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Asan Medical Center

Endothelial Dysfunction in Sepsis

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Disclosure statement

- **There are no conflicts of interest to declare**

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목차

1. Pathophysiology of endotheliopathy

2. Identification of endothelial dysfunction

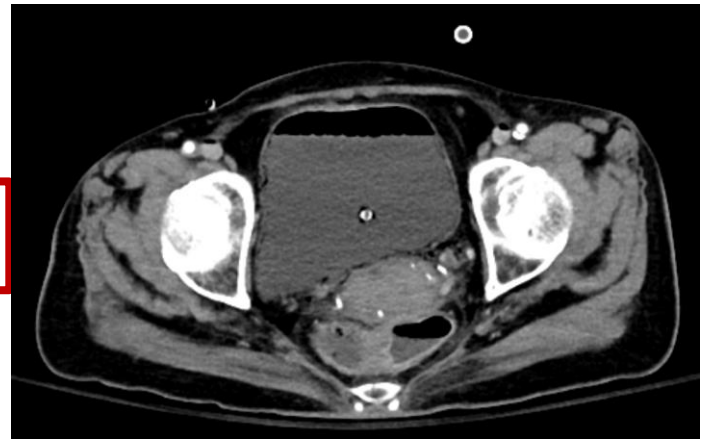
3. Therapeutic strategies targeting endotheliopathy

- **59세/여환, 당뇨병 이외 기저 질환 없던 분으로 내원 전날부터 발생한 복통, 구토, 및 기력저하로 응급실 내원**

2025-03-01 16:37:03	
WBC (Qn)[ChemR-I],Blood	3.6
RBC (Qn)[ChemR-I],Blood	3.27
Hb (Qn)[ChemR-I],Blood	9.7
Hct (Qn)[ChemR-I],Blood	28.8
MCV (Qn)[ChemR-I],Blood	88.1
MCH (Qn)[ChemR-I],Blood	29.7
MCHC (Qn)[ChemR-I],Blood	33.7
Platelet (Qn)[ChemR-I],Blood	68

2025-03-01 16:37:11	
PT(sec) (Qn)[ChemR-I],Blood	18.0
PT(%) (Qn)[ChemR-I],Blood	47.3
PT(INR) (Qn)[ChemR-I],Blood	1.59
aPTT (Qn)[ChemR-I],Blood	34.6
Fibrinogen (Qn)[ChemR-I],Blood	414
D-dimer (Qn),Blood	15.37

2025-03-01 16:37:18	
Total calcium (Qn)[ChemR-I],Blood	7.4
Phosphorus (Qn)[ChemR-I],Blood	4.6
Glucose (Qn)[ChemR-I],Blood	214
Creatinine (Qn)[ChemR-I],Blood	1.84
BUN (Qn)[ChemR-I],Blood	46
AST(SGOT) (Qn)[ChemR-I],Blood	106
ALT(SGPT) (Qn)[ChemR-I],Blood	20
Alkaline phosphatase (Qn)[ChemR-I],Blood	185
Total bilirubin (Qn)[ChemR-I],Blood	0.5
Sodium (Qn)[EM],Blood	139
Potassium (Qn)[EM],Blood	3.2
Chloride (Qn)[EM],Blood	96
LD (Qn)[ChemR-I],Blood	457
Magnesium (Qn)[ChemR-I],Blood	2.13
CRP (Qn),Blood	20.19
eGFR(CKD-EPI) (Qn),Blood	30
eGFR(MDRD) (Qn),Blood	28



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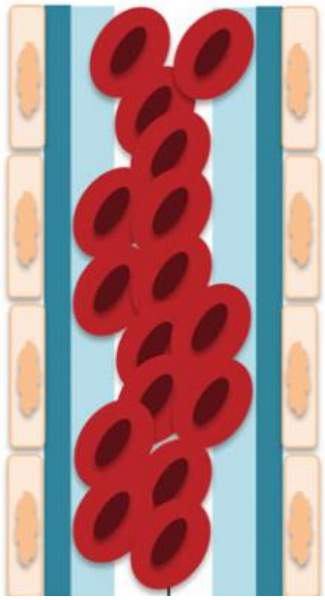
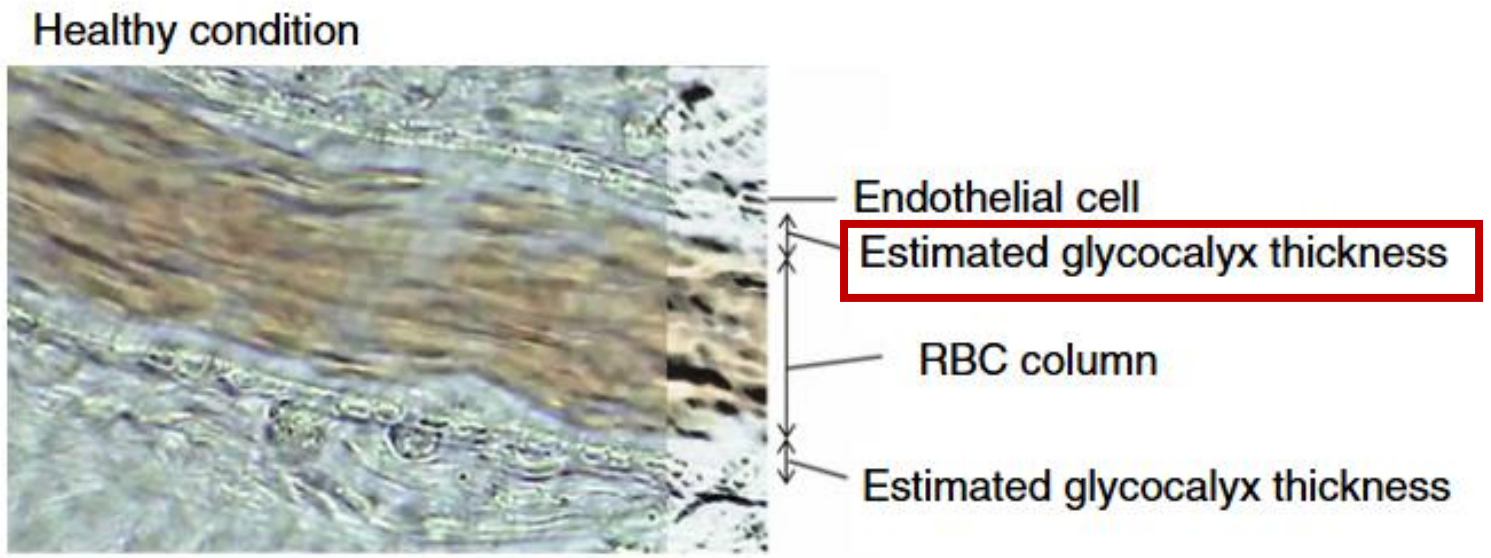
1. Endotheliopathy

Endothelial Cells (EC)

Endothelial cells are vascular, nonconventional immune cells that play a major role in the systemic response after bacterial infection



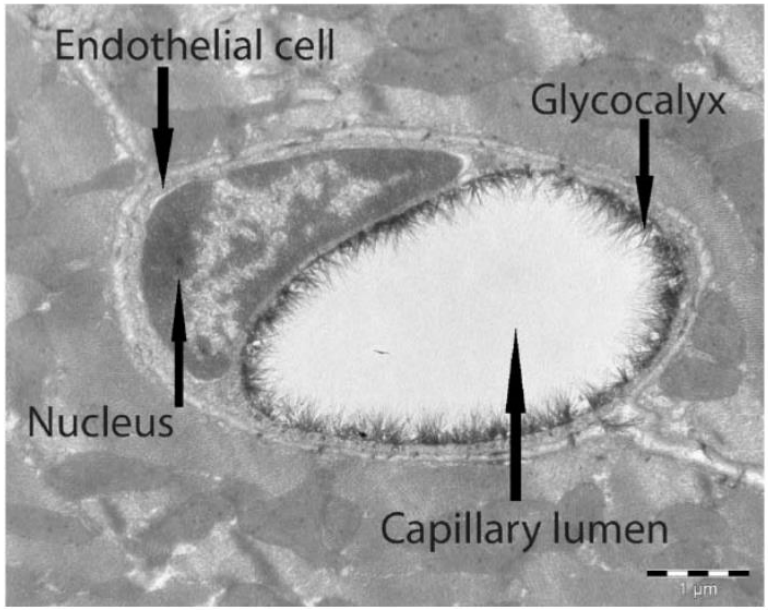


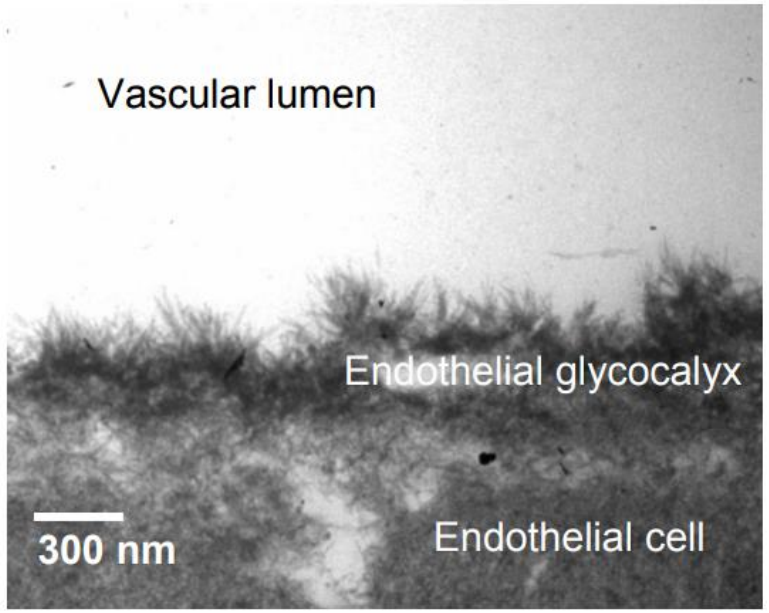
J Thromb Haemost. 2019 Feb;17(2):283-294.

1. Endotheliopathy

Endothelial Glycocalyx

The endothelial glycocalyx is a carbohydrate-rich gel-like layer up to 3 um thick that covers the entire luminal surface of the vasculature





Curr Neurovasc Res. 2016;13(3):249-60.

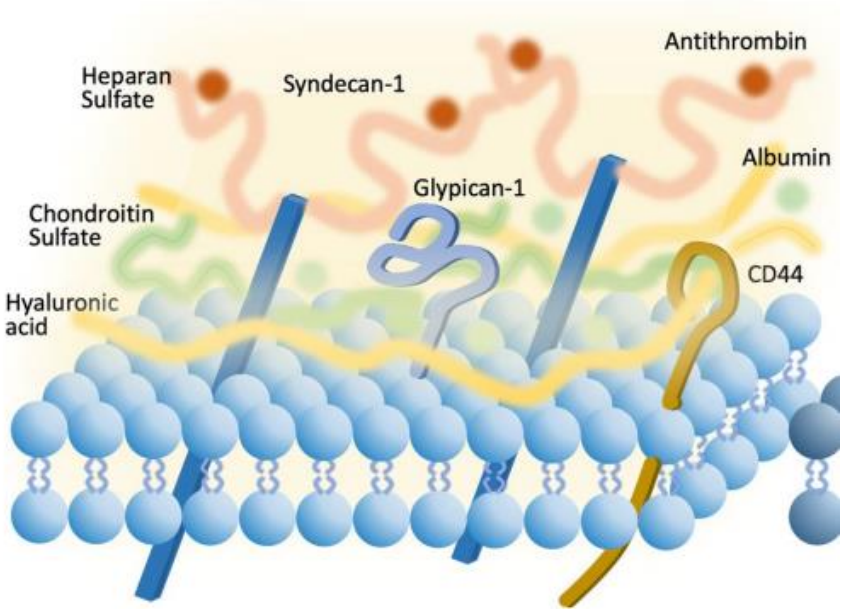
Crit Care. 2013 Sep 14;17(5):R203.

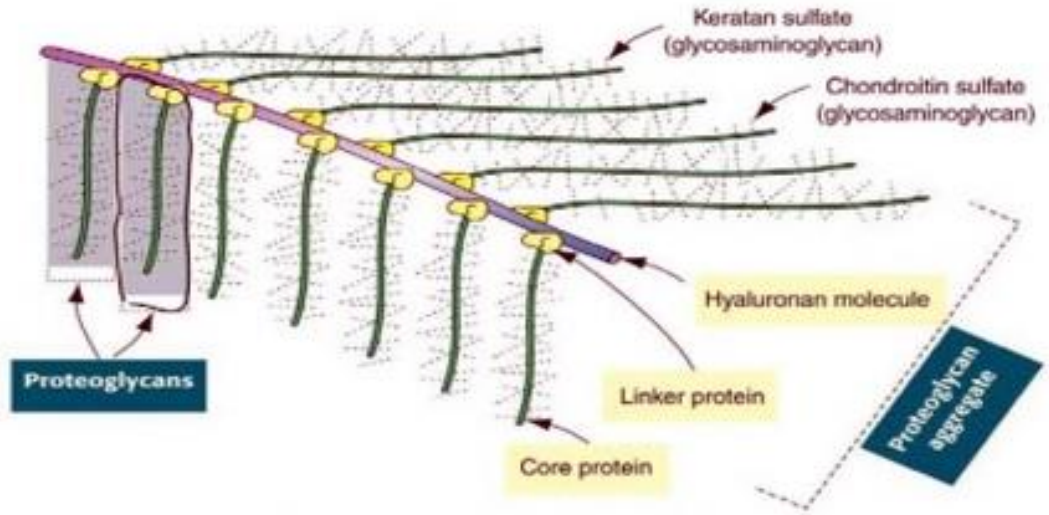
1. Endotheliopathy

Endothelial Glycocalyx

It consists largely of membrane-binding proteoglycans,

glycosaminoglycan side-chains, and polysaccharide hyaluronan





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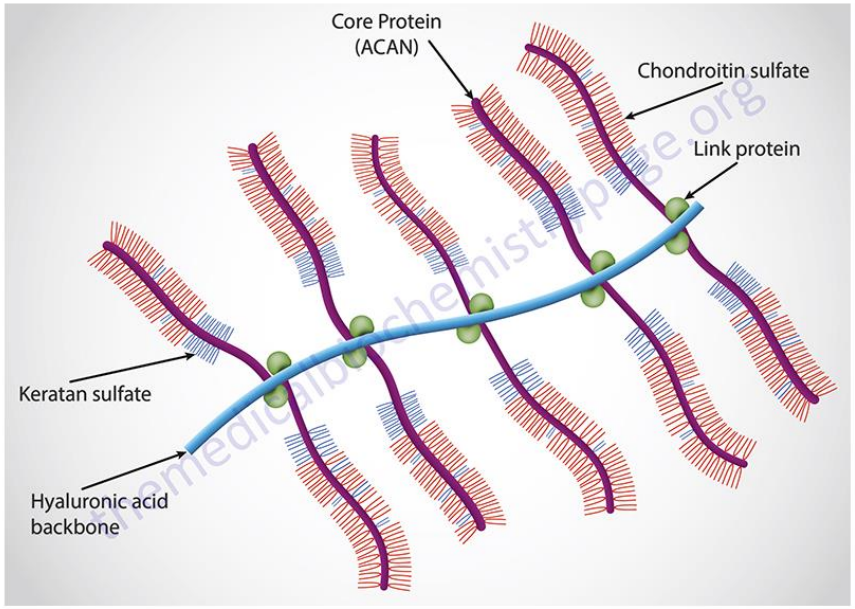
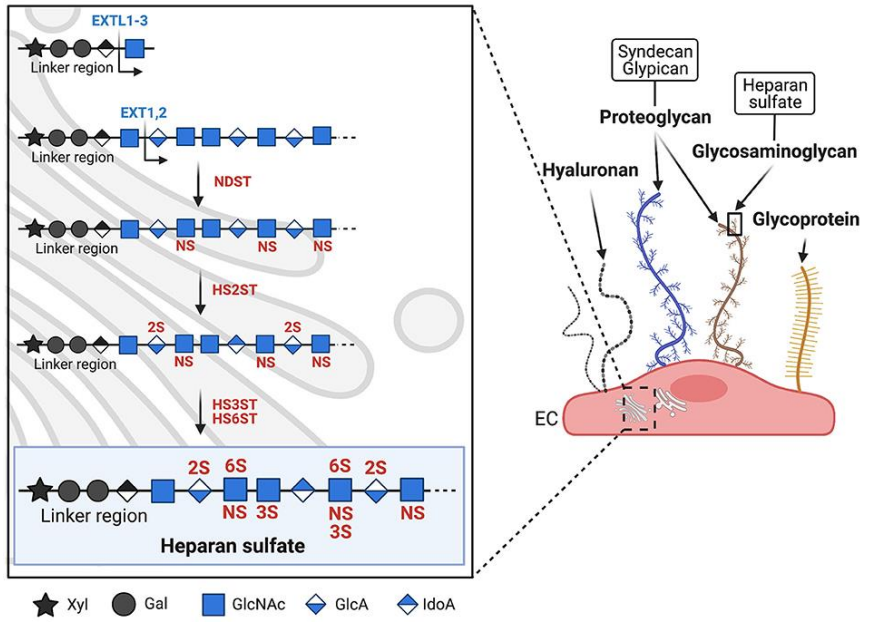
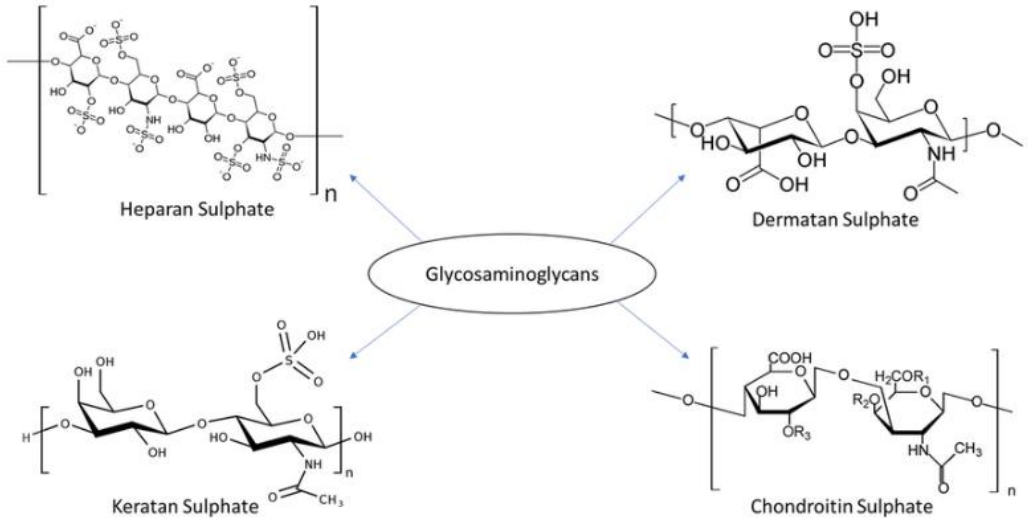


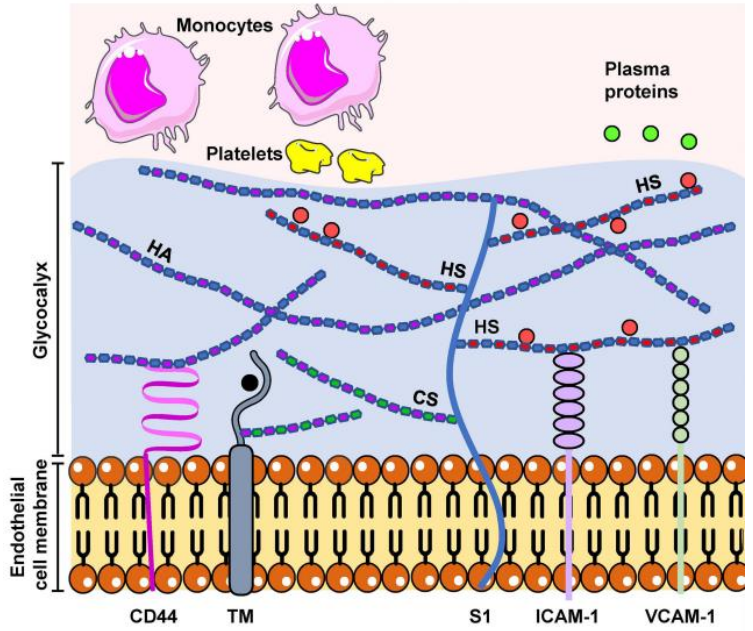


1. Endotheliopathy

Endothelial Glycocalyx

GAGs have negative electric charges to form a hydrated dense gel-like layer with a high reflection capability for albumin





Front Immunol. 2023 Oct 3:14:1251876.

