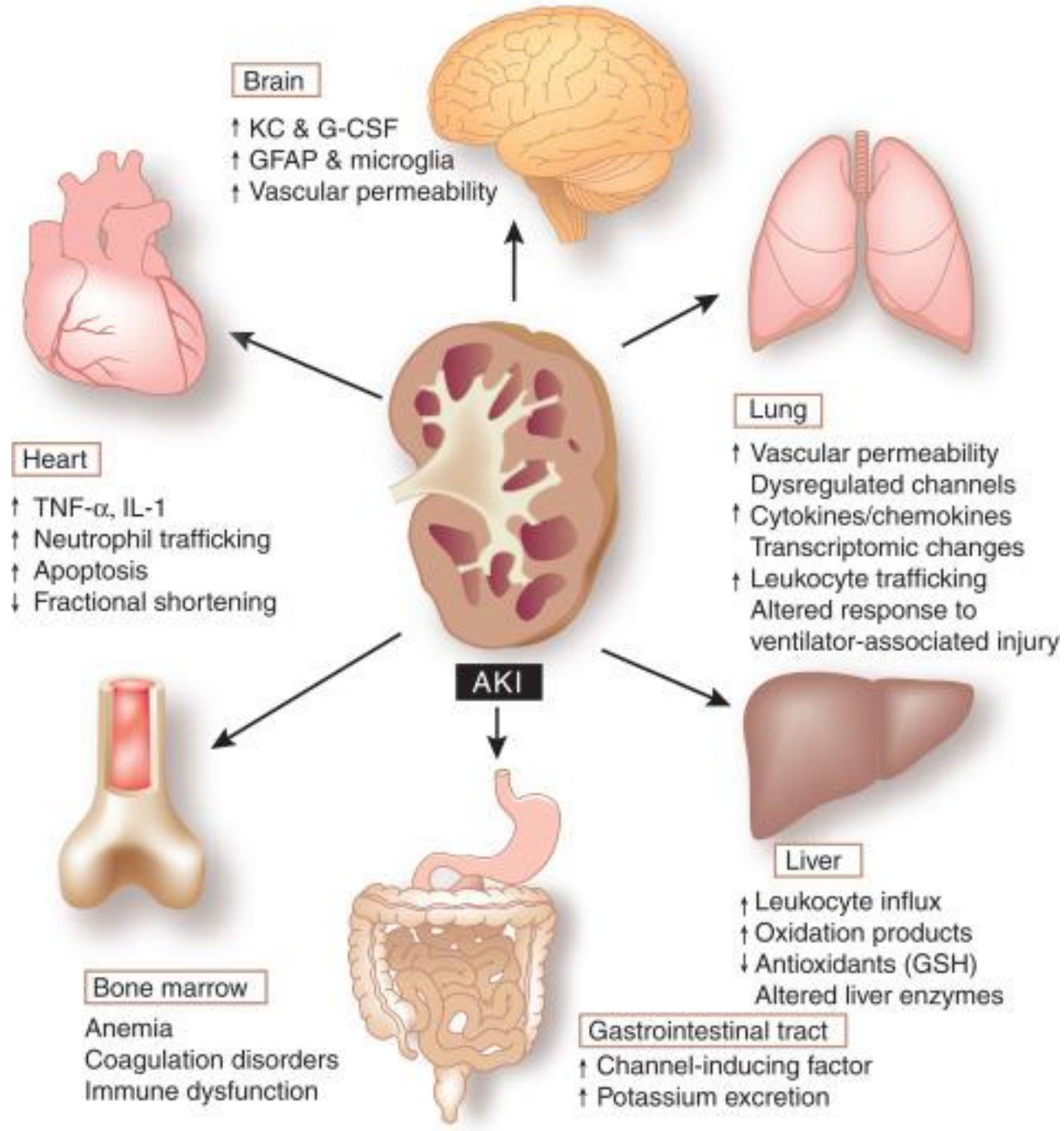
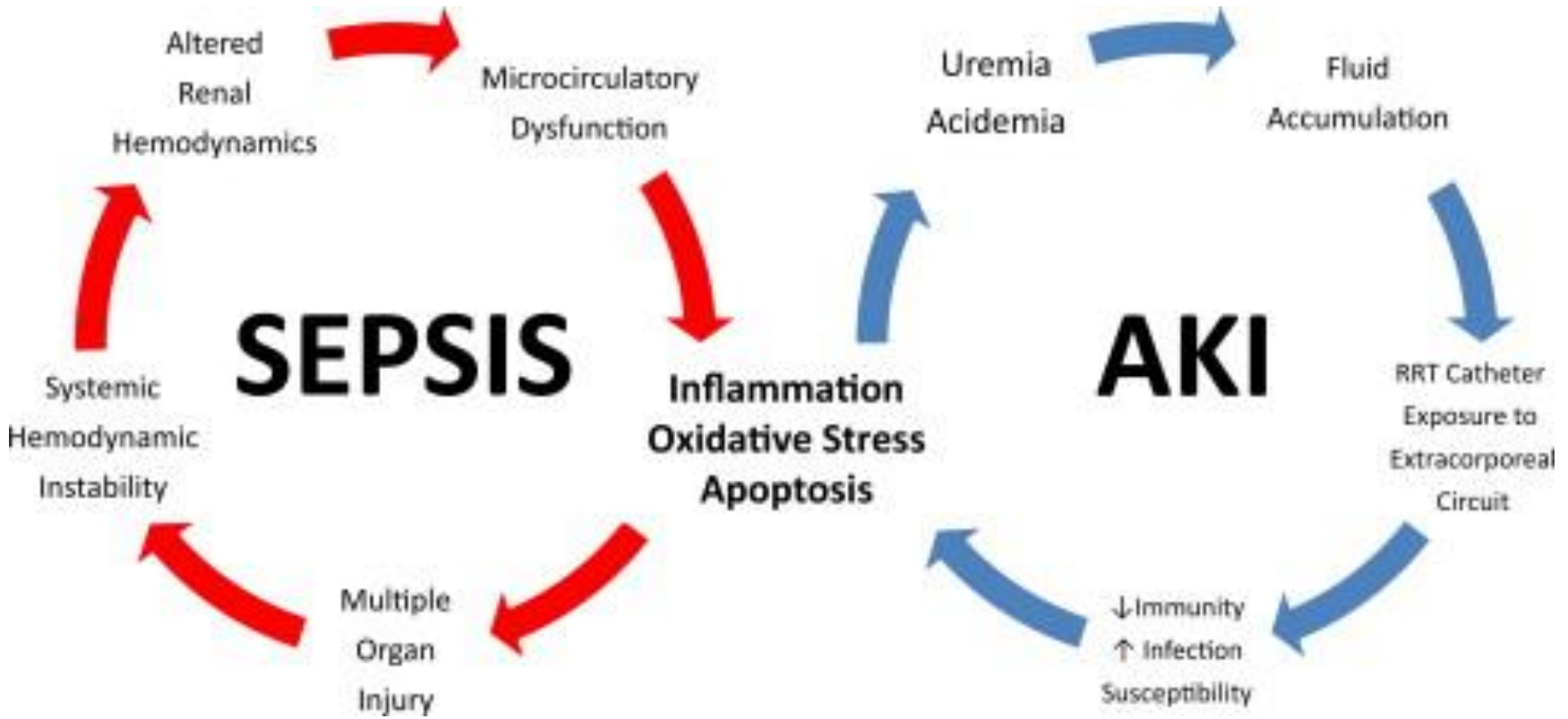
Blood Purification in the CIP with AKI

