechanical ventilation, median (IQR), d ^d	5 (2-10)	4 (2-9)	4 (2-9)	6 (3-13)	4 (2-9)
Administration of a vasopressor, median (IQR), d ^d	3 (2-5)	2 (2-4)	3 (2-4)	3 (2-5)	3 (2-5)
Admitted to intensive care unit, No. (%) ^d	9063 (45)	1644 (25)	1778 (32)	3381 (63)	2260 (85)
In-hospital mortality, No. (%)	2082 (10)	126 (2)	286 (5)	818 (15)	852 (32)

What's should we do next ?

Be smarter !

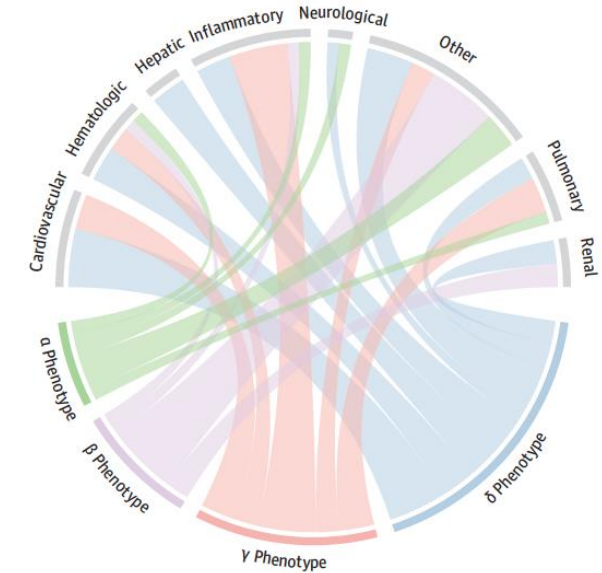
- Best triage for inclusion in clinical trials
- Meaningful readouts in RCTs
- **Open data sharing platform**

Use future opportunities for **bedside real-time sub-phenotyping**:

- AI driven clusterization
- Multiplex/ Omics driven approach
- Precision/ Personalized medicine (PK/PD, SNIP, ...)

Unleash opportunities for new therapeutics / adjuvant therapies:

- **Biotherapies** (rDrugs, Mab, MIR, cell therapy, ..)
- **Mitochondrial targeted therapy**
- Anti-infectious therapy (RNAs, phages, x-biote....)



"Open wide and say A-I-I-I-I-I-I-I-I-I-I-I-I-I-I-I."