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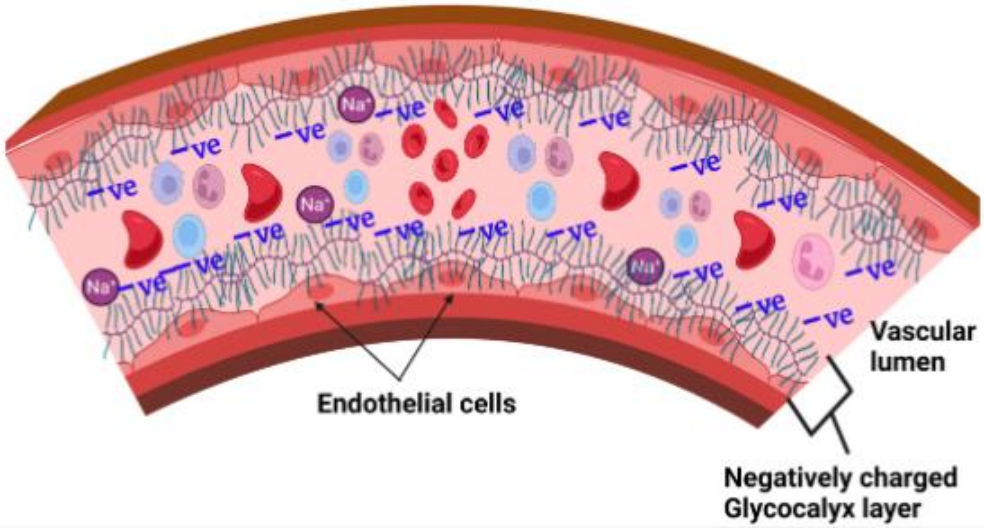
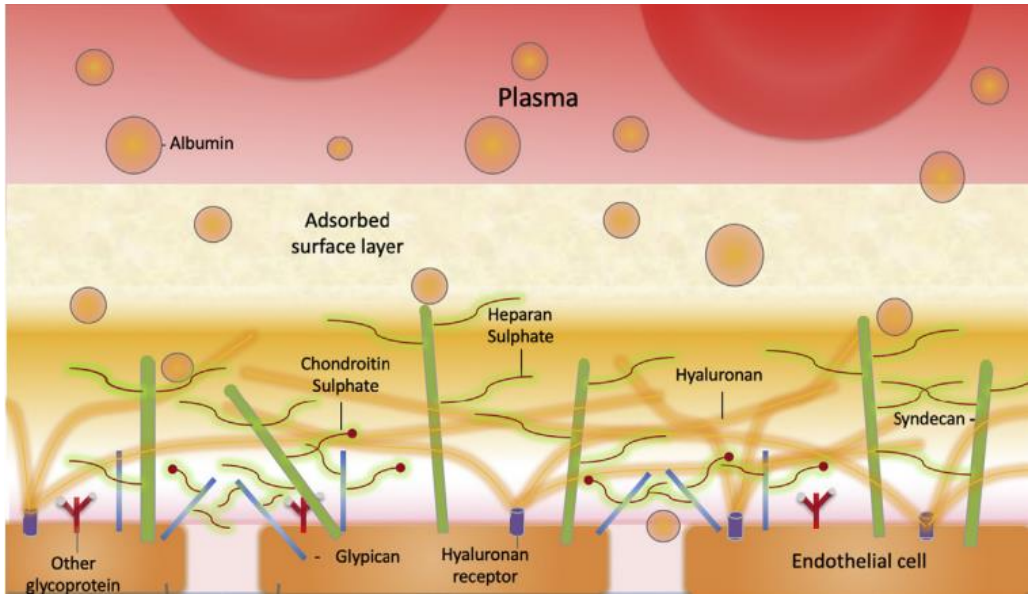


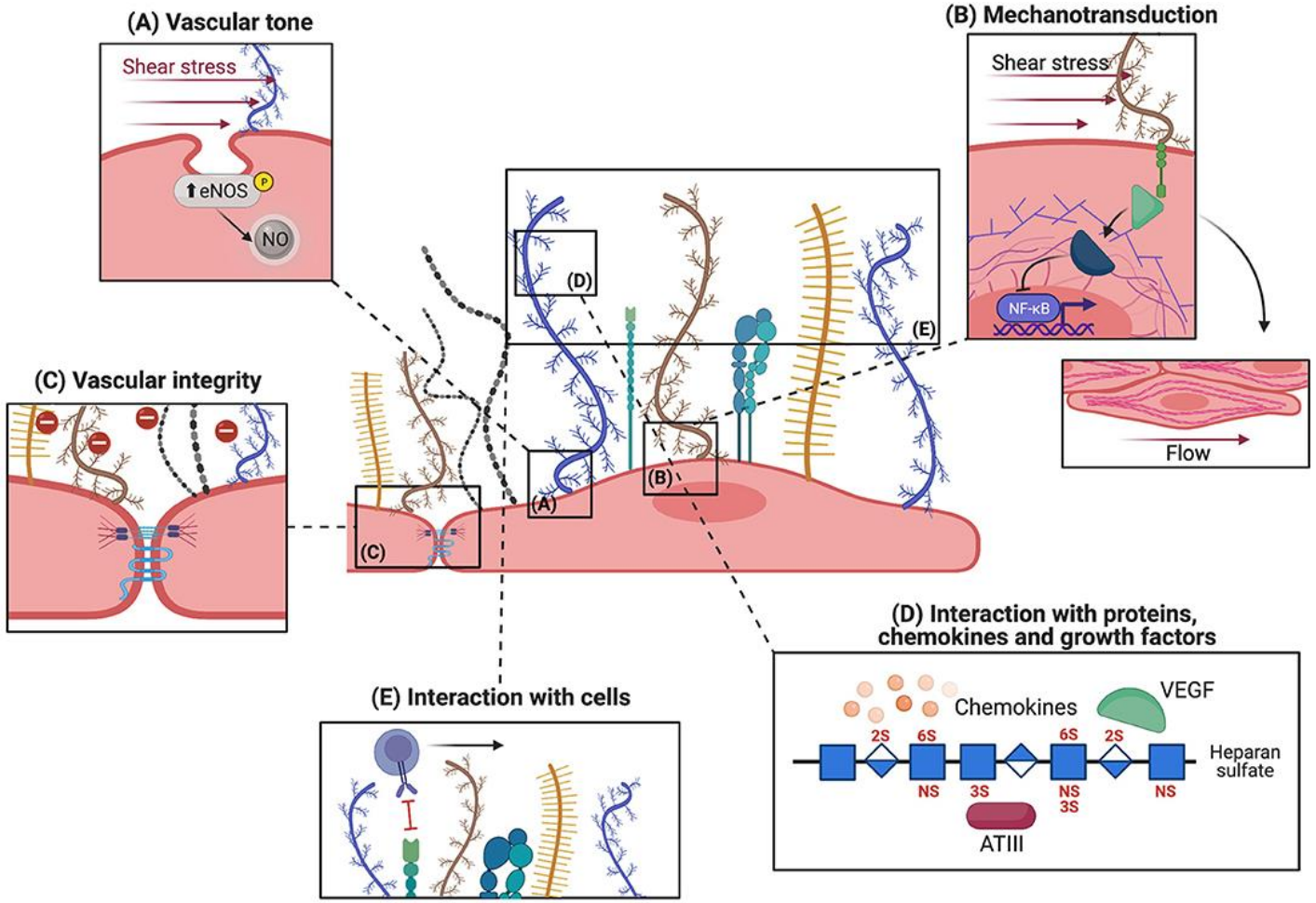


Nutrients. 2023 Jun 25;15(13):2873

Am J Pathol. 2020 Apr;190(4):742-751.

1. Endotheliopathy

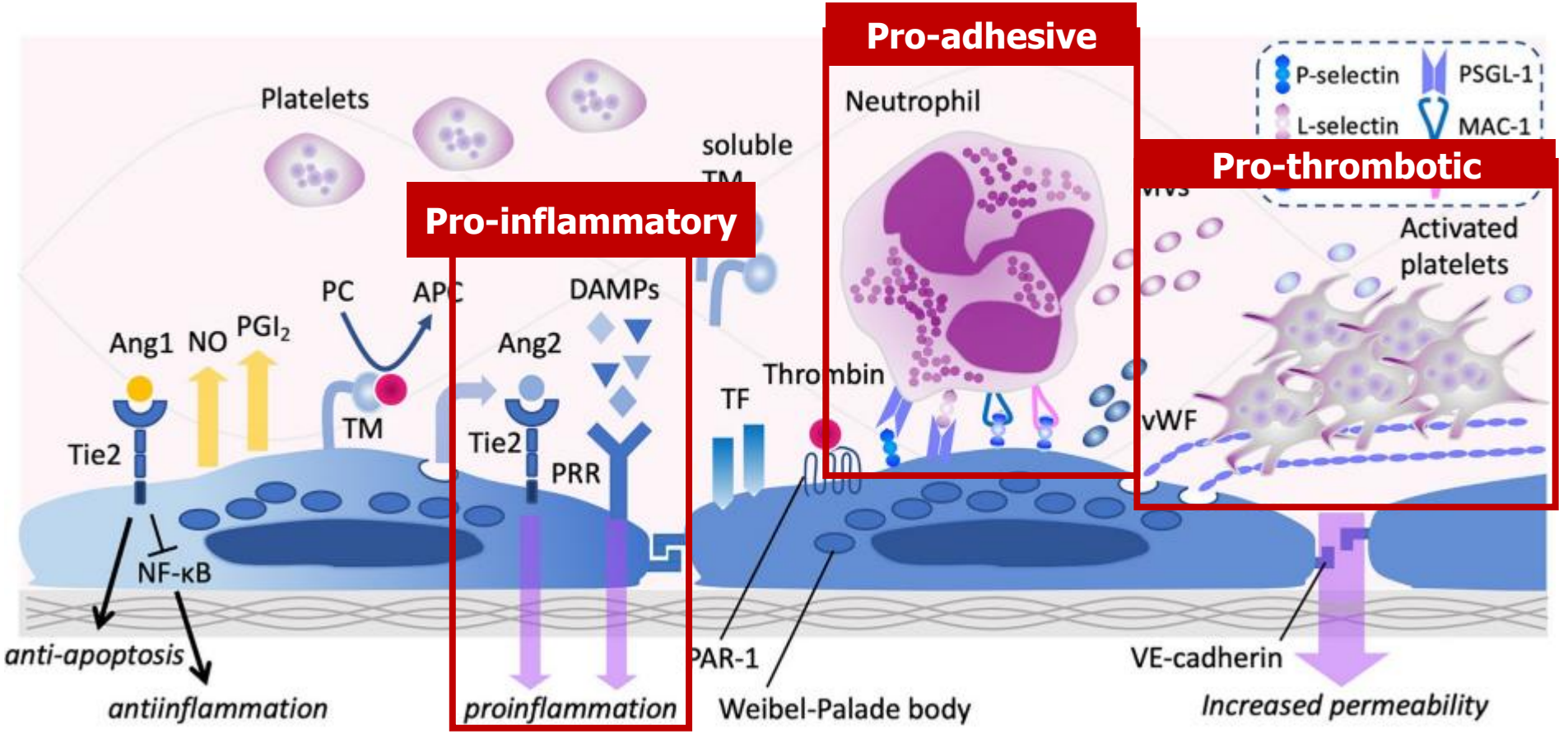
Endothelial Glycocalyx



Front Cardiovasc Med . 2022 May 13:9:897087.

1. Endotheliopathy

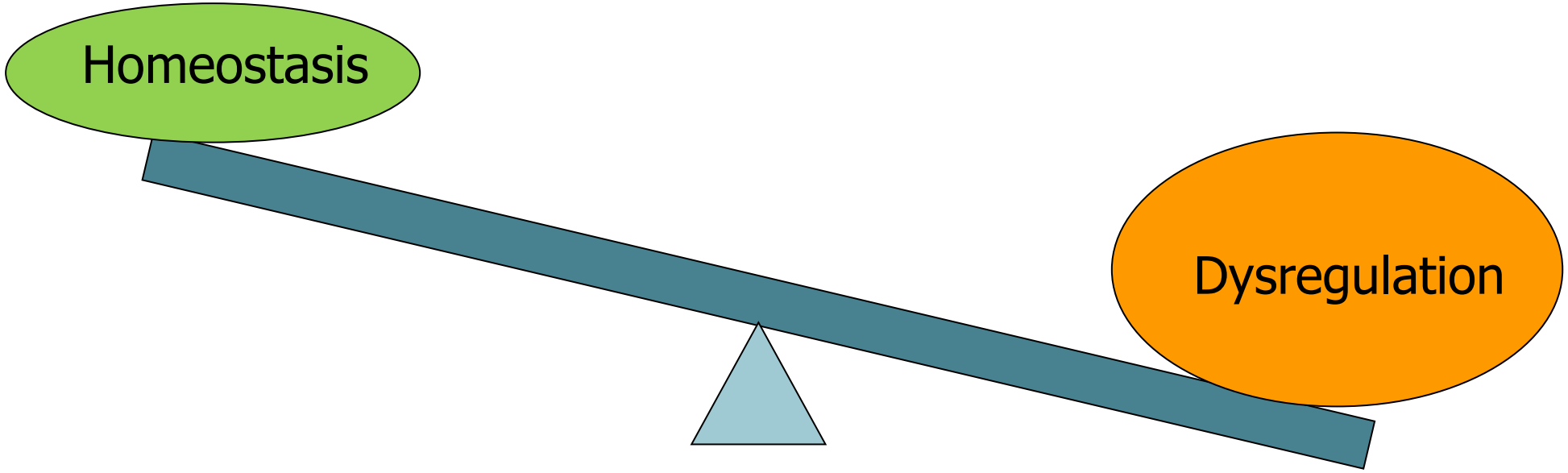
Endothelial Response in Sepsis



1. Endotheliopathy

Endothelial Response in Sepsis

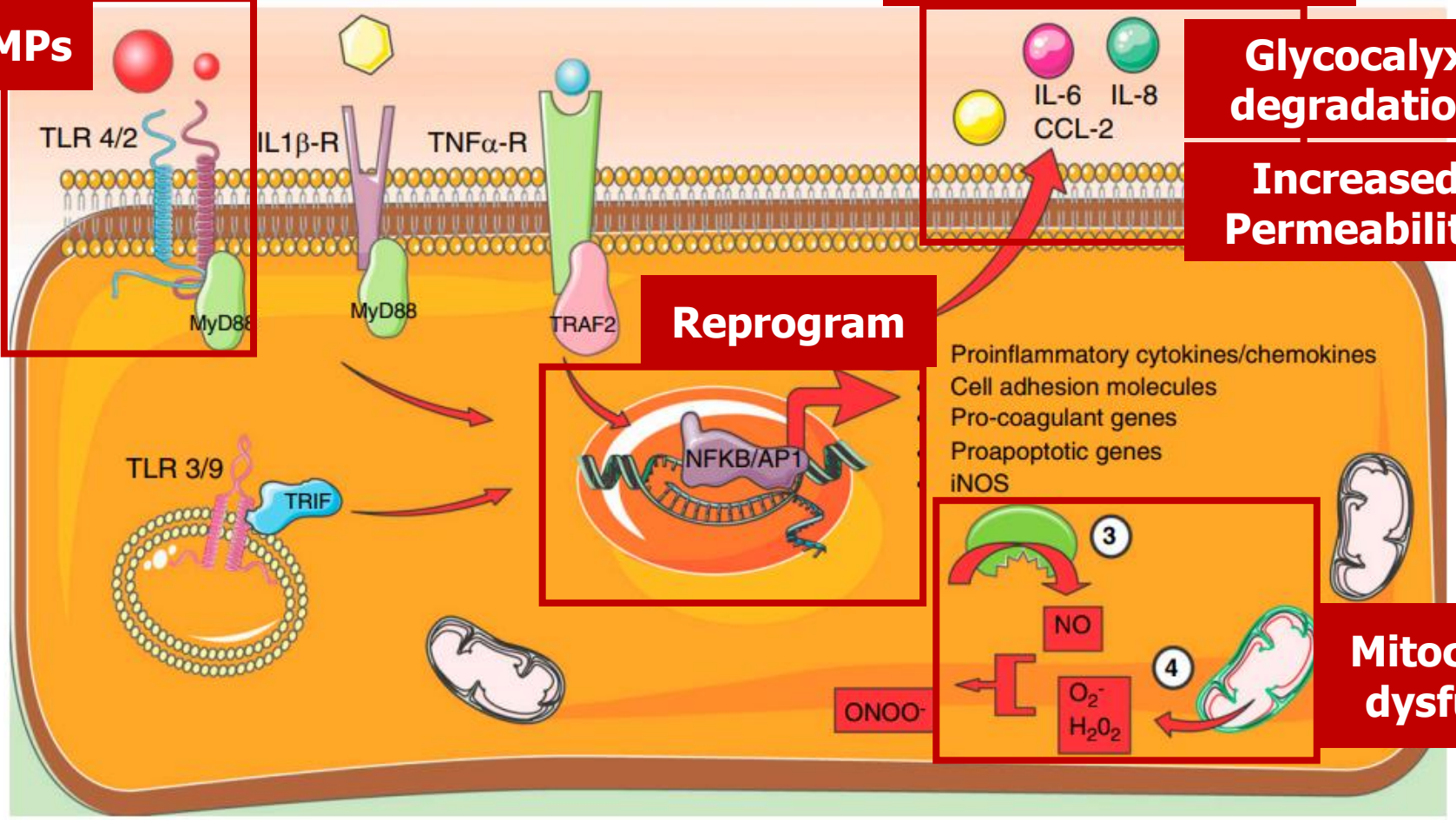
It is very challenging to discriminate between appropriate activation and endothelial dysfunction



Am J Respir Crit Care Med. 2020 Aug 1;202(3):361-370

1. Endotheliopathy

- **Pro-inflammatory EC Phenotype**



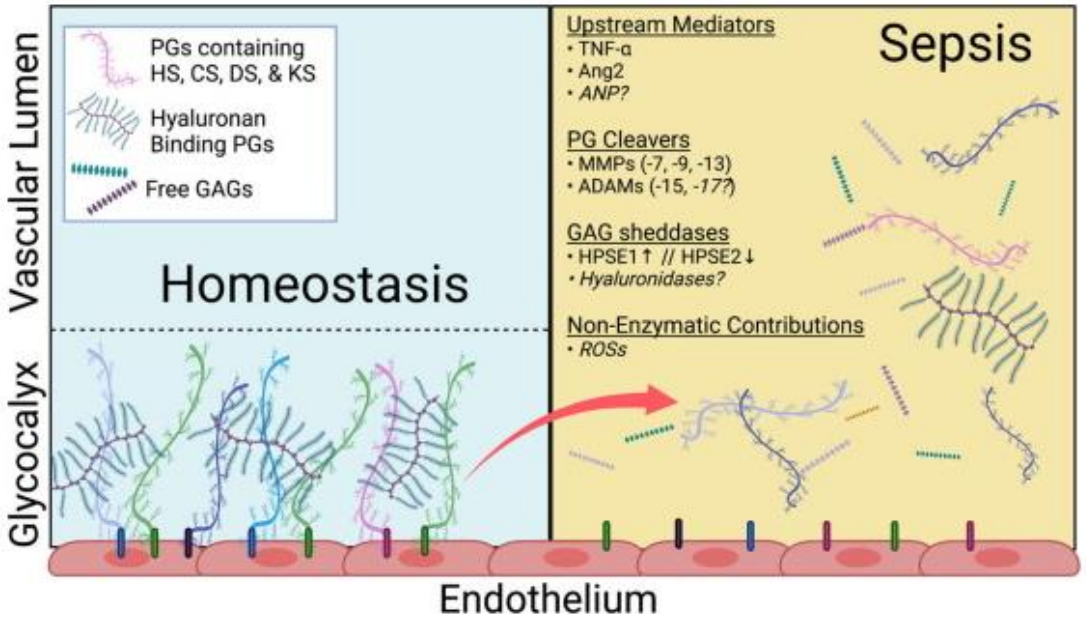
Am J Respir Crit Care Med. 2020 Aug 1;202(3):361-370

1. Endotheliopathy

- **The degradation of the endothelial glycocalyx**

Increased enzymatic and non-enzymatic proteolytic processes

Cause the changes in the glycocalyx



Matrix Biol Plus . 2021 Nov 27:12:100094.

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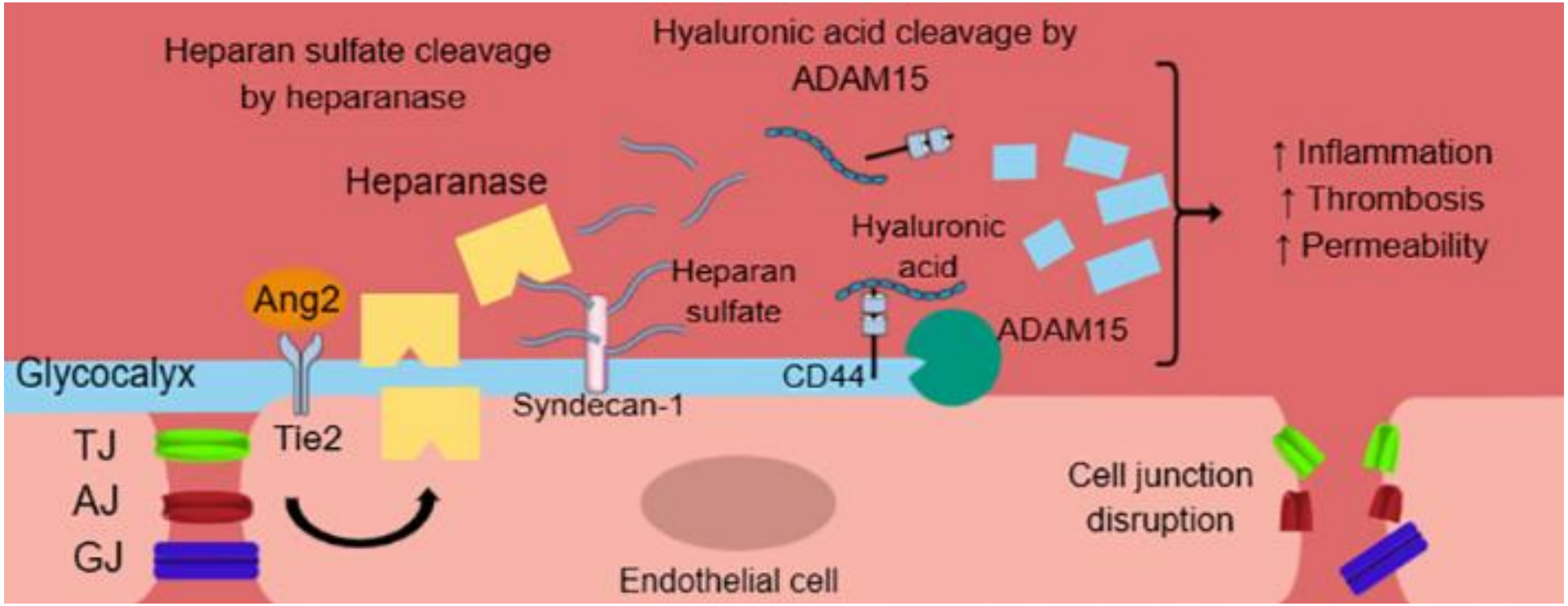

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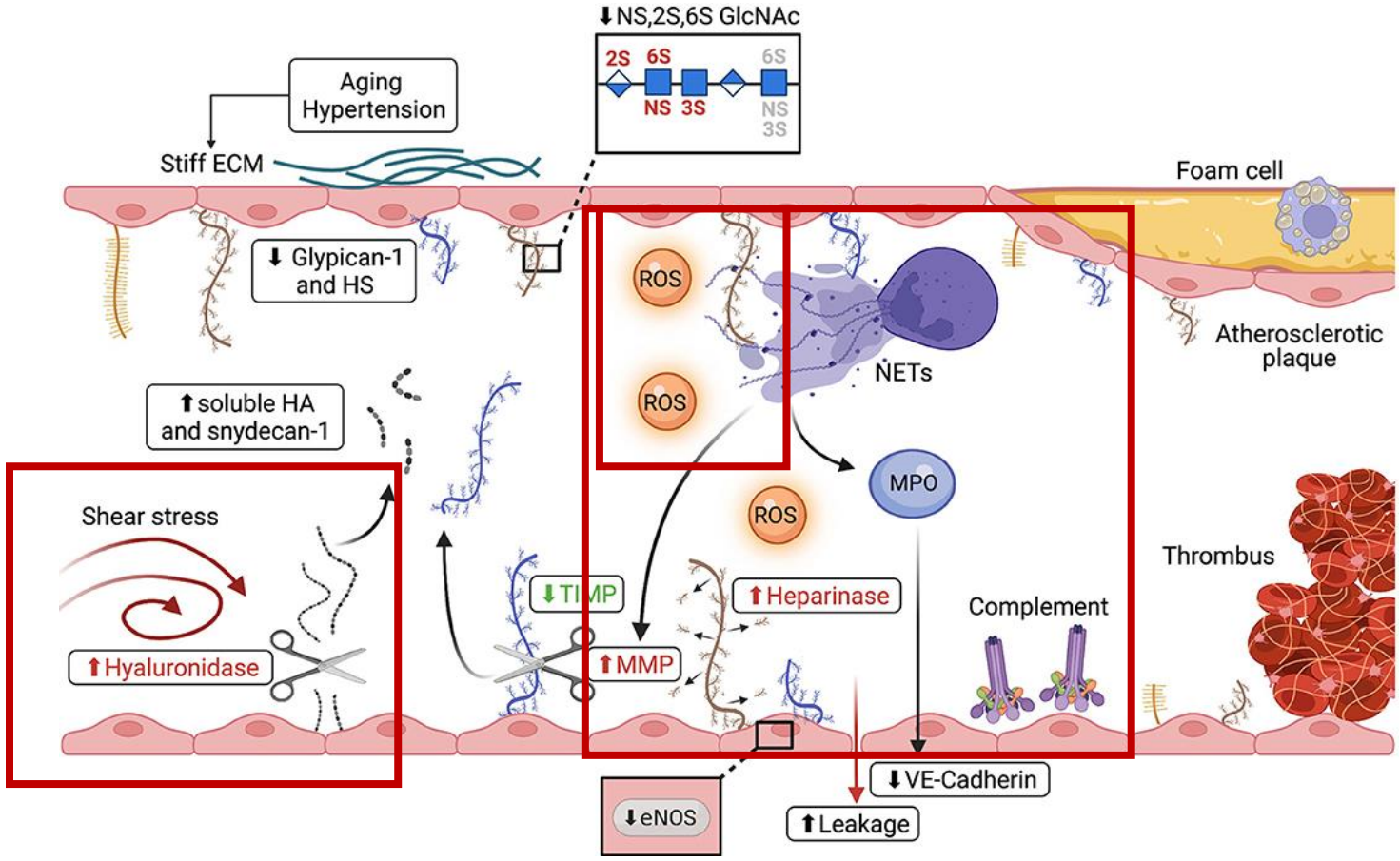

Front Cardiovasc Med . 2022 May 13:9:897087.