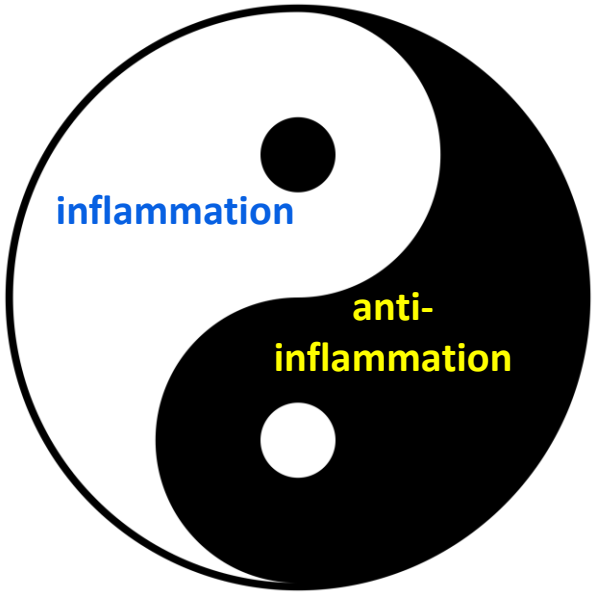
Amir A. Nassiri

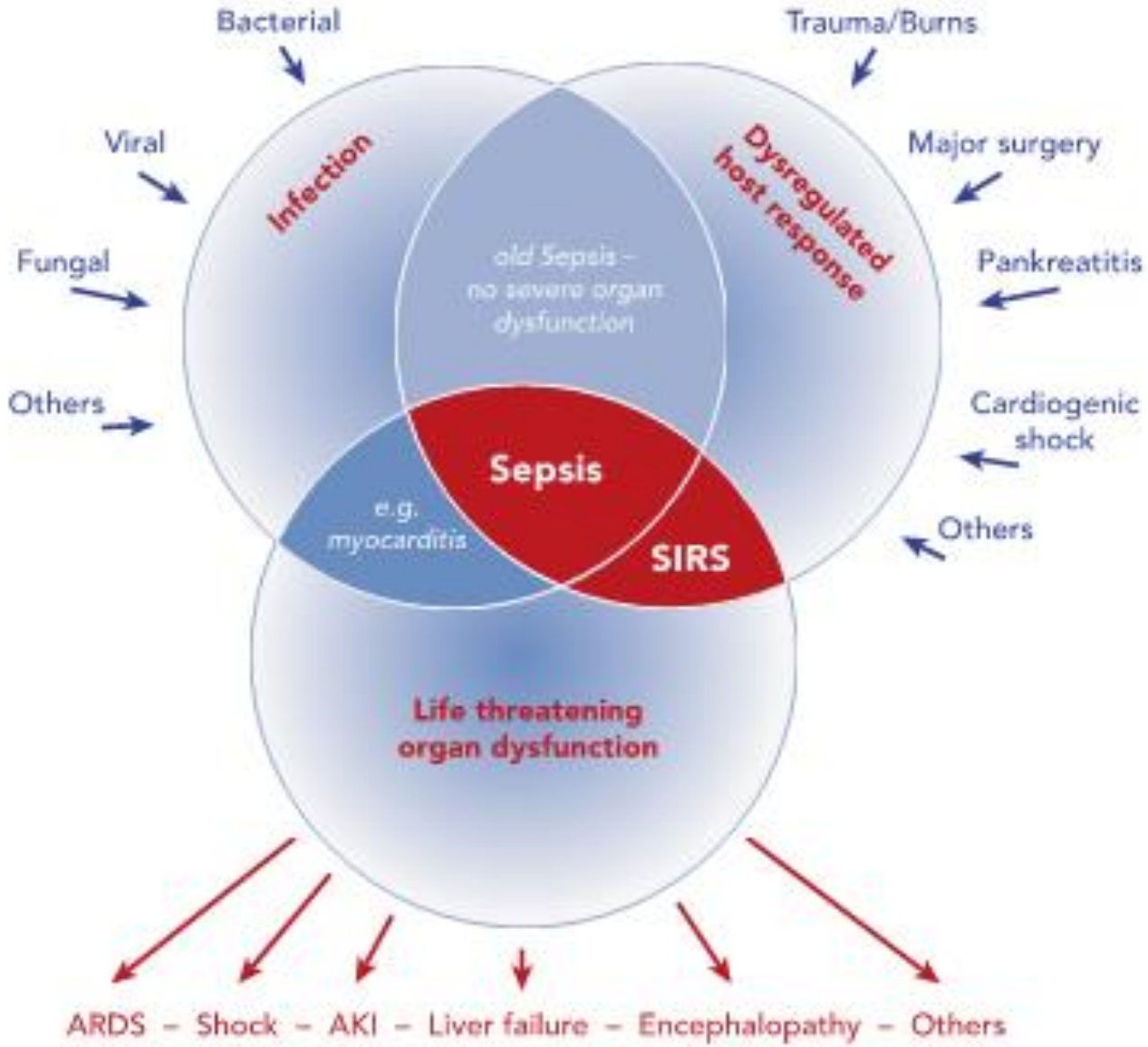

Brain
↑ KC & G-CSF
↑ GFAP & microglia
↑ Vascular permeability
Heart
↑ TNF-α, IL-1
↑ Neutrophil trafficking
↑ Apoptosis
↓ Fractional shortening
Lung
↑ Vascular permeability
Dysregulated channels
↑ Cytokines/chemokines
Transcriptomic changes
↑ Leukocyte trafficking
Altered response to