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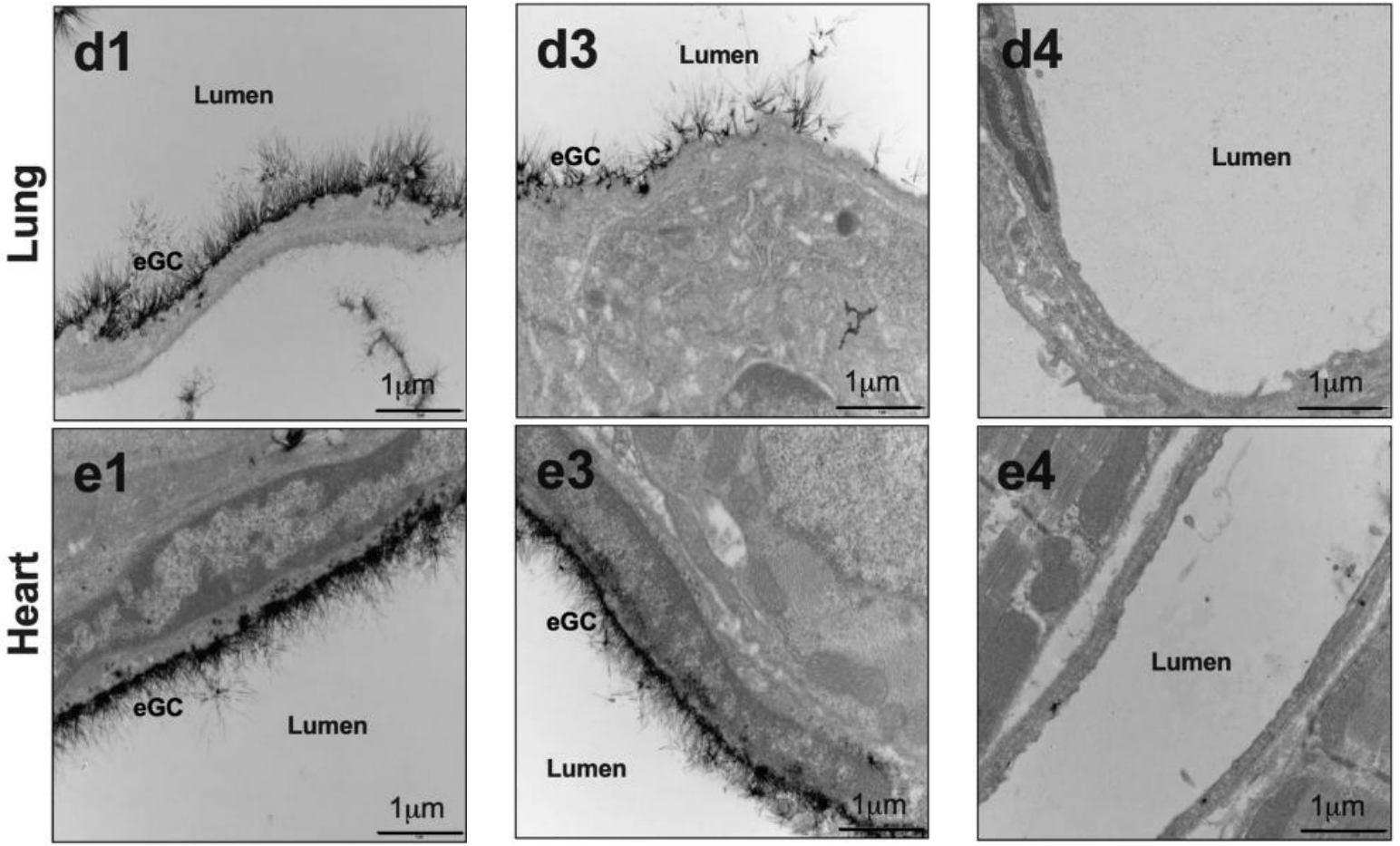
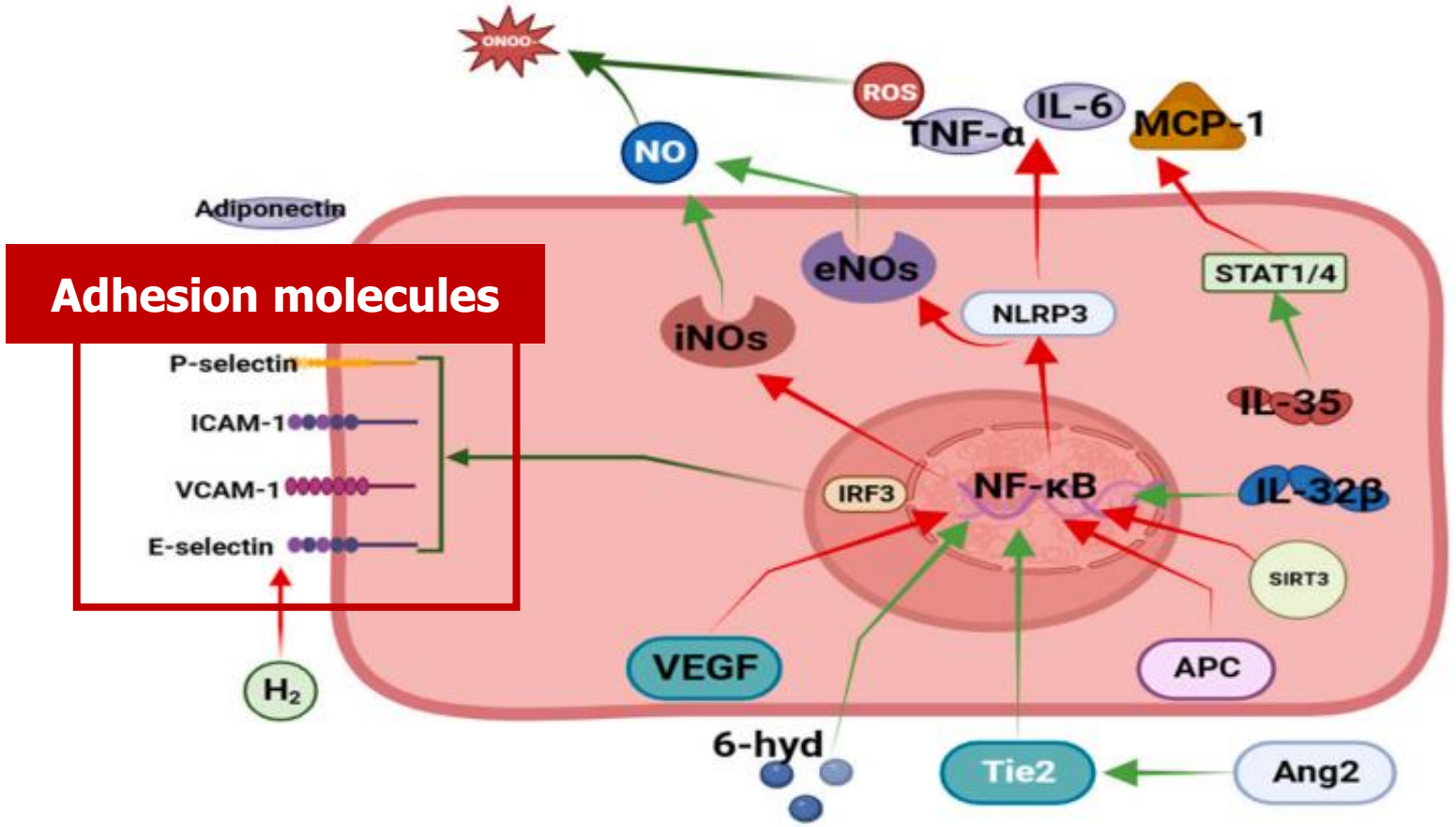


Sci Rep. 2024 May 7;14(1):10477

1. Endotheliopathy

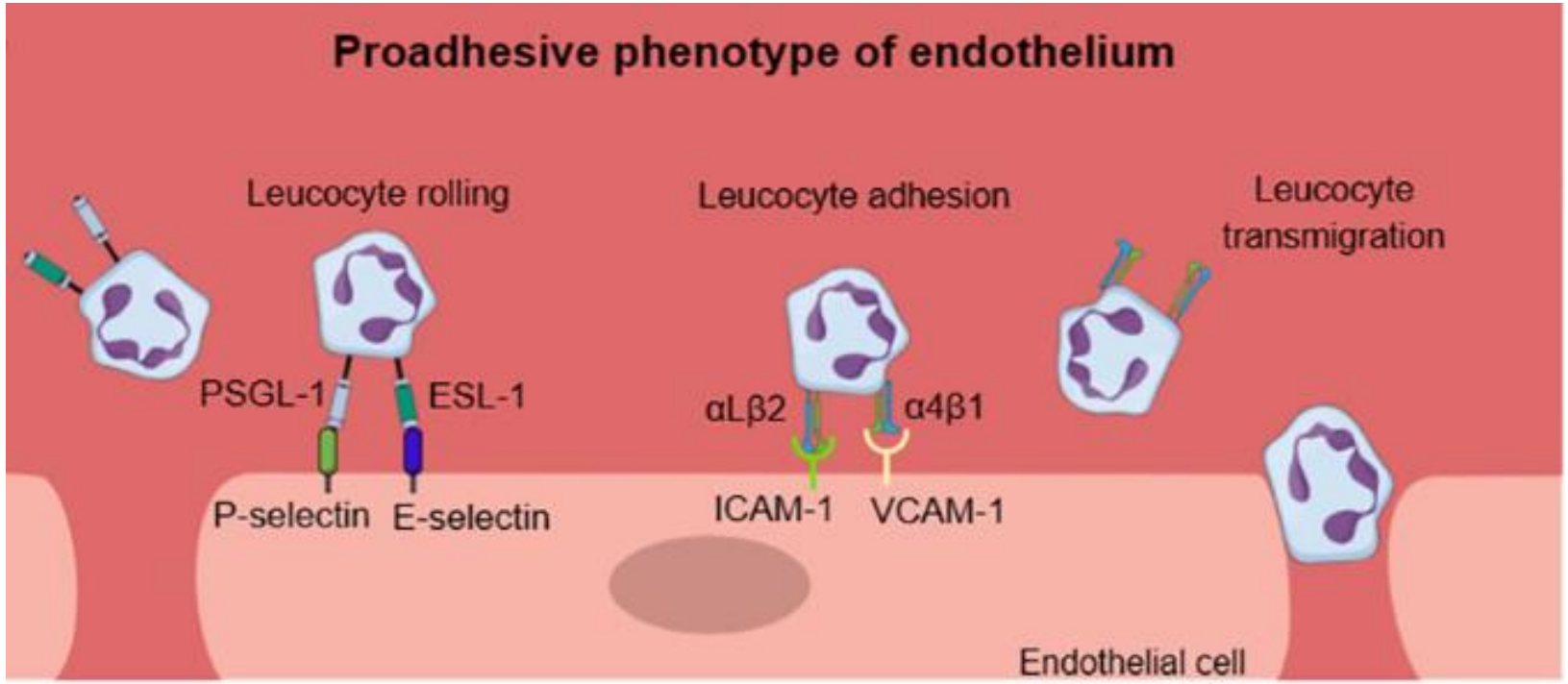
Pro-adhesive EC Phenotype



Biomed Pharmacother . 2024 Sep:178:117180.

1. Endotheliopathy

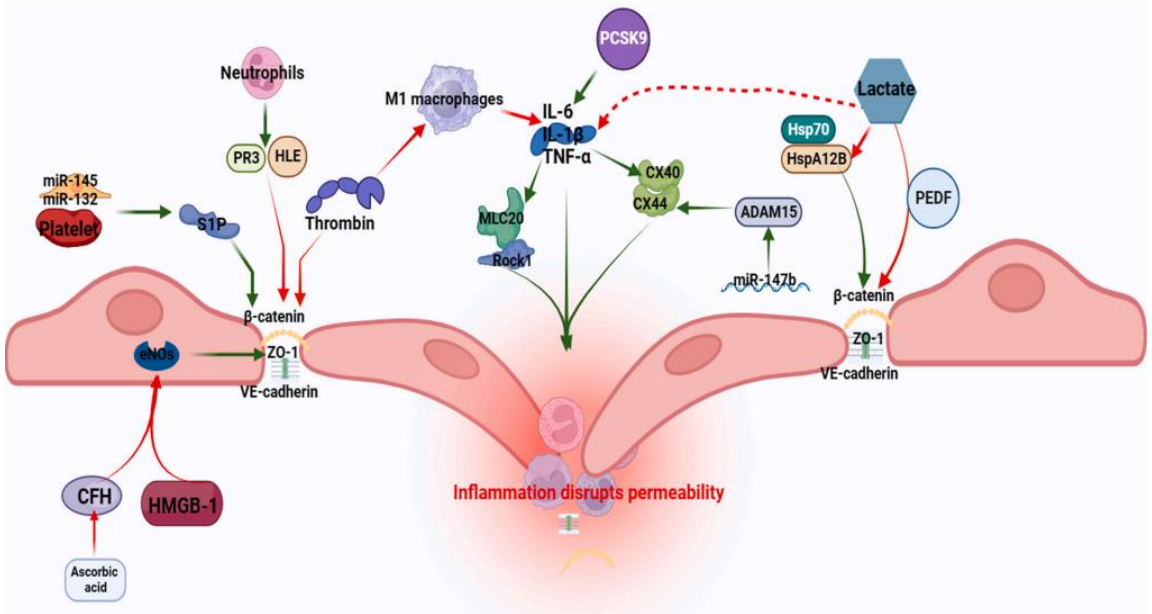
Pro-adhesive EC Phenotype



1. Endotheliopathy

Endothelial Cell hyper-permeability

The vascular barrier is impaired owing to glycocalyx breakd own, EC apoptosis, and junction protein dysregulation



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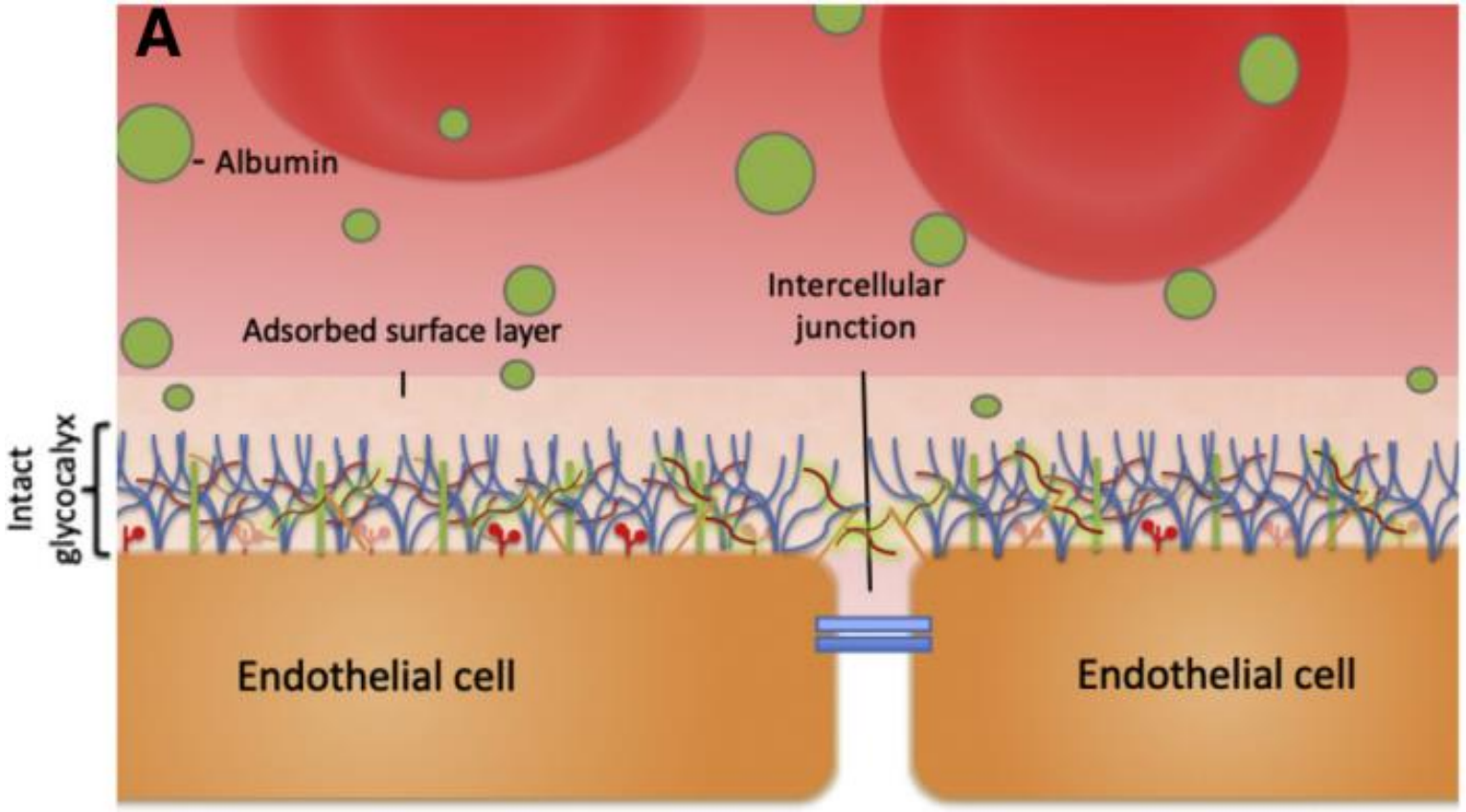

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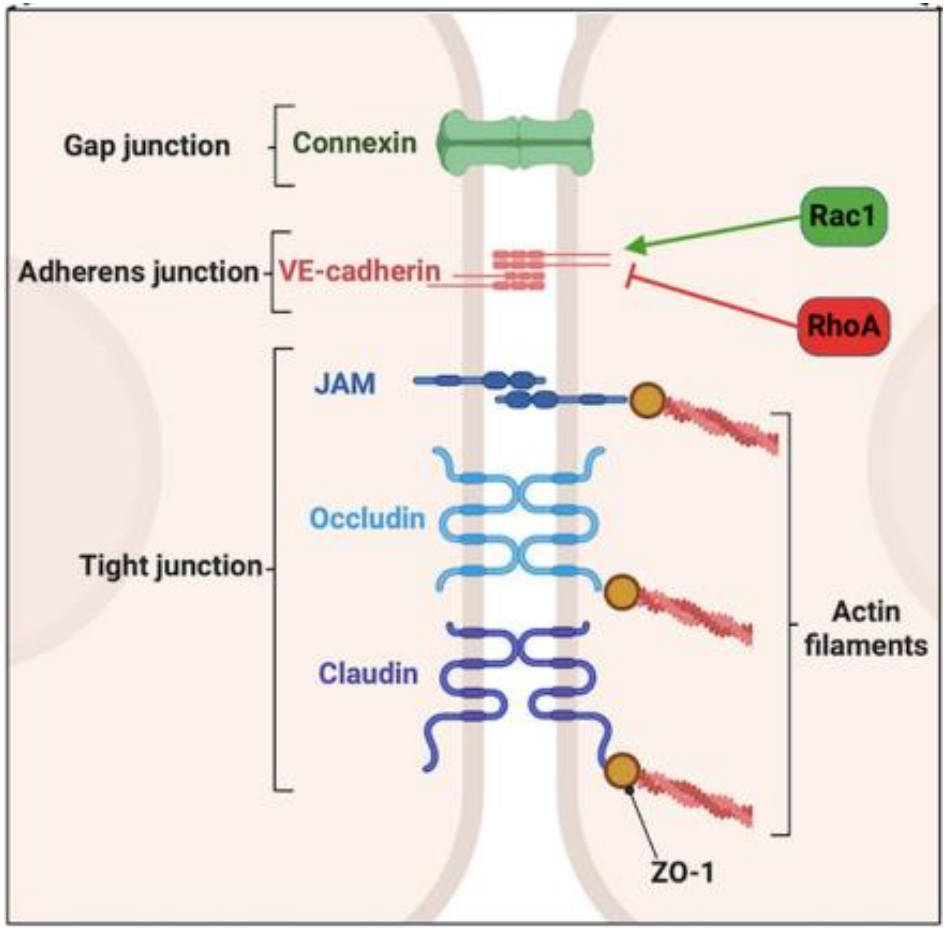

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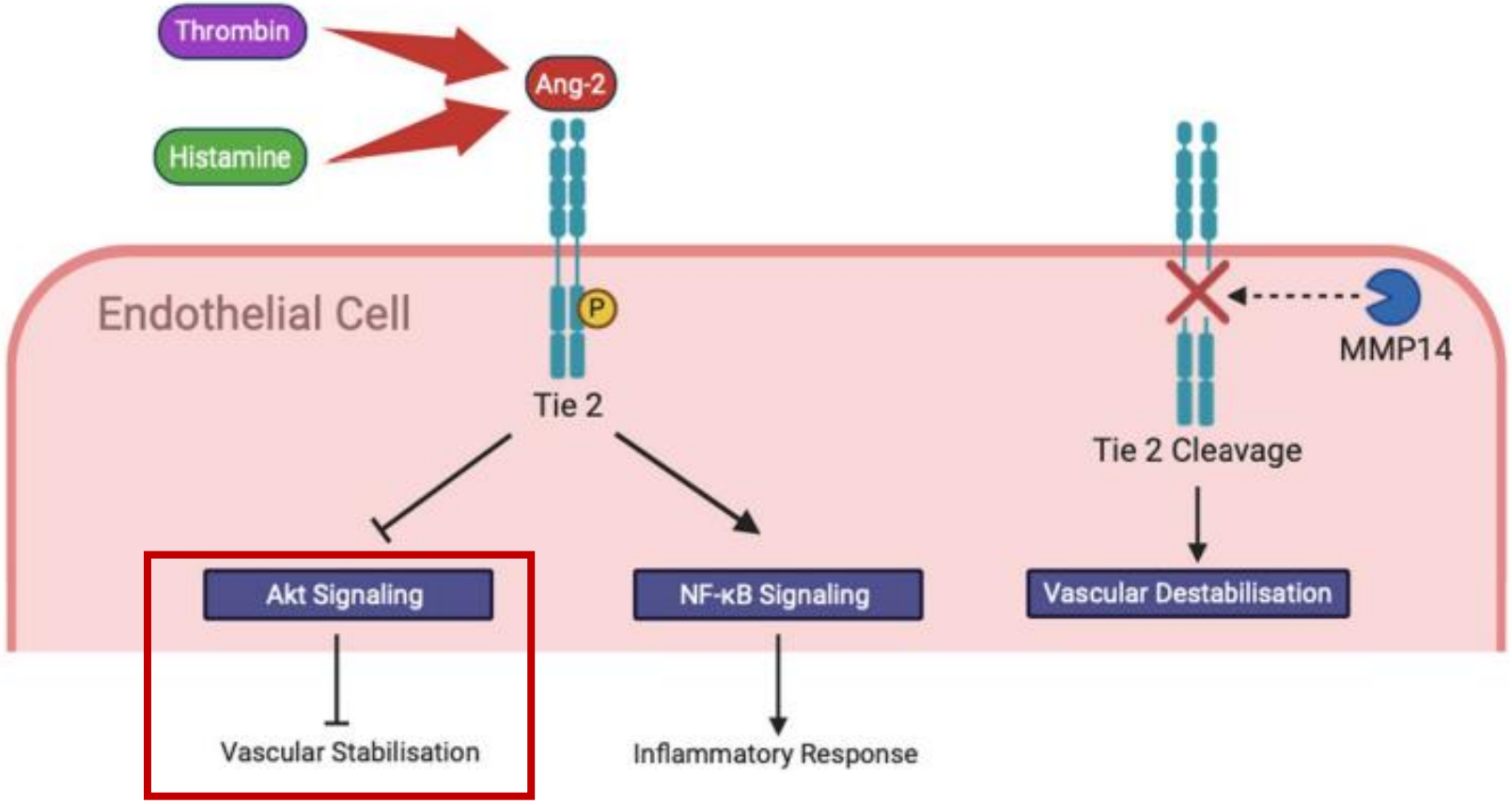