ventilator-associated injury
AKI
Bone marrow
Anemia
Coagulation disorders
Immune dysfunction
Gastrointestinal tract
↑ Channel-inducing factor
↑ Potassium excretion
Liver
↑ Leukocyte influx
↑ Oxidation products
↓ Antioxidants (GSH)
Altered liver enzymes

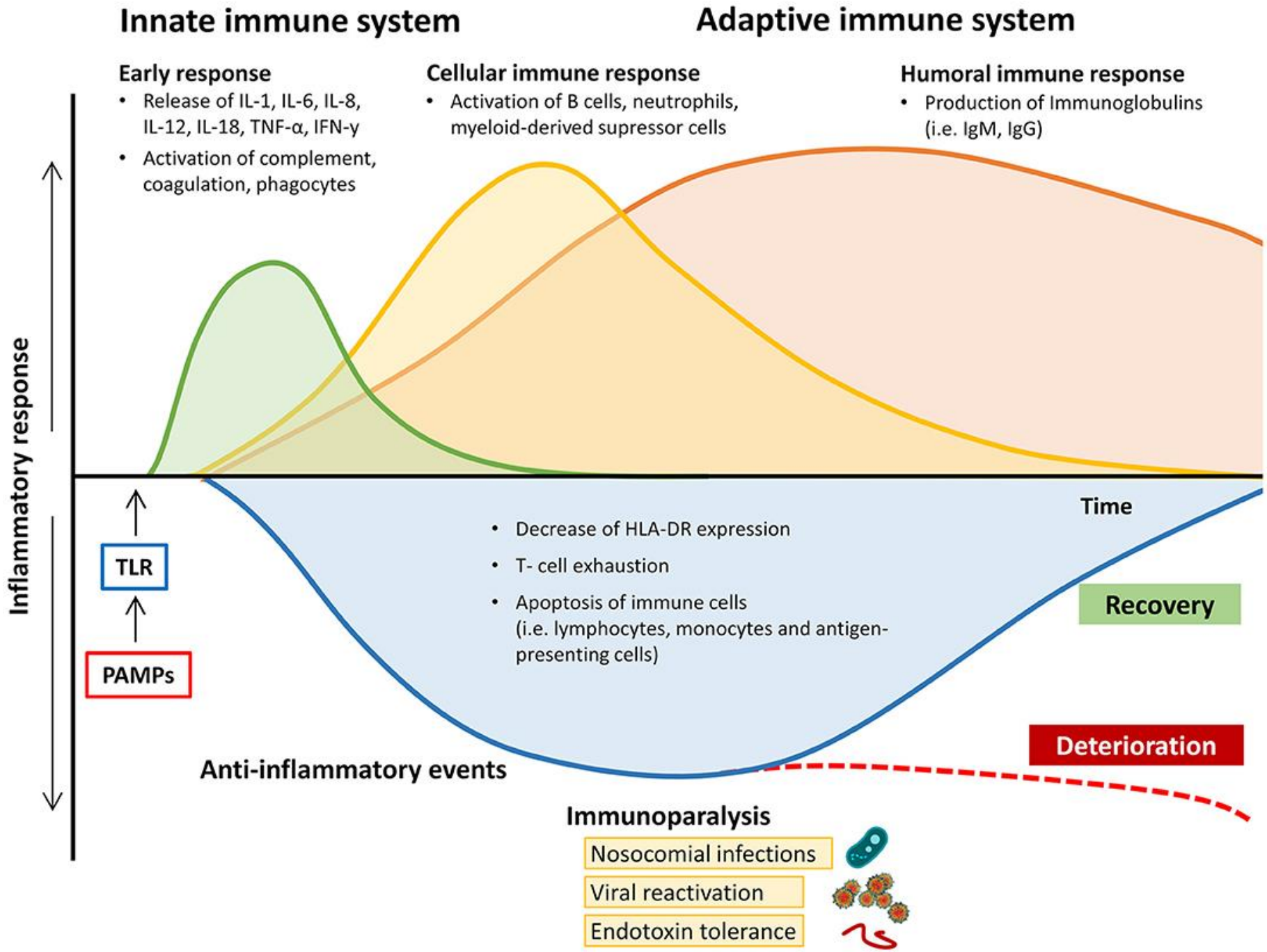
sepsis pt: almost never die without AKI
AKI pt: almost never die without sepsis

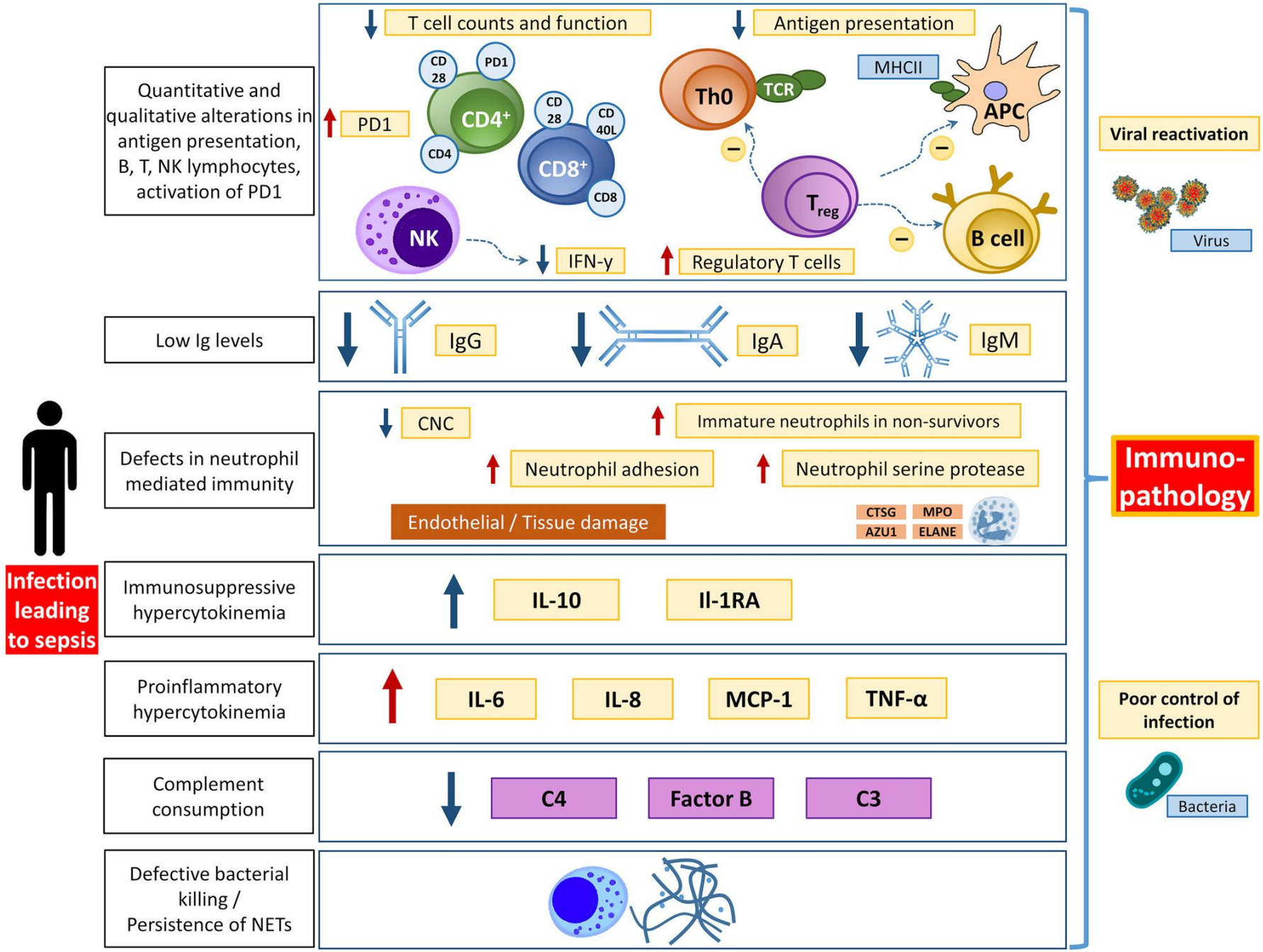


The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

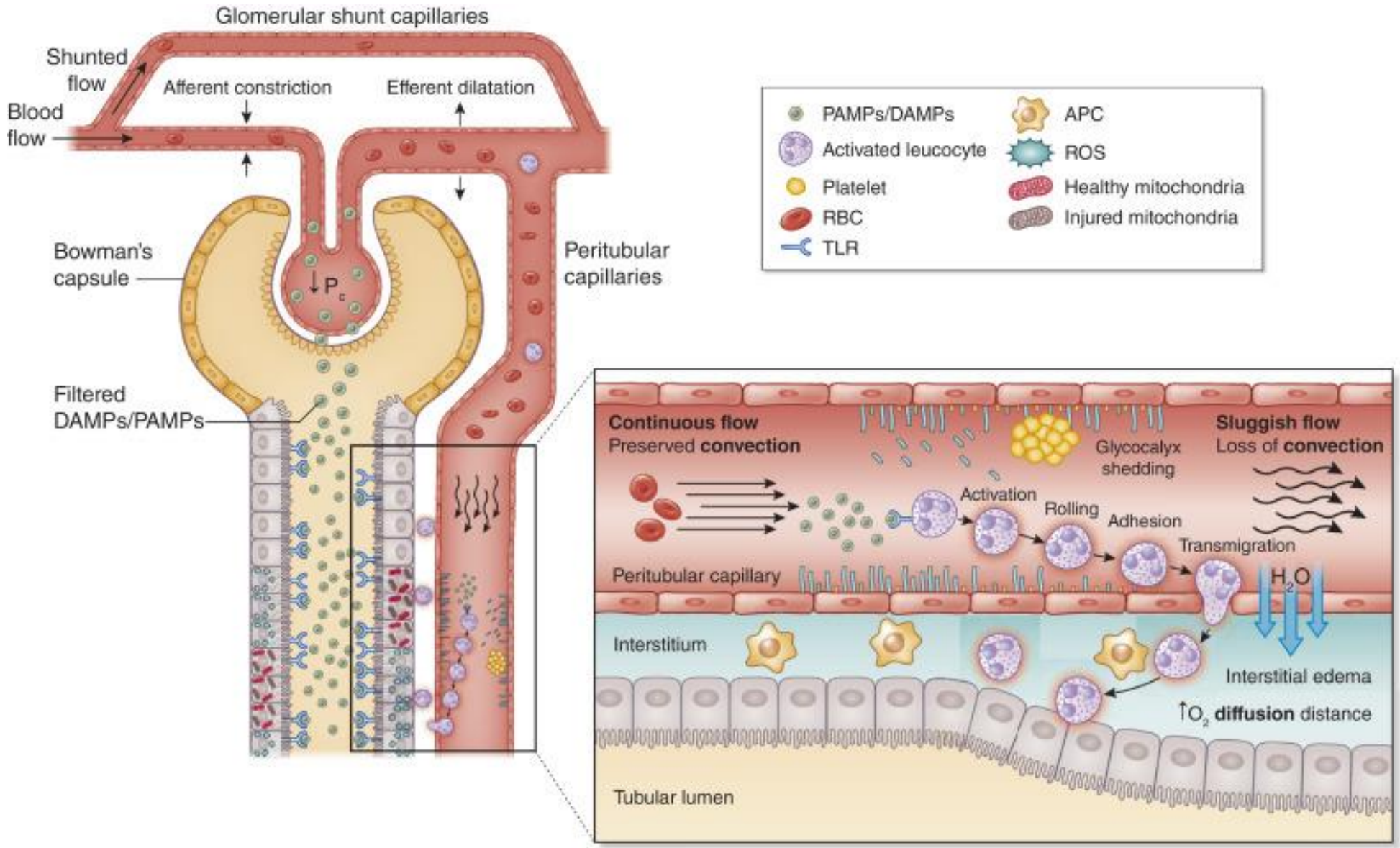


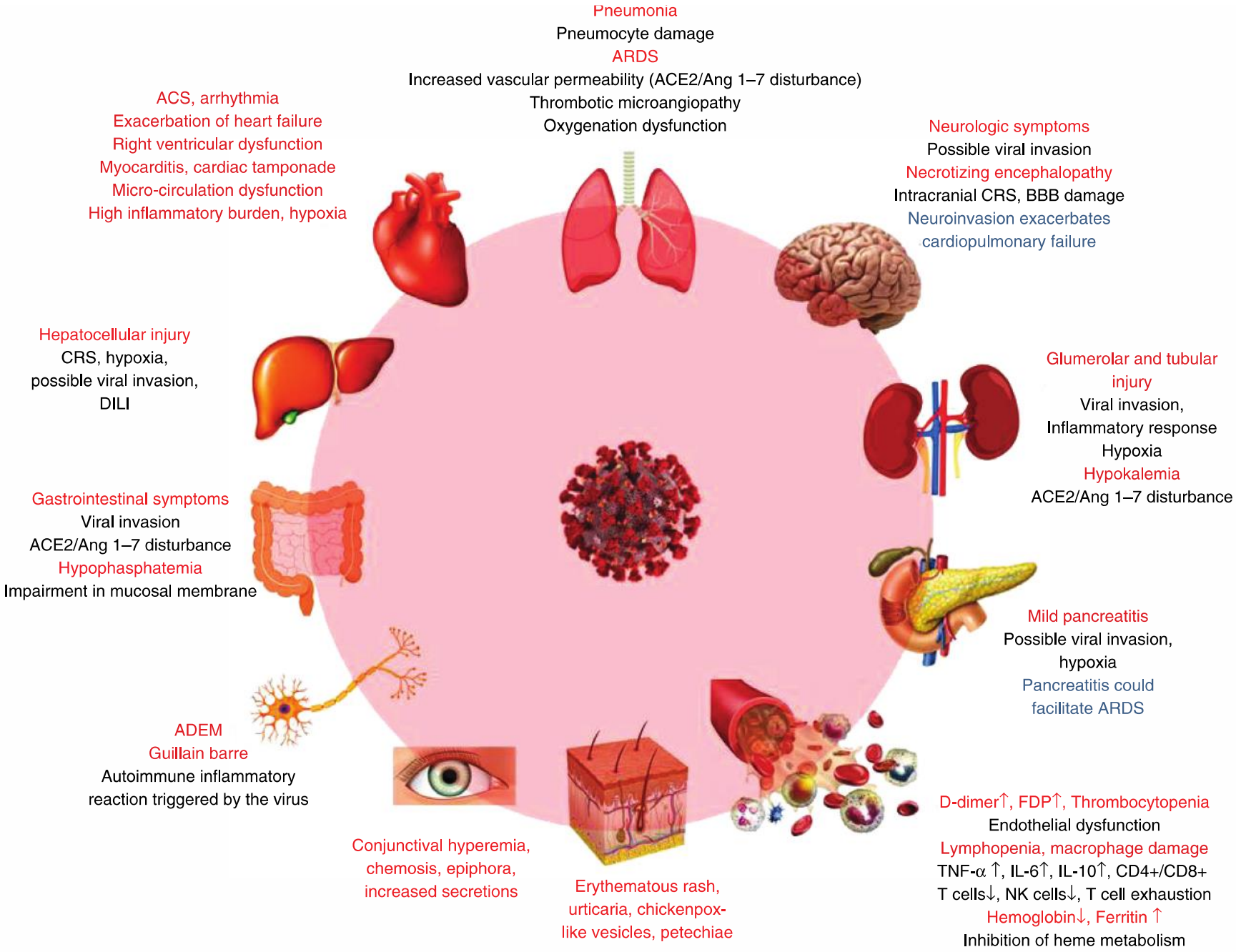


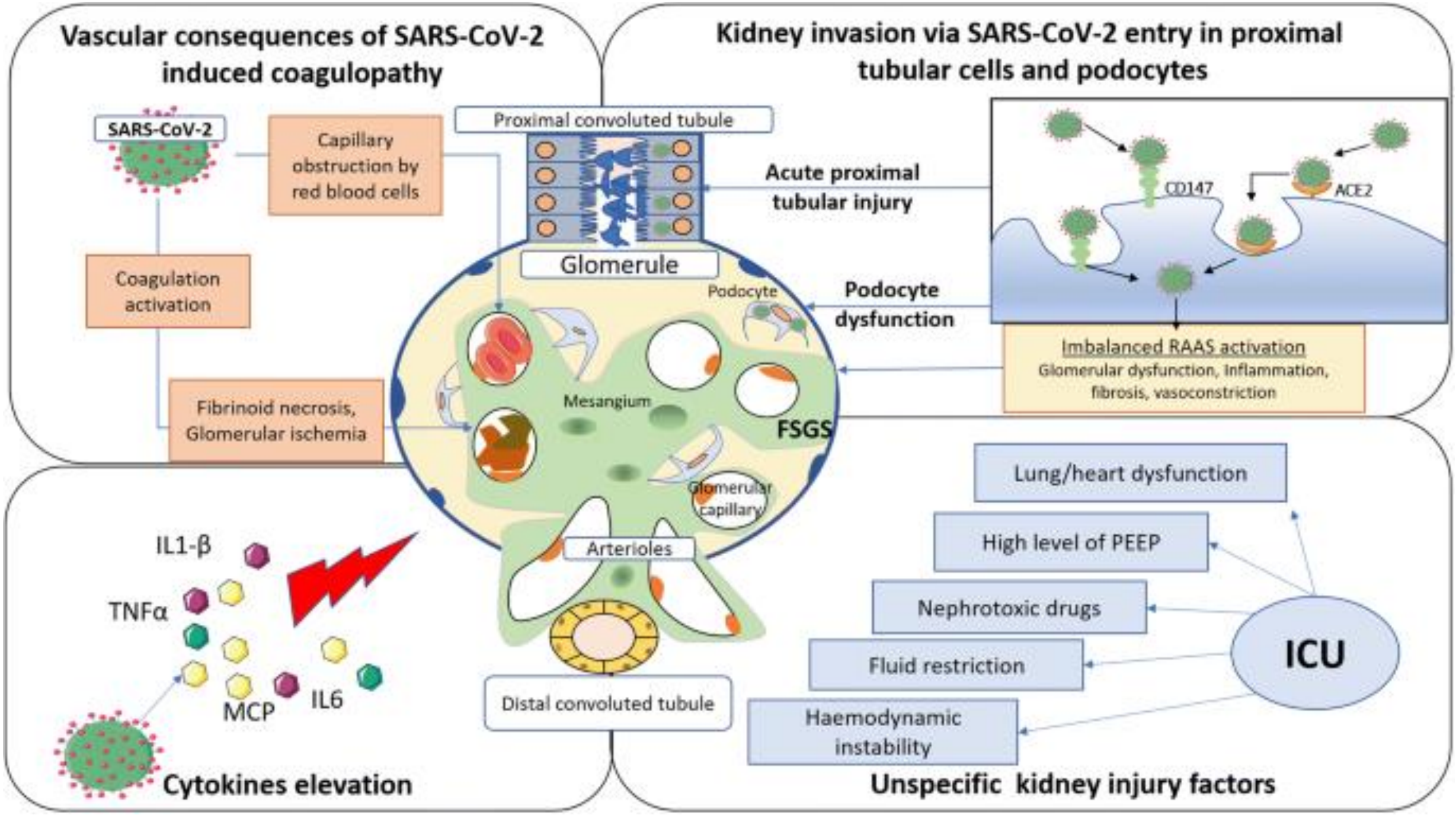

Innate immune system
Adaptive immune system
Early response
• Release of IL-1, IL-6, IL-8, IL-12, IL-18, TNF-α, IFN-γ
• Activation of complement, coagulation, phagocytes
Cellular immune response
• Activation of B cells, neutrophils, myeloid-derived supressor cells
Humoral immune response
• Production of Immunoglobulins (i.e. IgM, IgG)
Inflammatory response
TLR
PAMPs
Time
• Decrease of HLA-DR expression
• T- cell exhaustion
• Apoptosis of immune cells (i.e. lymphocytes, monocytes and antigen-presenting cells)
Recovery
Deterioration
Anti-inflammatory events
Immunoparalysis
Nosocomial infections
Viral reactivation
Endotoxin tolerance