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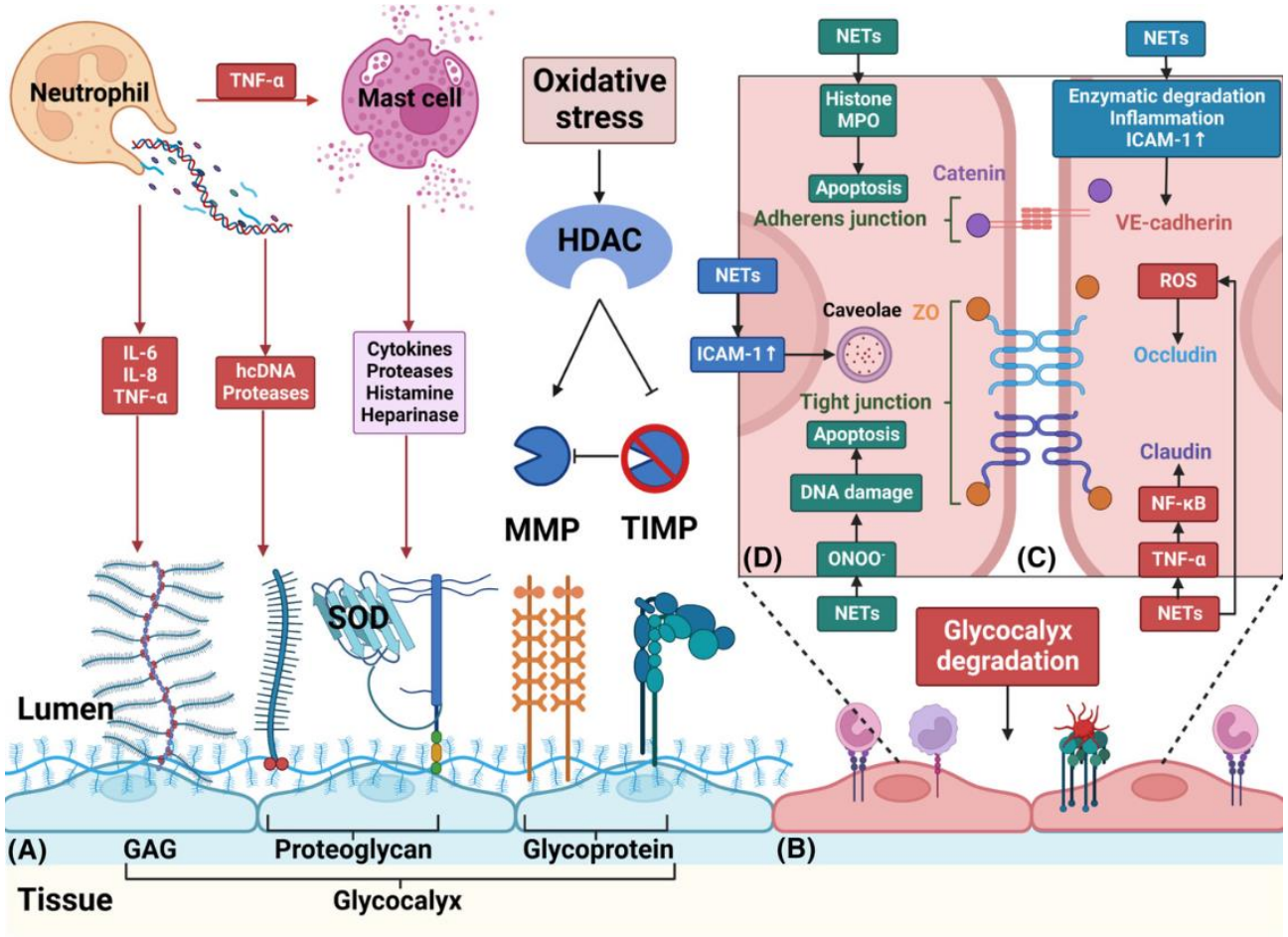

Clin Transl Med . 2023 Jan;13(1):e1170.

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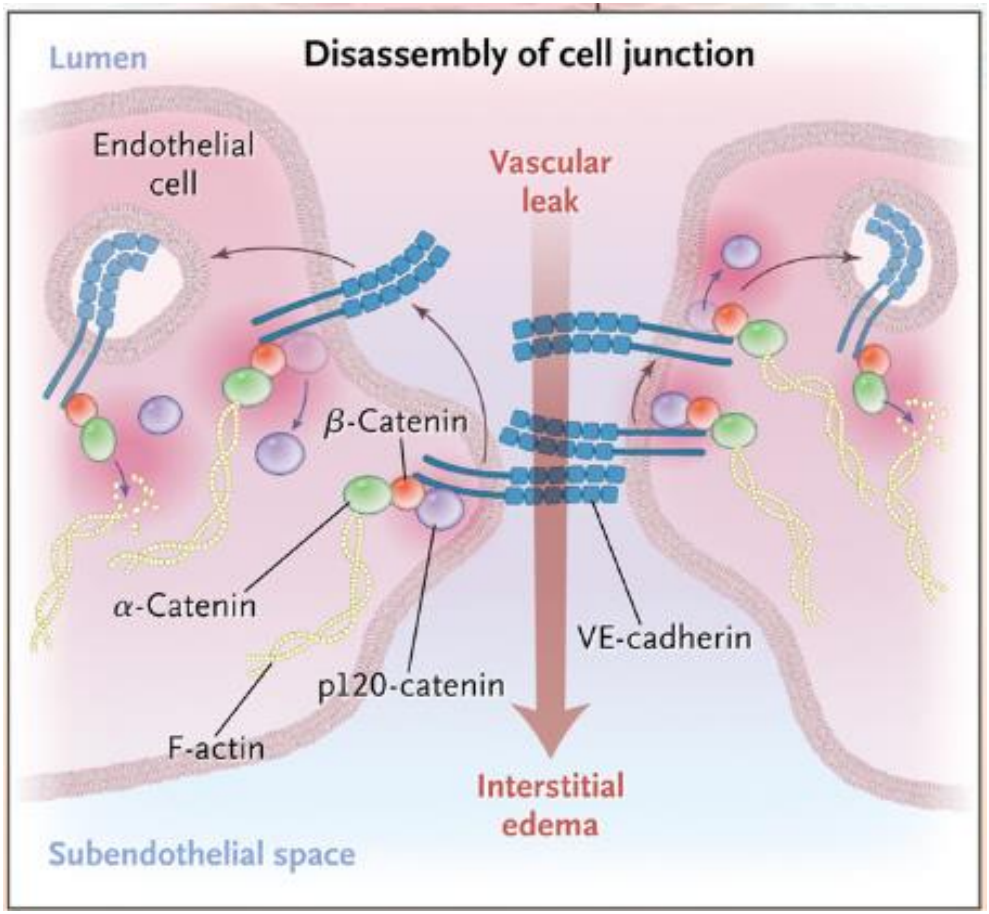
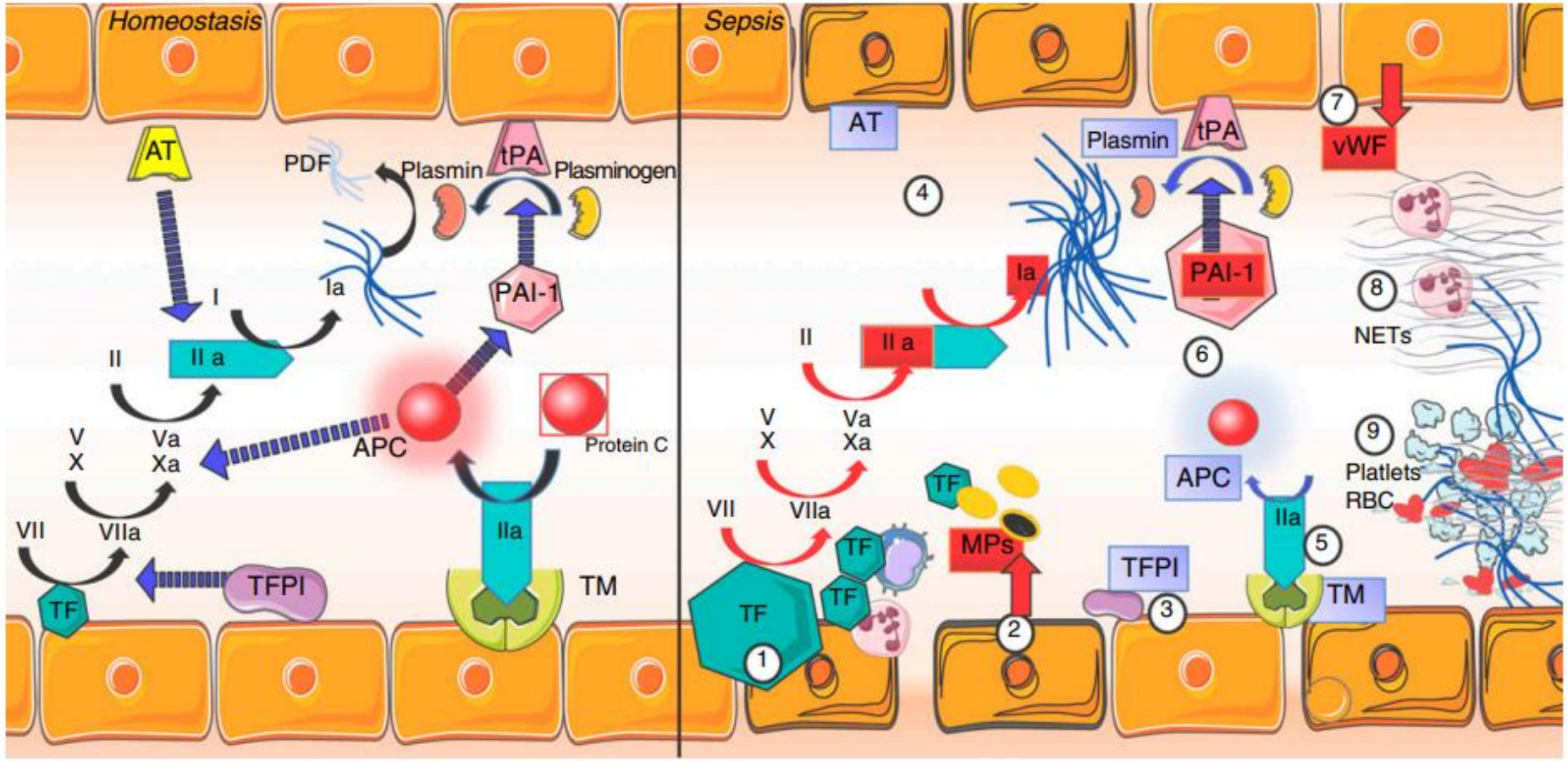


N Engl J Med 2010;363:689-691

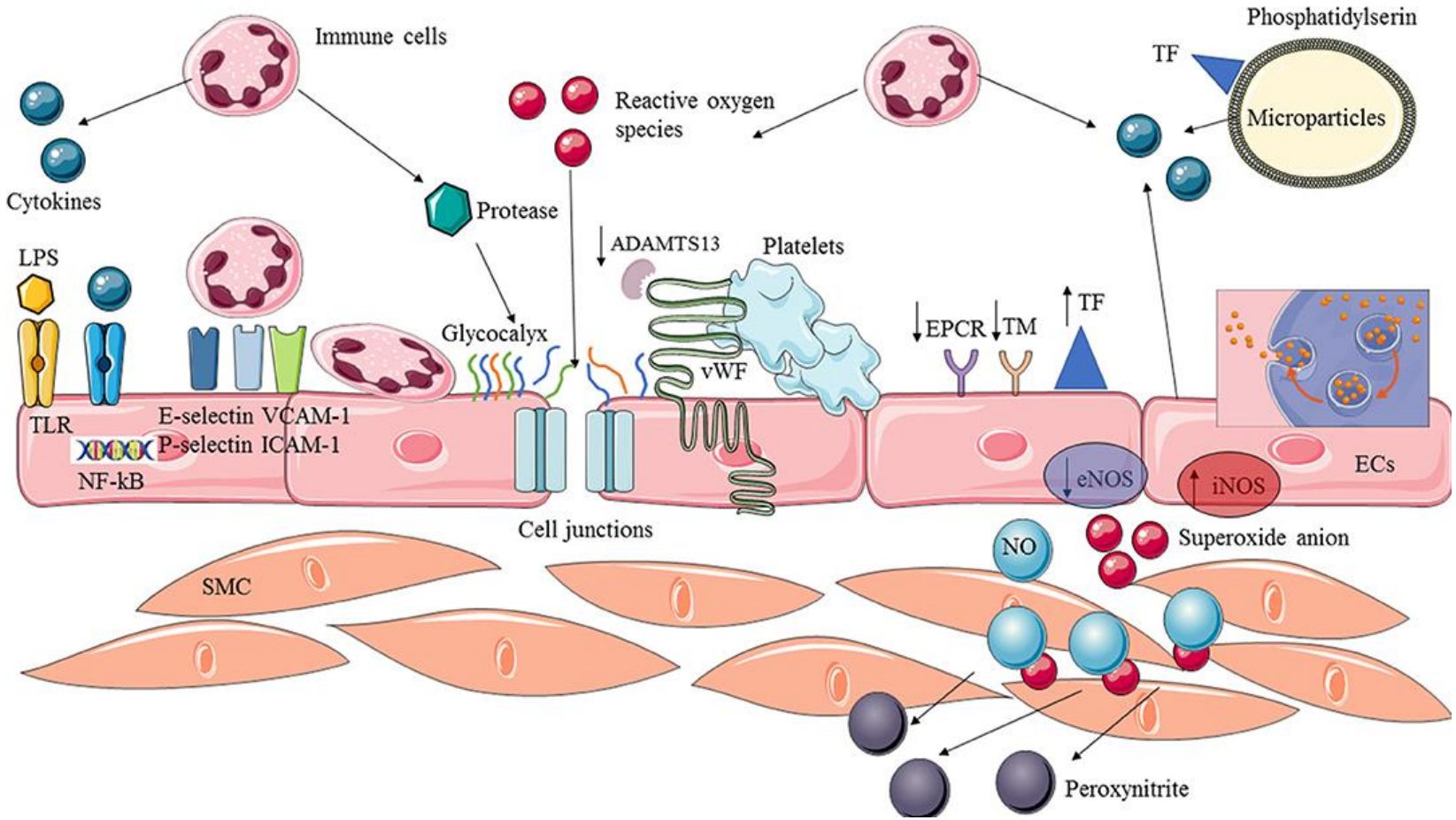
1. Endotheliopathy

- **Pro-thrombotic EC Phenotype**



1. Endotheliopathy

Vasodilation



Am J Respir Crit Care Med. 2020 Aug 1;202(3):361-370

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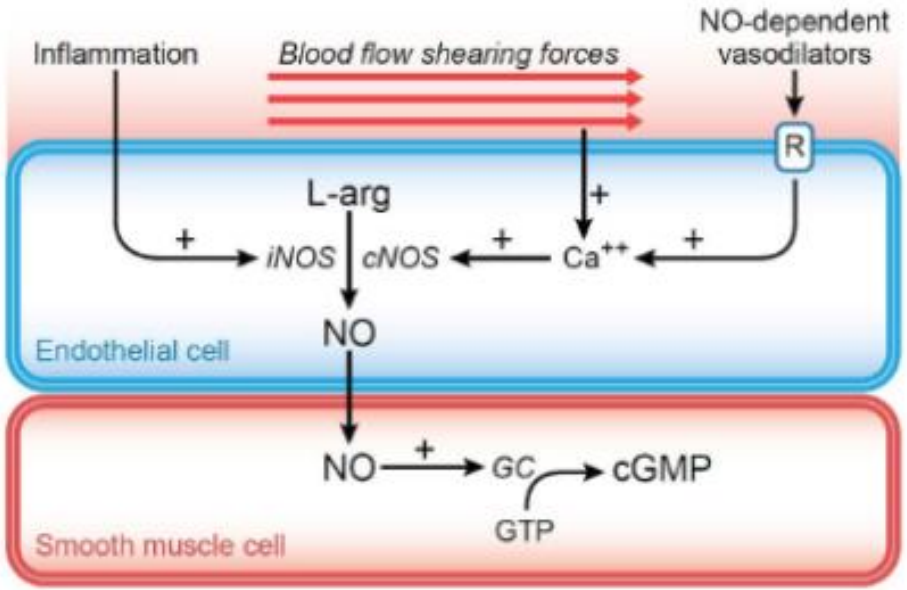

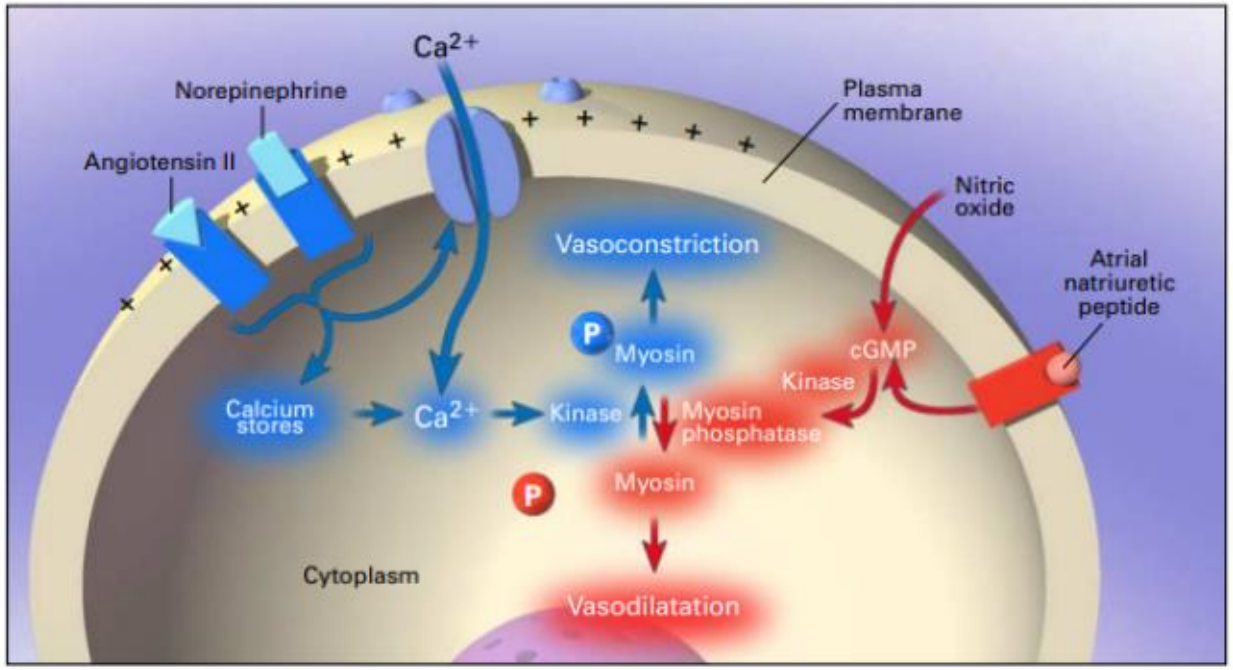

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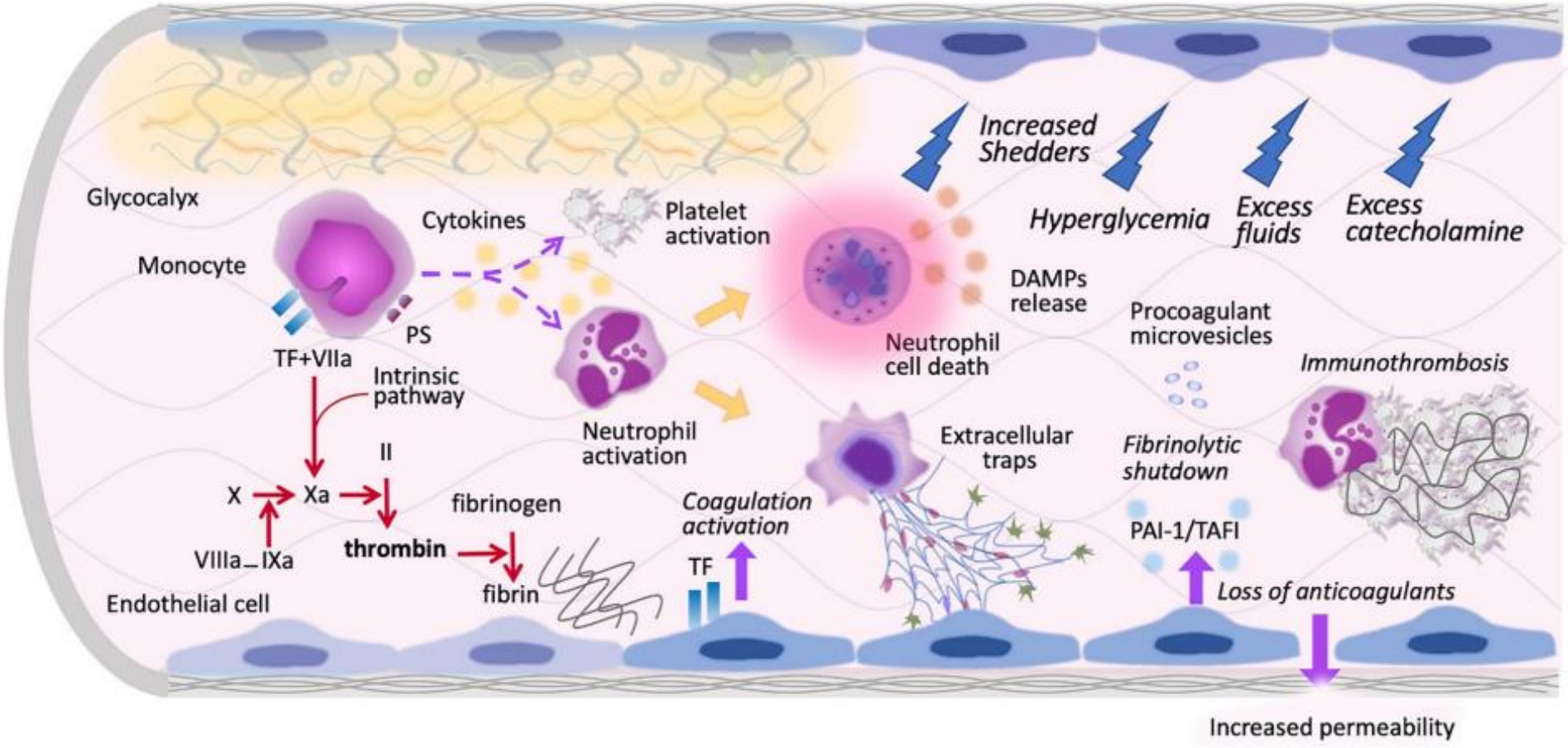