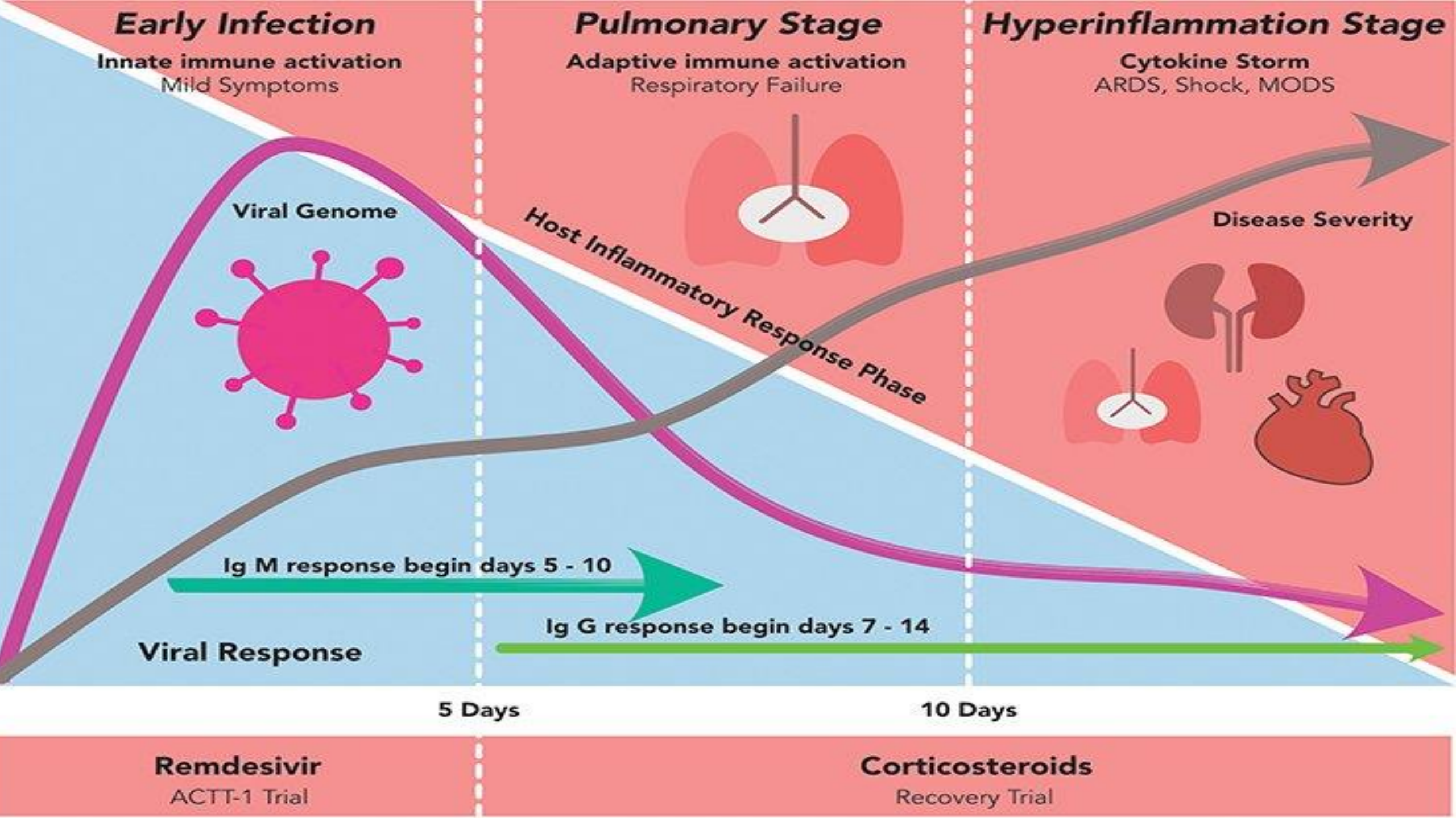

Infection leading to sepsis
Quantitative and qualitative alterations in antigen presentation, B, T, NK lymphocytes, activation of PD1
T cell counts and function
PD1
CD4+
CD8+
CD28
CD40L
CD4
CD8
NK
IFN-γ
Antigen presentation
MHCII
Th0
TCR
APC
Treg
B cell
Regulatory T cells
Low Ig levels
IgG
IgA
IgM
Defects in neutrophil mediated immunity
CNC
Immature neutrophils in non-survivors
Neutrophil adhesion
Neutrophil serine protease
Endothelial / Tissue damage
CTSG
MPO
AZU1
ELANE
Immunosuppressive hypercytokinemia
IL-10
Il-1RA
Proinflammatory hypercytokinemia
IL-6
IL-8
MCP-1
TNF-α
Complement consumption
C4
Factor B
C3
Defective bacterial killing / Persistence of NETs
Immuno-pathology
Viral reactivation
Virus
Poor control of infection
Bacteria

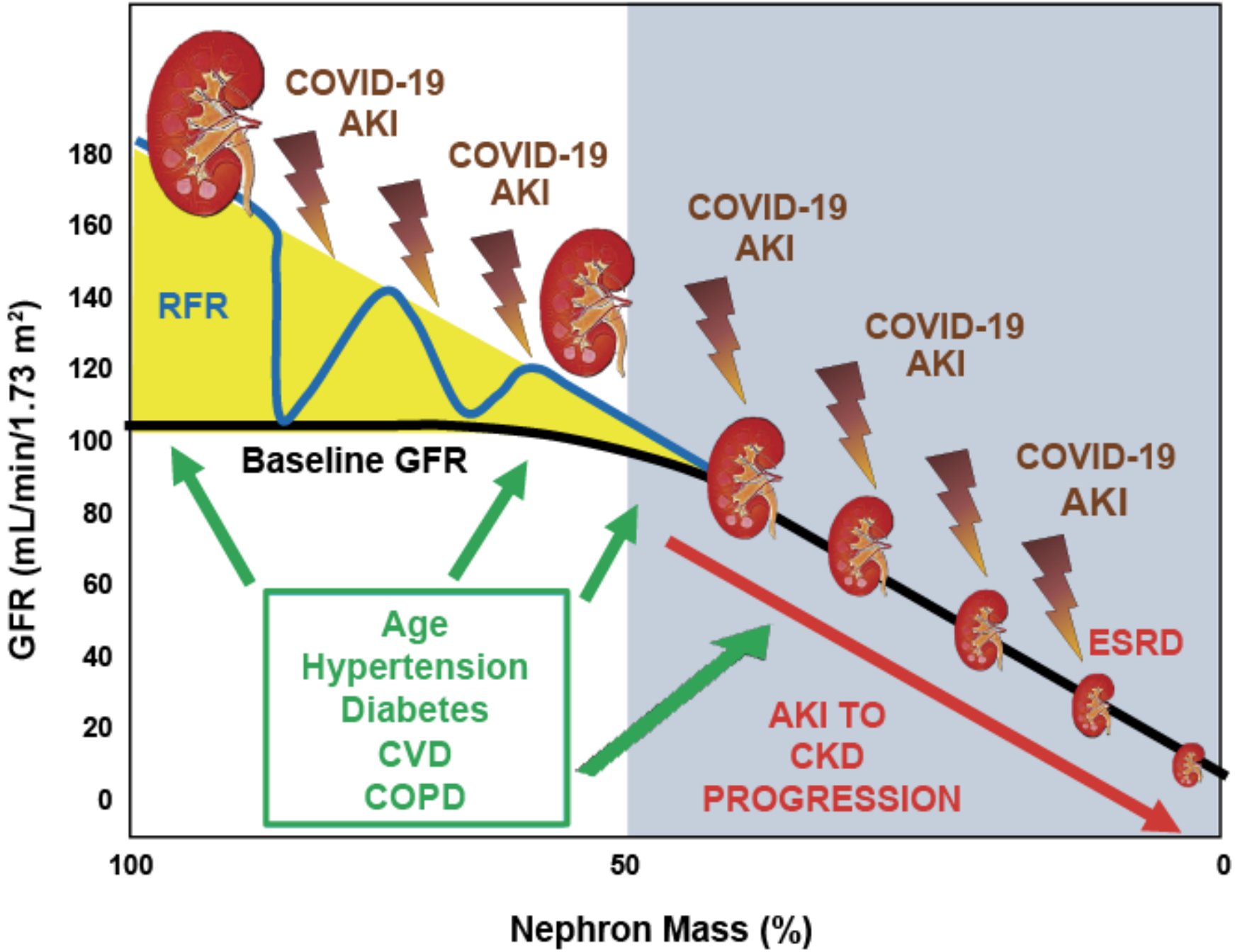
The net effect on the immunological phenotype
(hypo- vs. hyper-responsiveness)
remains highly individualized and
causes considerable diagnostic difficulties.