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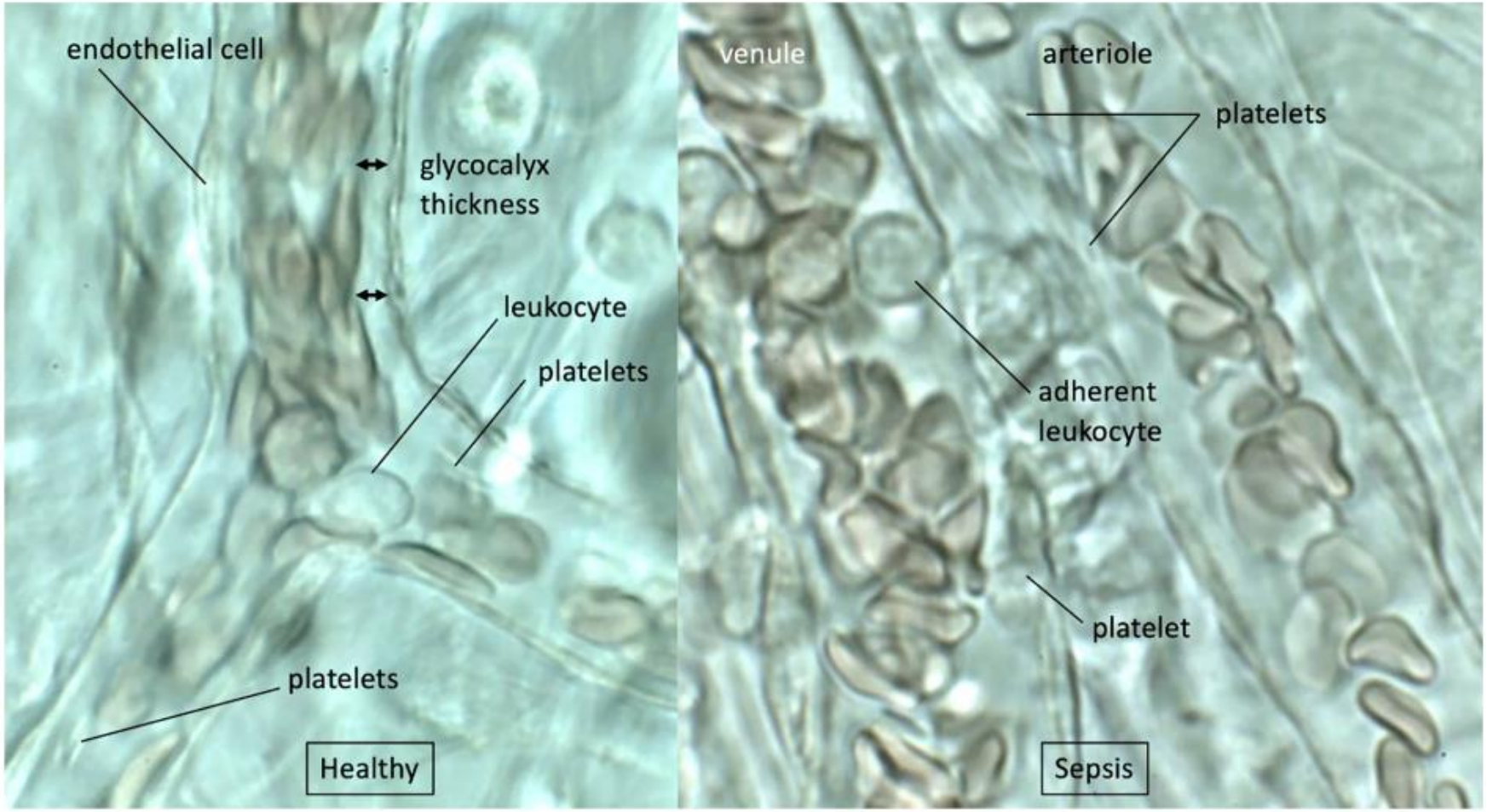

Ann Intensive Care. 2024 Apr 24;14(1):64.

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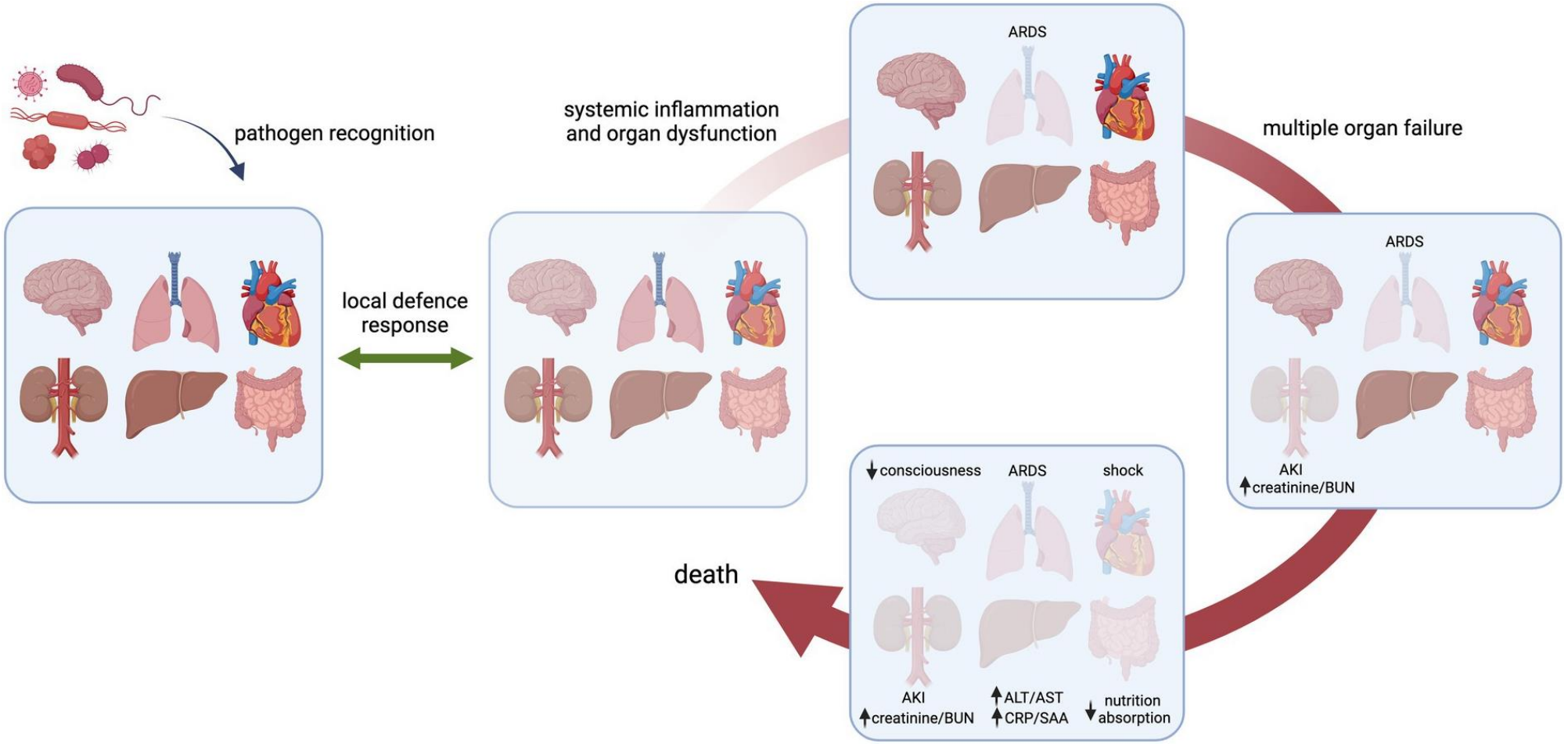


2. Identification

Identification of EC dysfunction

Two clinically applicable measures for the evaluation of endotheliopathy

Serologic markers

Microvascular assessment

2. Identification

Serologic markers

Biomarkers	Ref	Population	Results
Syndecan-1	Jones. J Crit Care 2016	175 patients with sepsis	Syndecan-1 was elevated in nonsurvivors
Angiopoetin-1, 2	Zhao. Critical Care 2015	440 patients with sepsis	Ang-2/Ang-1 ratio was associated with poor outcomes
Soluble Thrombomodulin	Jenson. Semin Thromb Hemost 2015	1,103 patients with sepsis	sTM predicted risk of multiple organ failure
Anti-thrombin III	Wang. Clin Exp Med 2021	251 patients with sepsis	Anti-thrombin III was an independent risk factor for mortality
Protein C	Rivers. Crit Care Med 2009	971 patients with sepsis	Protein C was predictive of poor outcomes
ICAM-1	Restrepo. Cytokine 2016	48 patients with sepsis	Serum ICAM-1 was associated with MOF

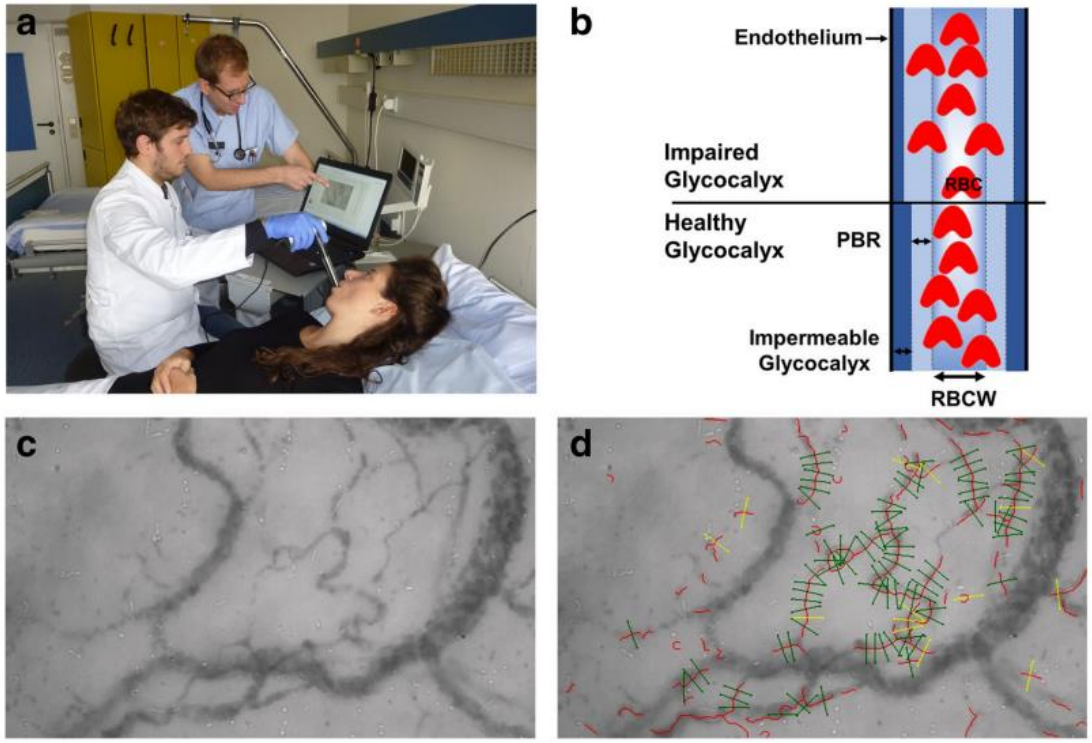
2. Identification

Microvascular assessment

GlycoCheck

ANALYZES THE ENDOTHELIAL, GLYCOCALYX AND CAPILLARY FUNCTION OF THE MICROVASCULAR SYSTEM

GlycoCheck is the most advanced system to unravel the mysteries of **microcirculation.**

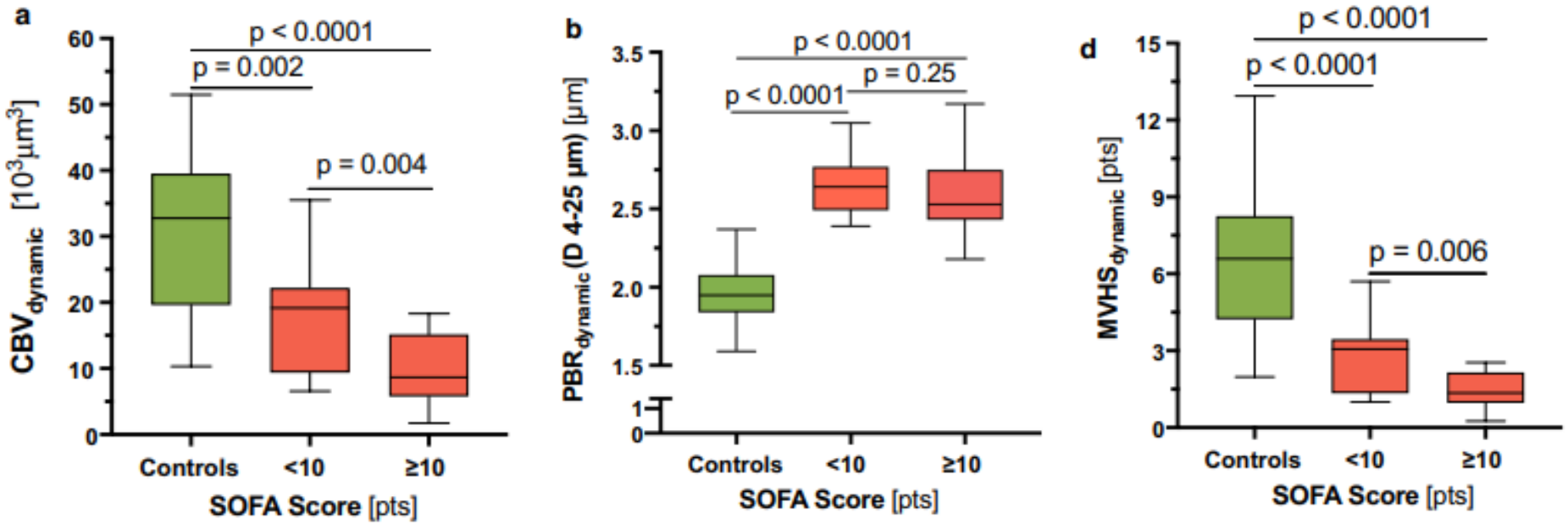


Scand J Trauma Resusc Emerg Med . 2018 Feb 14;26(1):16.

2. Identification

Microvascular assessment

This observational, prospective, cross-sectional study including 51 participants, of which 34 critically ill patients from ICU of a single center was to evaluate the associations between novel microvascular variables and clinical severity



2. Identification

Sepsis induced Coagulopathy

SIC: Sepsis Induced Coagulopathy

SIC	Points	
Platelet count ($\times 10^9\ L^{-1}$)	2	<100
	1	≧100, <150
PT-INR	2	>1.4
	1	>1.2, ≦1.4
Total SOFA score	2	≧2
	1	1

If SIC ≥ 4

DIC: Disseminated Intravascular Coagulation

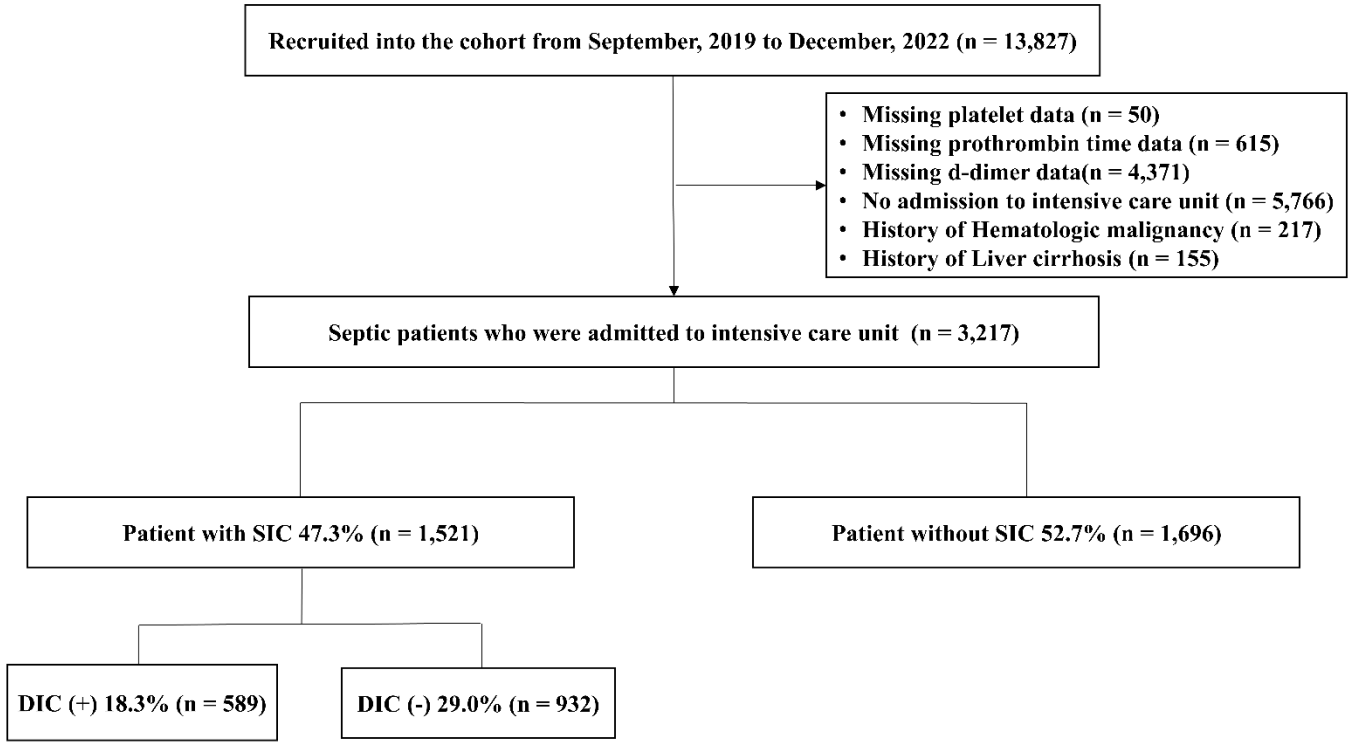
Parameters	ISTH Score
Platelets (G/L)	[0] > 100 [1] 50-99 [2] < 50
PT (%)	[0] > 64 [1] 35-64 [2] <35
Fibrinogen (g/L)	[0] > 1.0 [1] < 1.0
D-dimers (µg/mL)	[0] < 0.5 [2] 0.5-4.0 [3] > 4.0
DIC diagnosis	Score ≥ 5/8

Fig. 2 International Society on Thrombosis and Haemostasis diagnostic criteria for sepsis induced coagulopathy and overt disseminated intravascular coagulation. *SIC* sepsis induced coagulation, *DIC* disseminated intravascular coagulation, *PT* prothrombin time, *INR* international normalized ratio, *SOFA* simplified organ failure assessment

Intensive Care Med (2024) 50:1580–1592

2. Identification

Sepsis induced Coagulopathy



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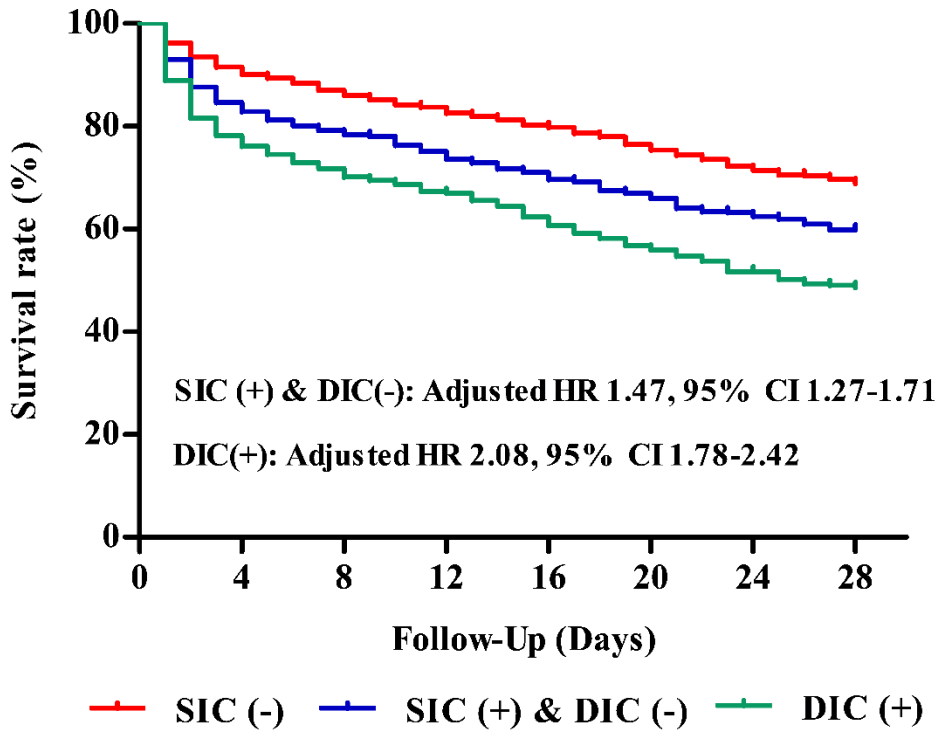
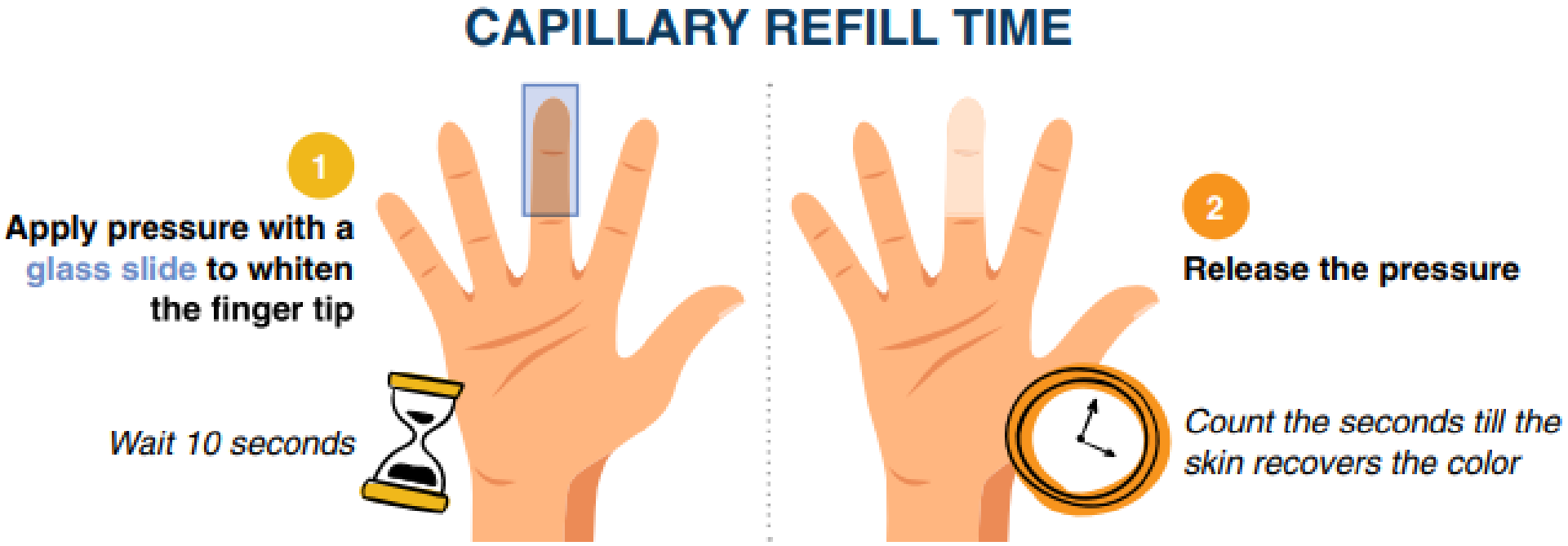
Sepsis induced Coagulopathy



2. Identification

Capillary Refill Time



2. Identification

Capillary Refill Time

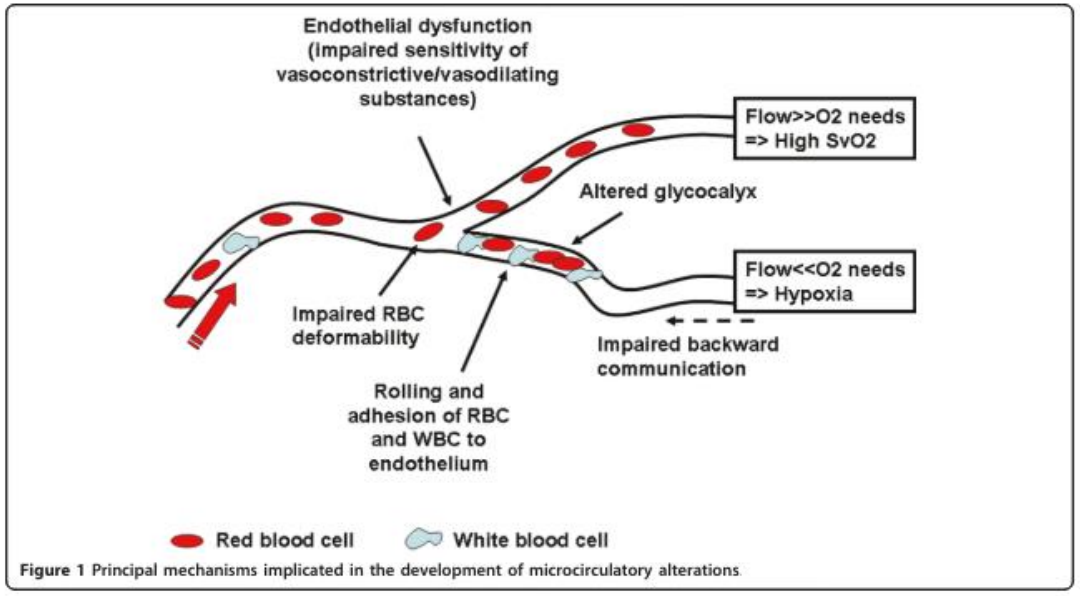
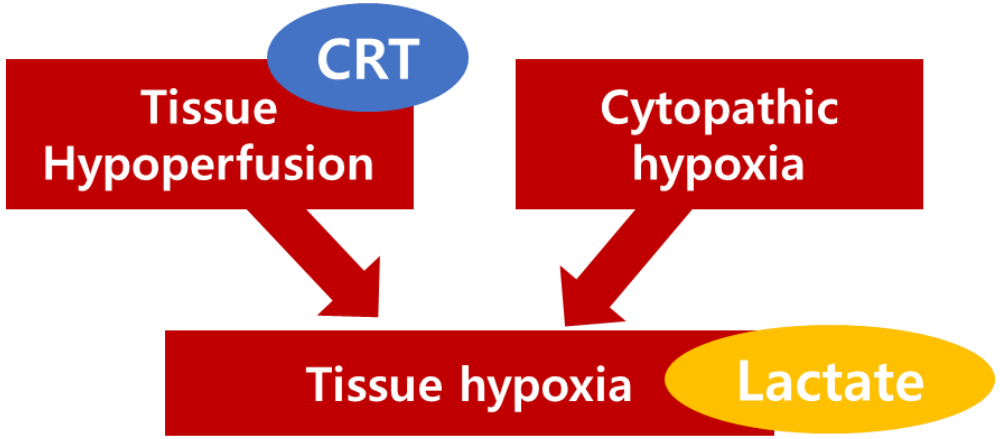


Figure 1 Principal mechanisms implicated in the development of microcirculatory alterations.

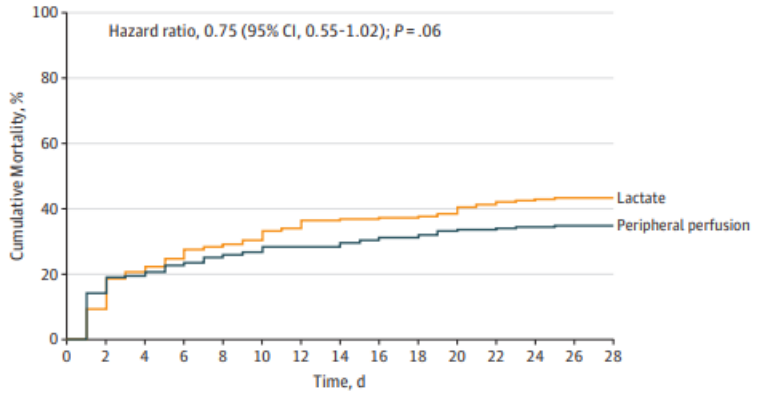


2. Identification

Capillary Refill Time

Multicenter, randomized trial included 424 patients with septic shock who were randomized to a step-by-step resuscitation protocol aimed at either normalizing capillary refill time (n = 212) or normalizing or decreasing lactate levels at rates greater than 20% per 2 hours (n = 212), during an 8-hour intervention period.

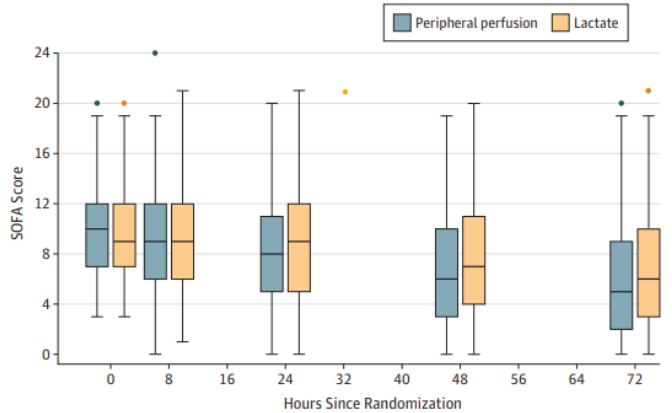
Figure 2. Kaplan-Meier Estimates of Cumulative Mortality Within 28 Days Among Patients Treated With Peripheral Perfusion–Targeted Resuscitation vs Lactate Level–Targeted Resuscitation



No. at risk

Lactate	212	192	168	160	152	148	140	135	134	133	130	124	122	120	120
Peripheral perfusion	212	182	171	164	159	155	152	152	148	146	142	141	139	138	138

Figure 4. Organ Dysfunction During the First 72 Hours After Randomization Among Patients Treated With Peripheral Perfusion–Targeted Resuscitation vs Lactate Level–Targeted Resuscitation



No. of patients

Peripheral perfusion	212	197	181	172	165
Lactate	212	203	189	173	166

JAMA. 2019;321(7):654-664.

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2. Identification

Capillary Refill Time

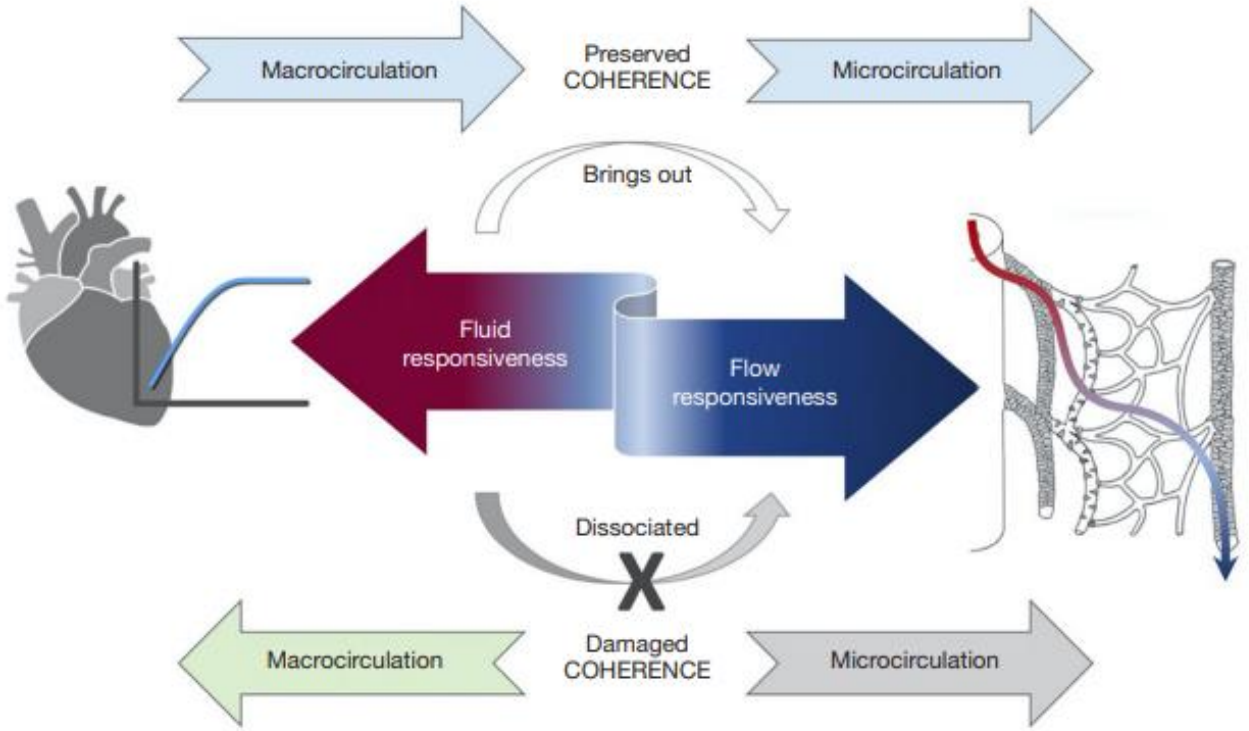


Figure 1 Relationship between fluid responsiveness, hemodynamic coherence, and flow responsiveness. This conceptual illustration indicates the link between fluid responsiveness and hemodynamic coherence as markers of macrocirculation and microcirculation, and flow responsiveness as a dynamic link between both territories.

Ann Transl Med. 2020 Jun;8(12):789.

2. Identification

Capillary Refill Time

Post-hoc analysis of the ANDROMEDA-SHOCK trial including 372 patients who had available data at 2 h after the enrollment were conducted to determine whether patients with normal CRT at T2 allocated the LT arm were associated with worse outcomes.

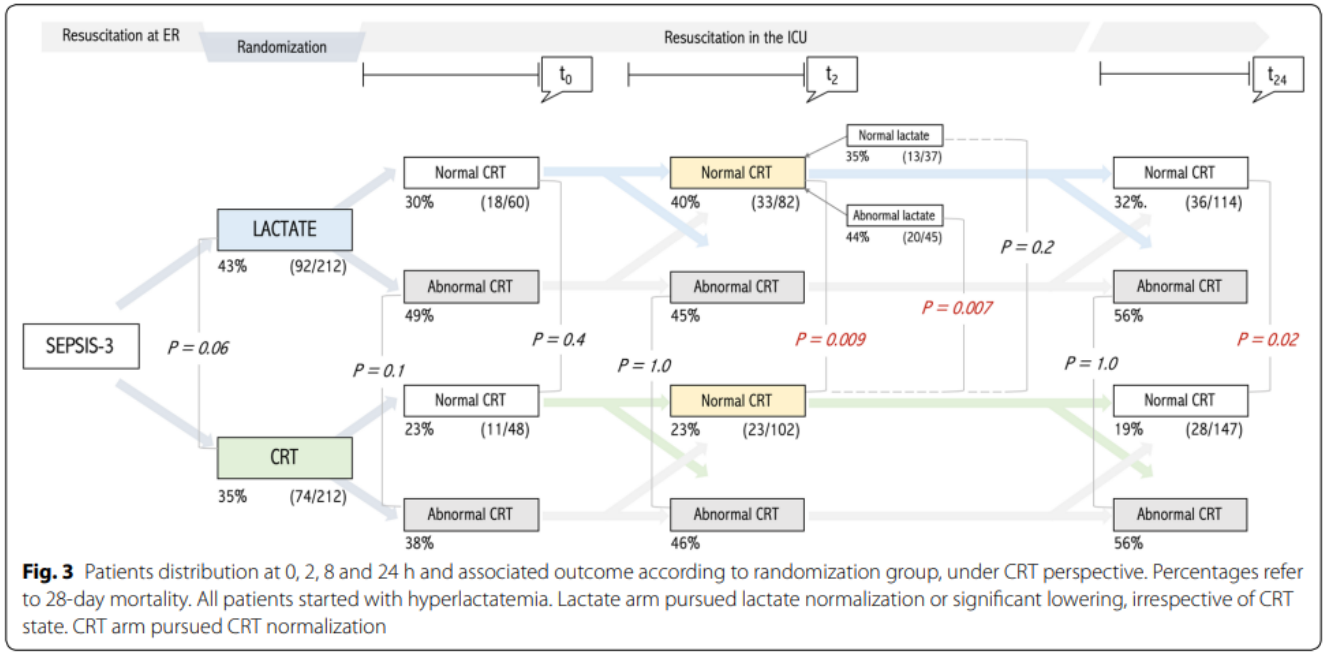


Fig. 3 Patients distribution at 0, 2, 8 and 24 h and associated outcome according to randomization group, under CRT perspective. Percentages refer to 28-day mortality. All patients started with hyperlactatemia. Lactate arm pursued lactate normalization or significant lowering, irrespective of CRT state. CRT arm pursued CRT normalization

Table 2 Clinical and interventions comparison between CRT responders at T2, according to study group

Original study arm	CRT Normal at 2 h ($n = 184$)		P
	CRT	Lactate	
Fluid bolus 0–8 h (ml)	500 [0–1500]	1000 [500–2000]	0.004
Fluid balance 8 h (ml)	1090 [319–2000]	1360 [559–2401]	0.038
Resuscitative interventions	1.25 [0.5–3]	3 [1.8–4.2]	0.001
28-day mortality	23 (23)	33 (40)	0.009

Ann Intensive Care. 2020 Aug 26;10:114.

3. Therapeutic strategy

- **Treatments targeting endothelial dysfunction**

The current global guidelines do not propose specific treat ments for endotheliopathy

ONLINE SPECIAL ARTICLE

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

Laura Evans[1]
Andrew Rhodes[2]
Waleed Alhazzani[3]
Massimo Antonelli[4]

3. Therapeutic strategy

- **Treatments targeting endothelial dysfunction**

Endothelial dysfunction

Inflammation

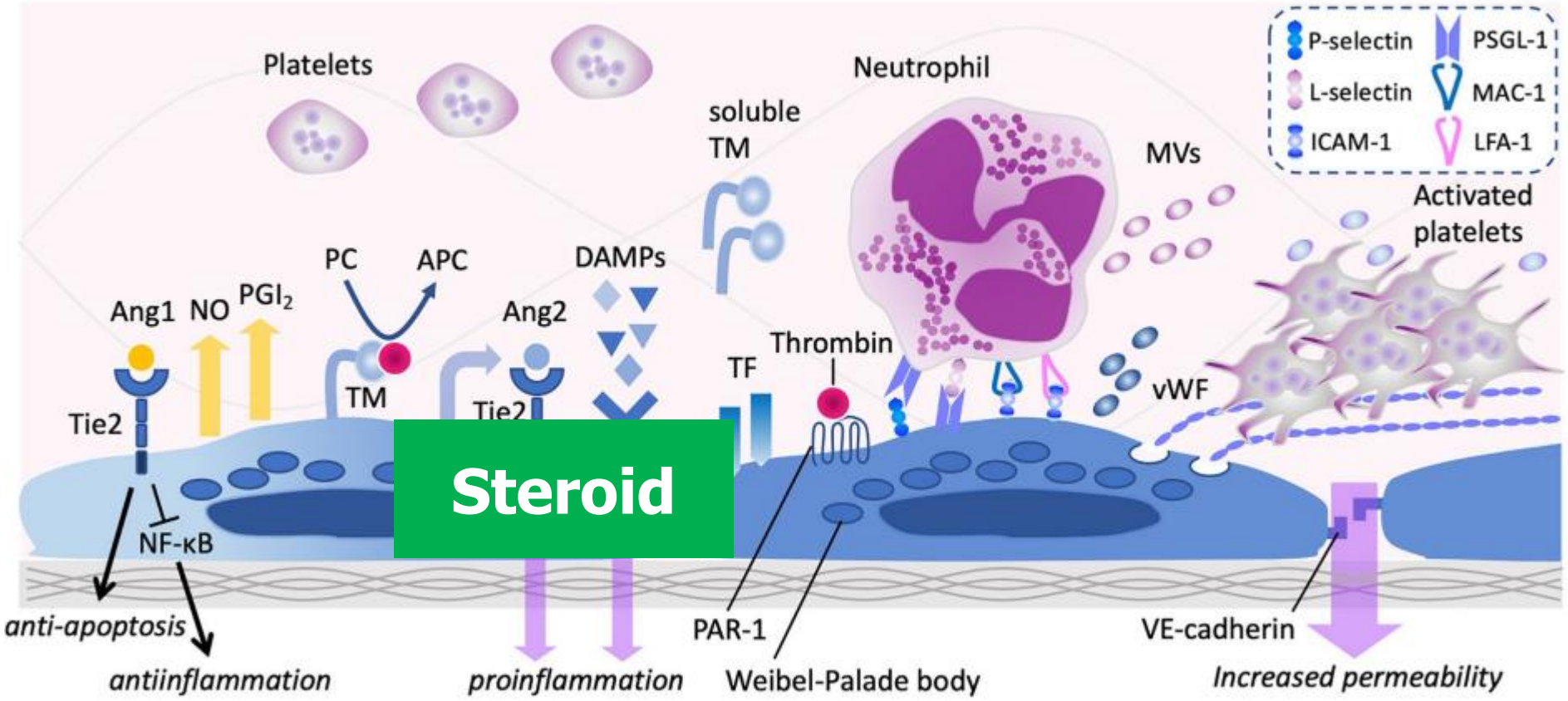
Glycocalyx

Vasodilatation

Thrombosis

3. Therapeutic strategy

Inflammation



3. Therapeutic strategy

- **Inflammation**

ONLINE SPECIAL ARTICLE

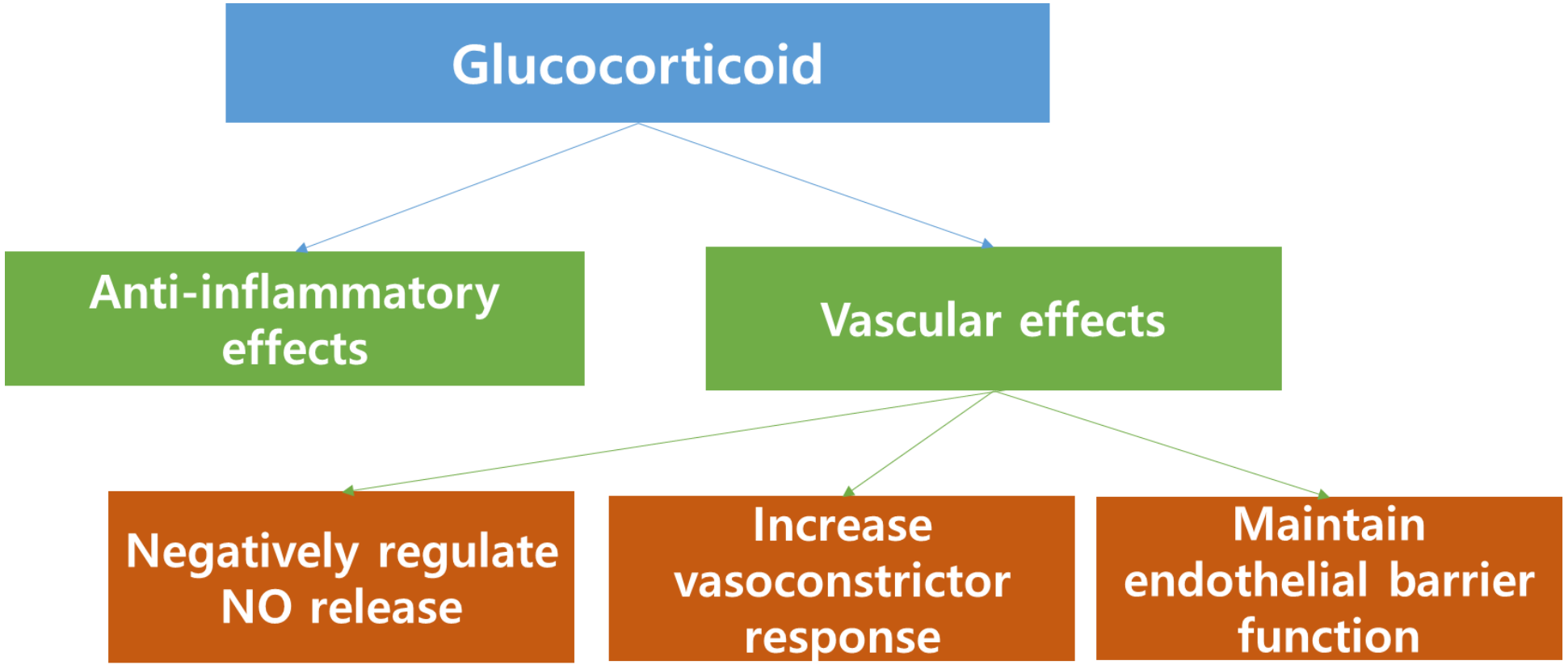
2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Sepsis and septic shock		
1A. We "suggest" administering corticosteroids to adult patients with septic shock	Conditional recommendation, low certainty evidence	We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence)
1B. We "recommend against" administration of high dose/short duration corticosteroids (> 400 mg/d hydrocortisone equivalent for less than 3 d) for adult patients with septic shock (strong recommendation, low certainty)	Strong recommendation, moderate certainty evidence	We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence)

Crit Care Med . 2024 May 1;52(5):e219-e233.

3. Therapeutic strategy

Inflammation



3. Therapeutic strategy

Inflammation

Disease State	Common Corticosteroid Regimens
Septic shock	Hydrocortisone 200 mg IV per day (continuous infusion or divided every 6 hr) with or without fludrocortisone 50 µg enteral daily for 7 d or until ICU discharge[a]

Study Characteristics

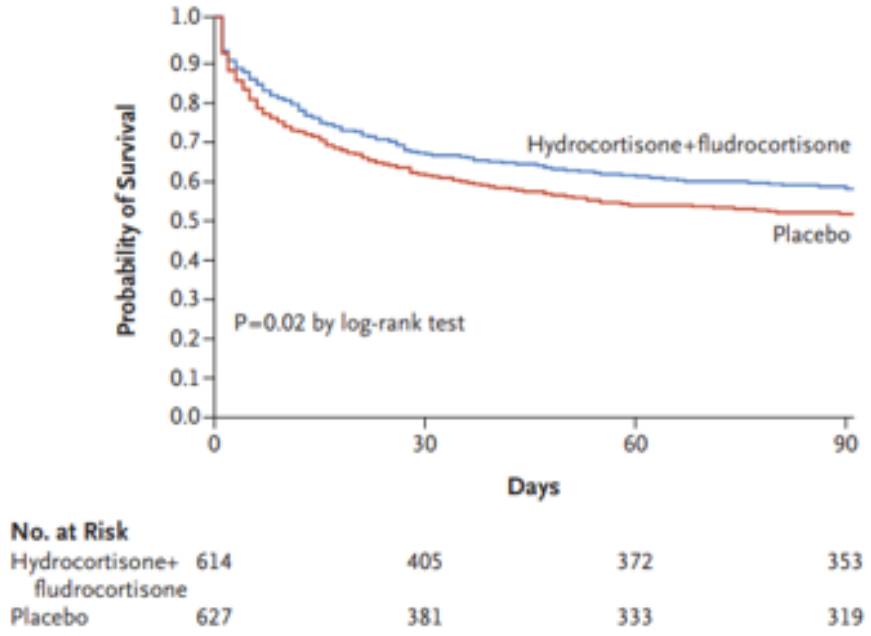
Study	Number of Randomized Patients	Population	Interventions	Primary Outcome
Annane 2002	Multicentre (19 sites) France N= 300	Adults with vasopressor and ventilator dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	28 day mortality
Annane 2018 (APROCCHSS)	Multicentre (34 sites) France N=1241 Originally a 2x2 factorial design with APC (terminated)	Adult patients with vasopressor dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	90 day mortality

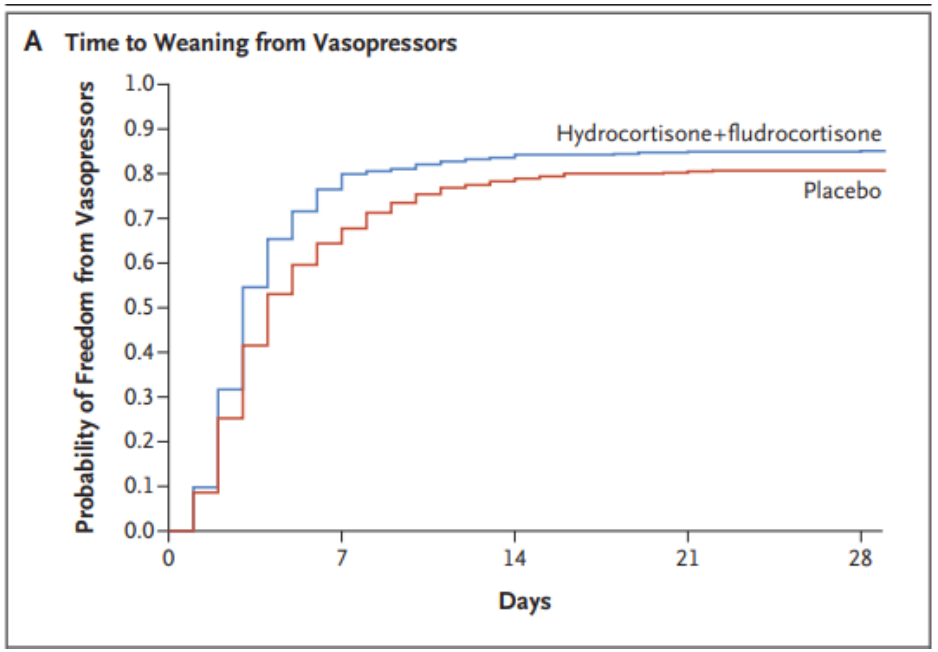
Crit Care Med . 2024 May 1;52(5):e219-e233.

3. Therapeutic strategy

Inflammation

A multicenter, double-blind, randomized, controlled trial included 1,241 adults patients with septic shock who received intravenous hydrocortisone 50 mg q 6 hr and Fludrocortisone 50 μg qd for 7 days without tapering versus placebo.





N Engl J Med 2018;378:809-18

3. Therapeutic strategy

Inflammation

This retrospective cohort study from 2016 to 2020 used the enhanced claims-based Premier Healthcare Database, which included approximately 25% of US hospitalizations. Participants were adult patients hospitalized with septic shock and receiving norepinephrine who began hydrocortisone treatment.

Figure 1. Study Flow Diagram

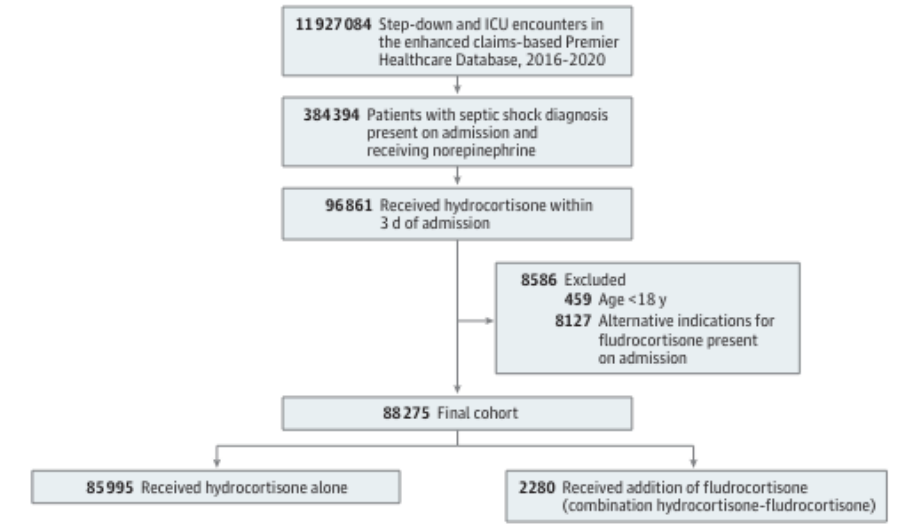
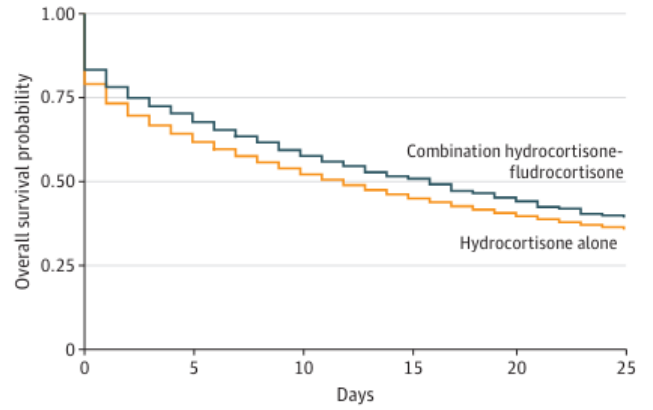


Figure 2. 28-Day Survival Among Patients With Septic Shock Treated With Hydrocortisone-Fludrocortisone or Hydrocortisone Alone



No. at risk						
Hydrocortisone alone	85 995	46 364	26 760	15 456	9205	5718
Combination hydrocortisone-fludrocortisone	2280	1378	828	491	286	181

JAMA Intern Med. 2023 May 1;183(5):451-459.

3. Therapeutic strategy

Inflammation

Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial

*Nicholas Heming, Alain Renault, Emmanuelle Kuperminc, Christian Brun-Buisson, Bruno Megarbane, Jean-Pierre Quenot, Shidasp Siami, Alain Cariou, Xavier Forceville, Carole Schwebel, Marc Leone, Jean-Francois Timsit, Benoît Misset, Mohamed Ali Benali, Gwenhael Colin, Bertrand Souweine, Karim Asehnoune, Emmanuelle Mercier, Loic Chimot, Claire Charpentier, Bruno François, Thierry Boulain, Frank Petitpas, Jean Michel Constantin, Gilles Dhonneur, François Baudin, Alain Combes, Julien Bohé, Jean-François Loriferne, Fabrice Cook, Michel Slama, Olivier Leroy, Gilles Capellier, Auguste Dargent, Tarik Hissem, Rania Bounab, Virginie Maxime, Pierre Moine, Eric Bellissant, Djillali Annane for the APROCCHSS investigators and CRICS-TRIGGERSEP network**

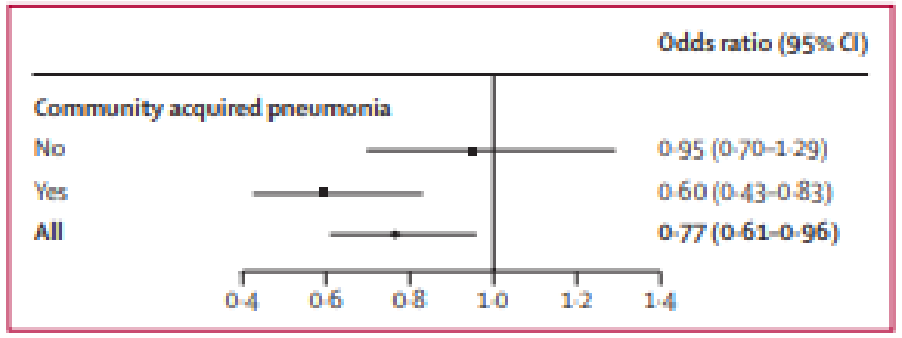


Figure 1: Forest plot of corticosteroid effects across subgroups with or without community acquired pneumonia

Odds ratio and 95% CI for 90-day all-cause mortality in the whole population and in the subgroups with or without community acquired pneumonia. There was a significant statistical heterogeneity in corticosteroid effects on 90-day mortality across subgroups with or without community acquired pneumonia (multiplicative interaction p=0·046 and additive interaction p=0·046).

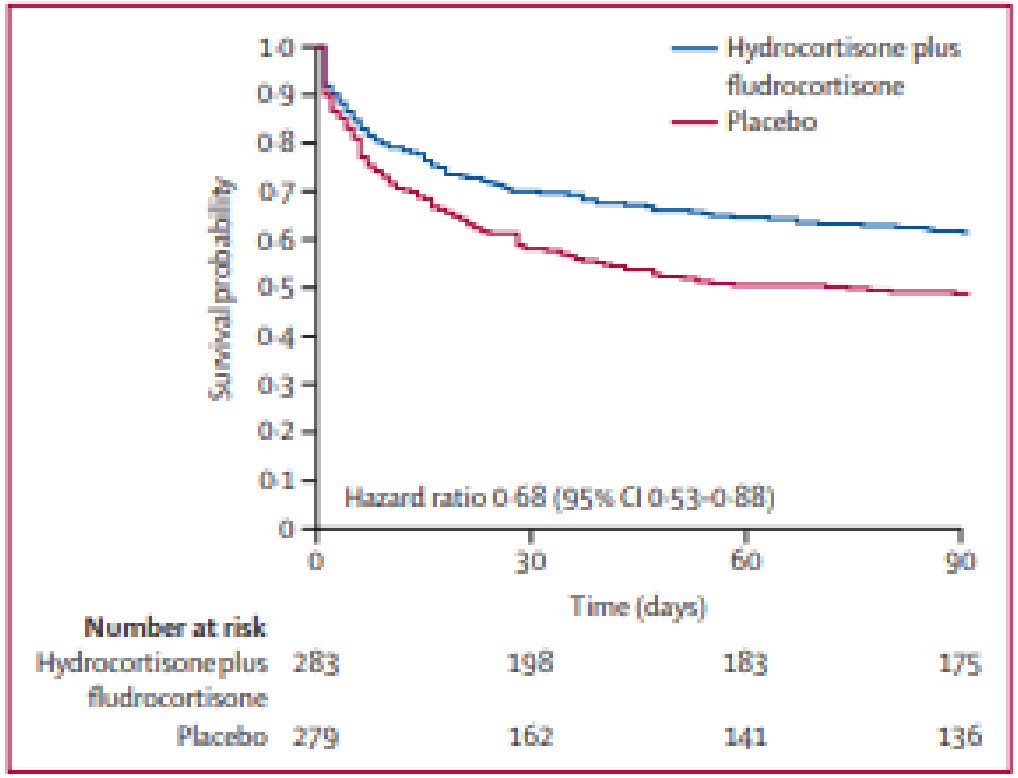


Figure 2: 90-day survival distributions

In patients with community acquired pneumonia. Survival curves from randomisation up to 90 days. Hydrocortisone and fludrocortisone therapy (blue line) versus placebo (red line). Interaction test, p=0·061. Only interaction tests are presented in this Article.

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3. Therapeutic strategy

- **Treatments targeting endothelial dysfunction**

Endothelial dysfunction

Inflammation

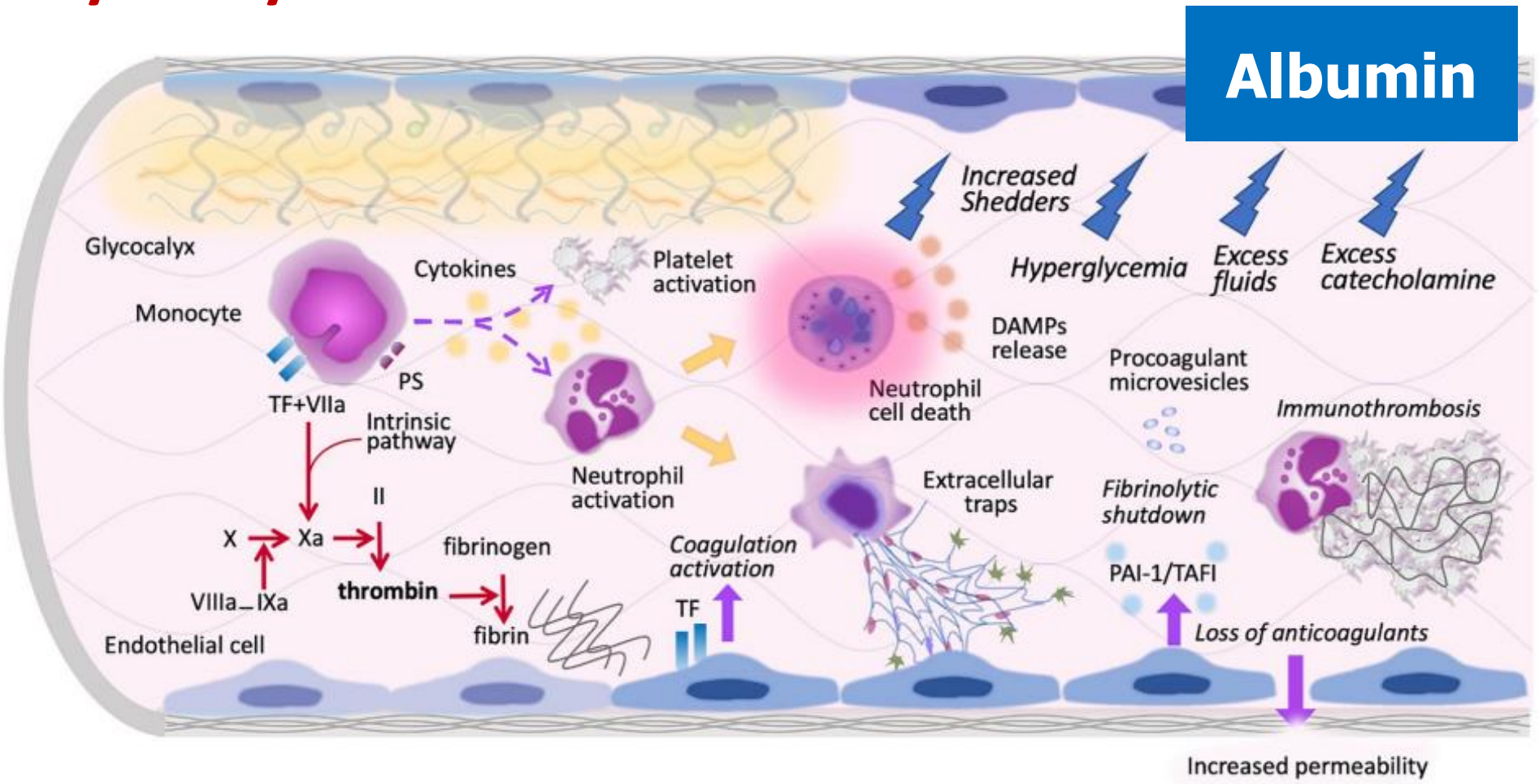
Glycocalyx

Vasodilatation

Thrombosis

3. Therapeutic strategy

Glycocalyx

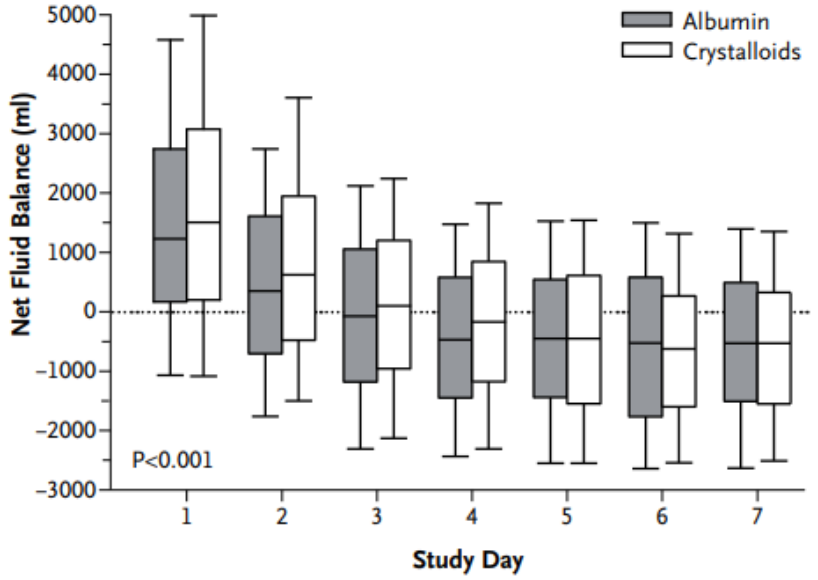


Ann Intensive Care. 2024 Apr 24;14(1):64.

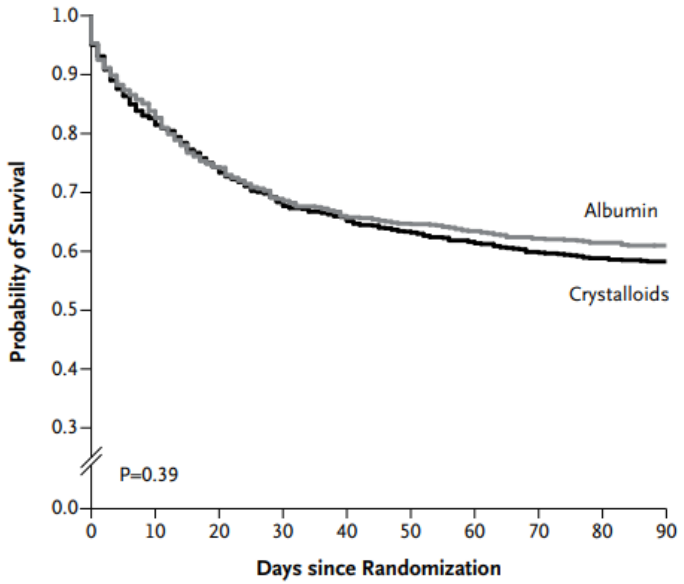
3. Therapeutic strategy

Glycocalyx

The multicenter, randomized trial including 1,818 patients with severe sepsis was to compare receiving either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 3.0 g/dL.



No. at Risk							
Albumin	840	789	742	701	639	586	542
Crystalloids	844	795	735	685	635	587	529



No. at Risk										
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

N Engl J Med . 2014 Apr 10;370(15):1412-21.

3. Therapeutic strategy

Glycocalyx

The sub-study of ALBIOS was aimed to evaluate the effects of albumin supplementation on endothelial dysfunction in patients with septic shock (n = 375)

Table 4 SYN-1, S1P and VE-cadherin concentrations over time in 375 patients and by ALBIOS treatment

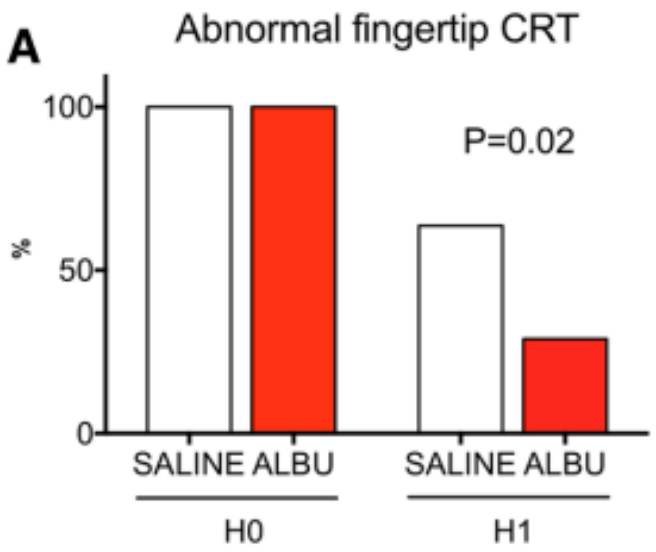
	ALBIOS patients			*p* value*
	Total (375)	Albumin (188)	Crystalloids (187)	
VE-cadherin (ng/mL)				
Day 1	1697 [1313–2199]	1636 [1270–2068]	1737 [1394–2317]	0.004
Day 2	1751 [1433–2310]	1662 [1381–2144]	1837 [1475–2398]	0.009
Day 7	1869 [1523–2332]	1781 [1494–2251]	1976 [1618–2395]	0.02
Mixed model analysis**		P time		4.5×10^{-13}
		P treatment		0.003
		P interaction time*treatment		0.193

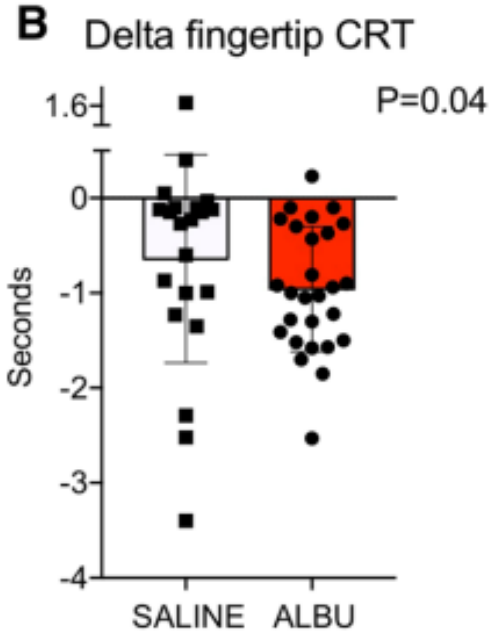
Crit Care. 2021;25(1):113.

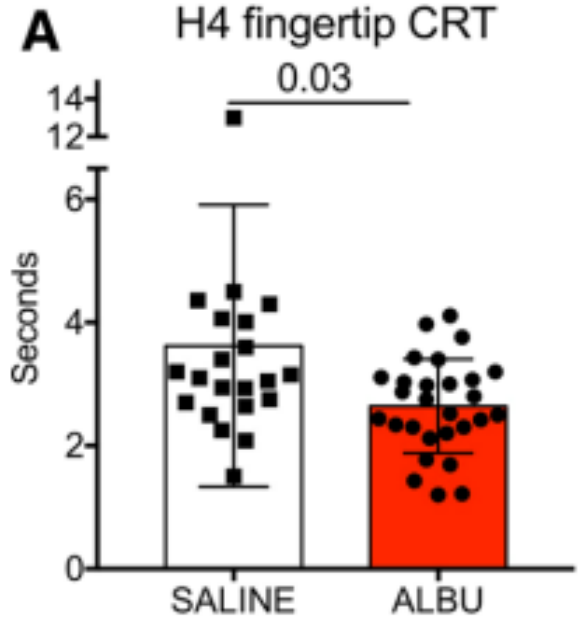
3. Therapeutic strategy

Glycocalyx

The proof-of concept study including 50 patients with sepsis and prolonged CRT > 3 s was to compare CRT normalization at 1 h between saline 500 mL and albumin 20% 100 mL over 15 min infusion







Crit Care . 2024 Feb 7;28(1):43.

3. Therapeutic strategy

- **Treatments targeting endothelial dysfunction**

Endothelial dysfunction

Inflammation

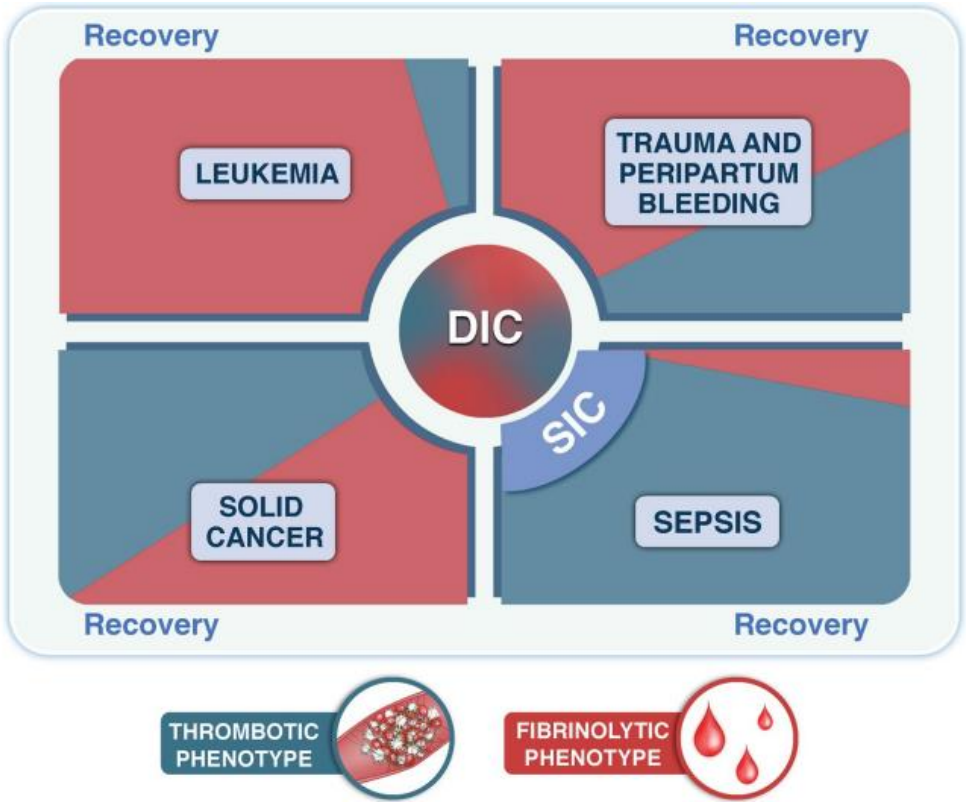
Glycocalyx

Vasodilatation

Thrombosis

3. Therapeutic strategy

Thrombosis



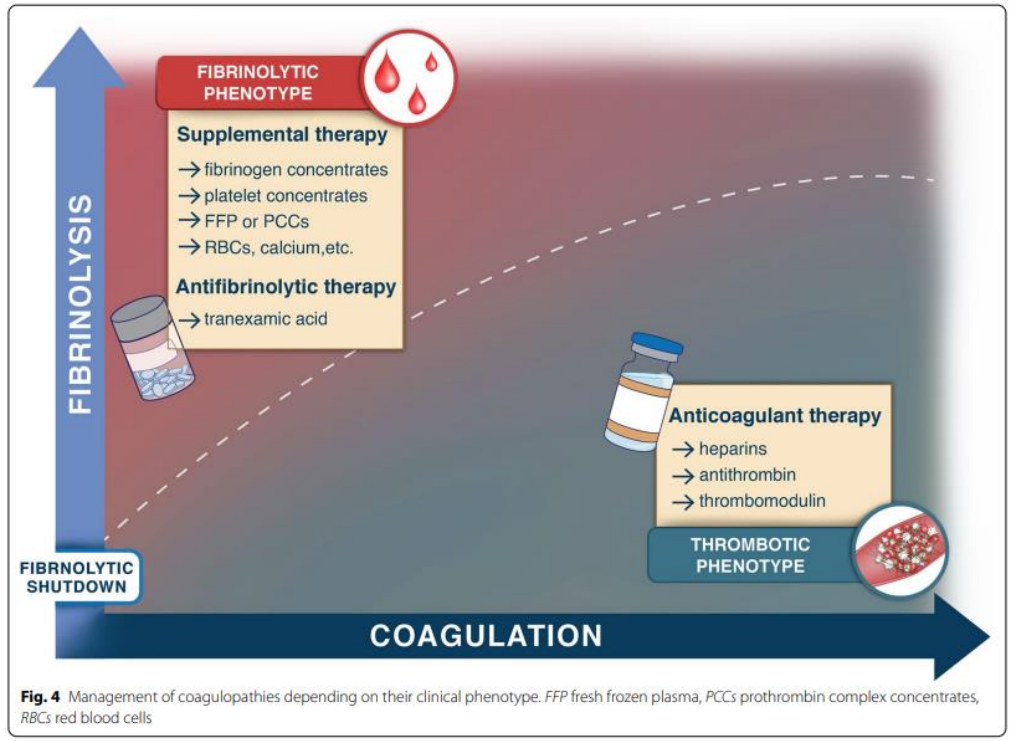


Fig. 4 Management of coagulopathies depending on their clinical phenotype. *FFP* fresh frozen plasma, *PCCs* prothrombin complex concentrates, *RBCs* red blood cells

Intensive Care Med . 2023 Mar;49(3):273-290.

3. Therapeutic strategy

Thrombosis

ONLINE SPECIAL ARTICLE

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

Laura Evans[1]
Andrew Rhodes[2]
Waleed Alhazzani[3]
Massimo Antonelli[4]

64. For adults with sepsis or septic shock, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication to such therapy exists.	***Strong,*** *moderate-quality evidence*
65. For adults with sepsis or septic shock, we recommend using low molecular weight heparin over unfractionated heparin for VTE prophylaxis	***Strong,*** *moderate-quality evidence*

3. Therapeutic strategy

Thrombosis

Shime *et al. Journal of Intensive Care* (2025) 13:15
https://doi.org/10.1186/s40560-025-00776-0

Journal of Intensive Care

GUIDELINE Open Access

Check for updates

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024

CQ5 Disseminated intravascular coagulation

Suggested

- Antithrombin — GRADE 2B
- Thrombomodulin — GRADE 2B

FRQ

- Combination of antithrombin and thrombomodulin
- Heparin/ Heparin analogs

BQ

- Diagnostic method for sepsis-induced DIC
- Differential diagnoses for sepsis-induced DIC

3. Therapeutic strategy

Thrombosis

CQ5-3: Is antithrombin administered for sepsis-induced DIC?

Answer: We suggest the administration of antithrombin for sepsis-induced DIC (GRADE 2B).

Rationale

We conducted a meta-analysis of five RCTs using a decrease in mortality and recovery from DIC as desirable effects [370–374]. Concerning the desirable effects of antithrombin, the analysis of the five RCTs [370–374] showed that mortality yielded a RD of 147 fewer per 1000 (95% CI 214 fewer to 67 fewer), and analysis of three RCTs [370, 371, 374] showed that recovery from DIC yielded an RD of 448 more per 1000 (95% CI 161 more to 999 more). Concerning the undesirable effect of antithrombin, analysis of the three RCTs [370, 373, 374] showed that bleeding complications yielded an RD of 8 more per 1000 (95% CI 24 fewer to 89 more). Considering the relative value of each outcome, the desirable effects were large, and the undesirable effects were trivial. Thus, we concluded that the balance of effects was better for the intervention (Additional file 3).

Evidence profile

Certainty assessment							Number of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomized trials	not serious	not serious	serious	serious	none	62/198 (31.3%)	86/193 (44.6%)	RR 0.67 (0.52 to 0.85)	147 fewer per 1,000 (from 214 fewer to 67 fewer)	⊕⊕◯◯ Low	Critical
Bleeding complications												
3	randomized trials	not serious	not serious	not serious	very serious	none	8/158 (5.1%	7/163 (4.3%)	RR 1.18 (0.45 to 3.08)	8 more per 1,000 (from 24 fewer to 89 more)	⊕⊕◯◯ Low	Critical
Recovery from disseminated intravascular coagulation												
2	randomized trials	serious	not serious	not serious	serious	none	32/51 (62.7%)	8/55 (14.5%)	RR 4.08 (2.11 to 7.87)	448 more per 1,000 (from 161 more to 999 more)	⊕⊕◯◯ Low	Important

CI: confidence interval; RR: risk ratio.

3. Therapeutic strategy

Thrombosis

CQ5-4: Is recombinant thrombomodulin administered for sepsis-induced DIC?

Answer: We suggest the administration of recombinant thrombomodulin for sepsis-induced DIC (GRADE 2B).

Rationale

We conducted a meta-analysis of four RCTs [379–382], using a decrease in mortality as a desirable effect. The results showed that mortality yielded an RD of 39 fewer per 1000 (95% CI 75 fewer to 3 more). Additionally, a meta-analysis of three RCTs [380–382] showed that recovery from DIC yielded an RD of 120 more per 1000 (95% CI 4 more to 274 more), also considered a desirable effect.

For adverse effects, another meta-analysis of four RCTs [379–382] showed that bleeding complications yielded an RD of 12 more per 1000 (95% CI 6 fewer to 41 more). Considering the relative value of each outcome, we found that the beneficial effects were substantial, while the adverse effects were minimal. Thus, we concluded that the balance of effects was probably better for the intervention (Additional file 3).

Evidence profile

Certainty assessment							Number of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomized trials	not serious	not serious	not serious	serious	none	163/753 (21.6%)	199/774 (25.7%)	RR 0.85 (0.71 to 1.01)	39 fewer per 1,000 (from 75 fewer to 3 more)	⊕⊕⊕◯ Moderate	Critical
Bleeding complications												
4	randomized trials	not serious	not serious	not serious	serious	none	44/842 (5.2%)	34/851 (4.0%)	RR 1.31 (0.84 to 2.02)	12 more per 1,000 (from 6 fewer to 41 more)	⊕⊕⊕◯ Moderate	Critical
Recovery from disseminated intravascular coagulation												
3	randomized trials	not serious	not serious	not serious	serious	none	61/122 (50.0%)	46/126 (36.5%)	RR 1.33 (1.01 to 1.75)	120 more per 1,000 (from 4 more to 274 more)	⊕⊕⊕◯ Moderate	Important

CI: confidence interval; RR: risk ratio.

3. Therapeutic strategy

- **Treatments targeting endothelial dysfunction**

Endothelial dysfunction

Inflammation

Glycocalyx

Vasodilatation

Thrombosis

3. Therapeutic strategy

- **Vasodilatation**

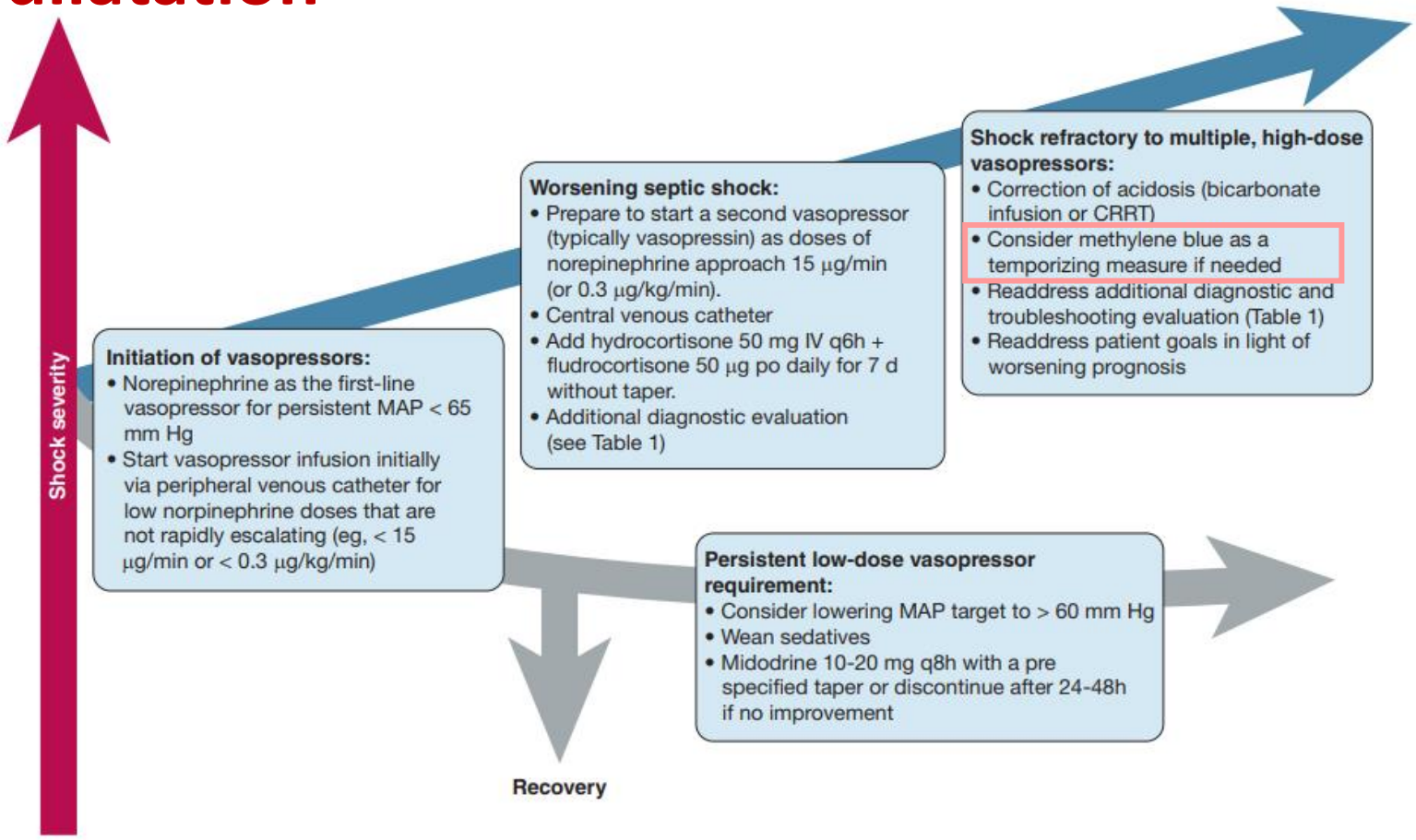


Figure 1 – *Diagram showing suggested approach to treatment of hypotension at various stages of septic shock. The y-axis represents severity of shock and the x-axis represents possible trajectories over time. CRRT = continuous renal replacement therapy; MAP = mean arterial pressure.*

CHEST 2023; 163(3):567-574

3. Therapeutic strategy

Vasodilatation

A single-center randomized controlled trial assigned 91 patients with septic shock to MB or placebo. Patients assigned to MB group received an intravenous (IV) infusion of 100 mg of MB in 500 ml of 0.9% sodium chloride solution over 6 h once daily for a total of 3 doses.

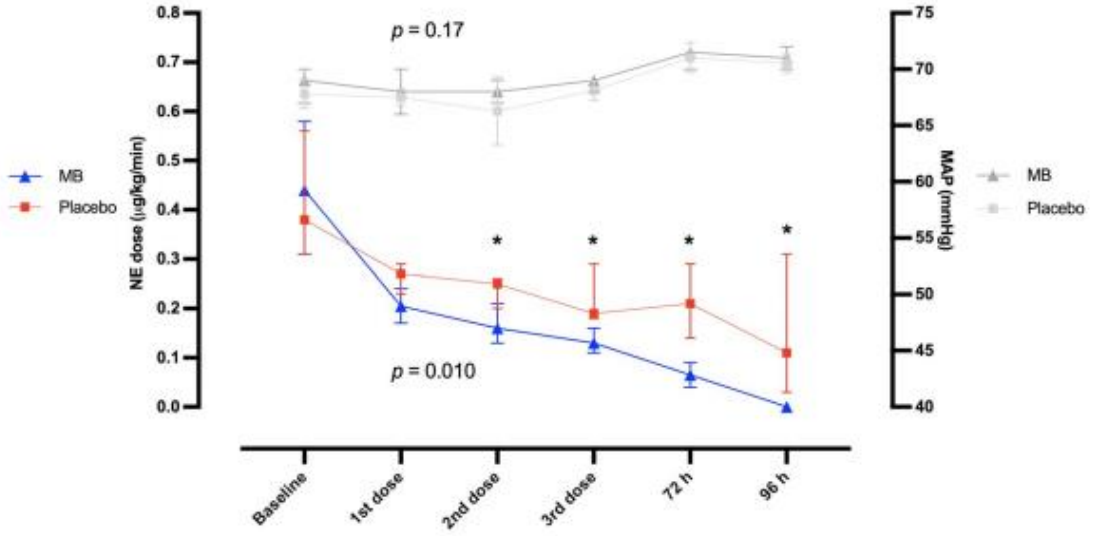


Fig. 2 Trends of mean arterial pressure and norepinephrine requirement along the first 4 days after recruitment. *p* values reflect the between subjects (groups) comparison test. * $p < 0.05$ between groups

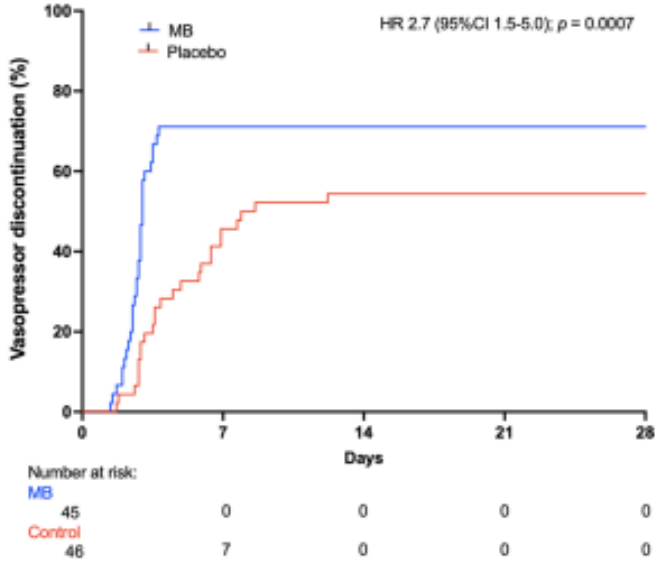


Fig. 3 Kaplan–Meier plot of the cumulative incidence of vasopressor discontinuation. Adjusted hazard ratio with death as a competing risk analysis. *MB* methylene blue, *HR* hazard ratio

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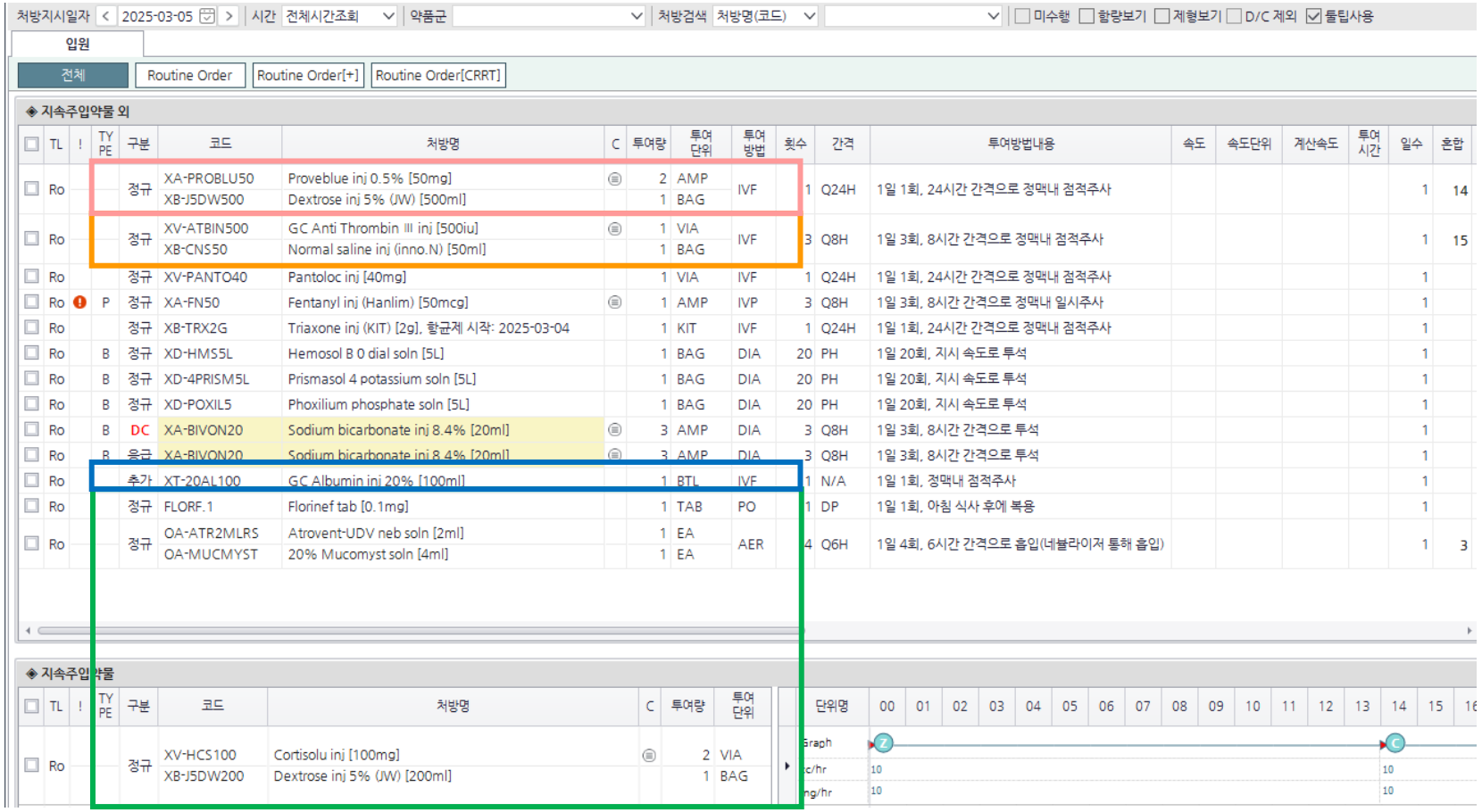
- **59세/여환, 당뇨병 이외 기저 질환 없던 분으로 내원 전날부터 발생한 복통, 구토, 및 기력저하로 응급실 내원**



경청 해주셔서 감사합니다 !