Glomerular shunt capillaries
Shunted flow
Blood flow
Afferent constriction
Efferent dilatation
Bowman's capsule
$\downarrow P_c$
Peritubular capillaries
Filtered DAMPs/PAMPs
PAMPs/DAMPs
Activated leucocyte
Platelet
RBC
TLR
APC
ROS
Healthy mitochondria
Injured mitochondria
Continuous flow
Preserved convection
Glycocalyx shedding
Sluggish flow
Loss of convection
Activation
Rolling
Adhesion
Transmigration
Peritubular capillary
H_2O
Interstitium
Interstitial edema
$\uparrow O_2$ diffusion distance
Tubular lumen


Pneumonia
Pneumocyte damage
ARDS
Increased vascular permeability (ACE2/Ang 1–7 disturbance)
Thrombotic microangiopathy
Oxygenation dysfunction
ACS, arrhythmia
Exacerbation of heart failure
Right ventricular dysfunction
Myocarditis, cardiac tamponade
Micro-circulation dysfunction
High inflammatory burden, hypoxia
Neurologic symptoms
Possible viral invasion
Necrotizing encephalopathy
Intracranial CRS, BBB damage
Neuroinvasion exacerbates
cardiopulmonary failure
Hepatocellular injury
CRS, hypoxia,
possible viral invasion,
DILI
Glumerolar and tubular
injury
Viral invasion,
Inflammatory response
Hypoxia
Hypokalemia
ACE2/Ang 1–7 disturbance
Gastrointestinal symptoms
Viral invasion
ACE2/Ang 1–7 disturbance
Hypophasphatemia
Impairment in mucosal membrane
Mild pancreatitis
Possible viral invasion,
hypoxia
Pancreatitis could
facilitate ARDS
ADEM
Guillain barre
Autoimmune inflammatory
reaction triggered by the virus
Conjunctival hyperemia,
chemosis, epiphora,
increased secretions
Erythematous rash,
urticaria, chickenpox-
like vesicles, petechiae
D-dimer↑, FDP↑, Thrombocytopenia
Endothelial dysfunction
Lymphopenia, macrophage damage
TNF-α ↑, IL-6↑, IL-10↑, CD4+/CD8+
T cells↓, NK cells↓, T cell exhaustion
Hemoglobin↓, Ferritin ↑
Inhibition of heme metabolism


Vascular consequences of SARS-CoV-2 induced coagulopathy
SARS-CoV-2
Capillary obstruction by red blood cells
Coagulation activation
Fibrinoid necrosis, Glomerular ischemia
Proximal convoluted tubule
Glomerule
Podocyte
Mesangium
FSGS
Glomerular capillary
Arterioles
Distal convoluted tubule
Kidney invasion via SARS-CoV-2 entry in proximal tubular cells and podocytes
Acute proximal tubular injury
Podocyte dysfunction
CD147
ACE2
Imbalanced RAAS activation
Glomerular dysfunction, Inflammation, fibrosis, vasoconstriction
IL1-β
TNFα
MCP
IL6
Cytokines elevation
Lung/heart dysfunction
High level of PEEP
Nephrotoxic drugs
Fluid restriction
Haemodynamic instability
ICU
Unspecific kidney injury factors

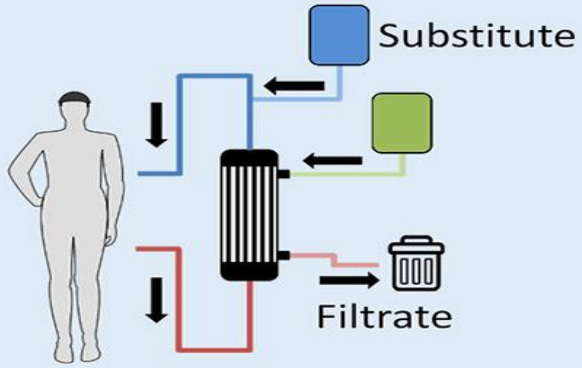

Early Infection
Innate immune activation
Mild Symptoms
Pulmonary Stage
Adaptive immune activation
Respiratory Failure
Hyperinflammation Stage
Cytokine Storm
ARDS, Shock, MODS
Viral Genome
Host Inflammatory Response Phase
Disease Severity
Ig M response begin days 5 - 10
Ig G response begin days 7 - 14
Viral Response
5 Days
10 Days
Remdesivir
ACTT-1 Trial
Corticosteroids
Recovery Trial

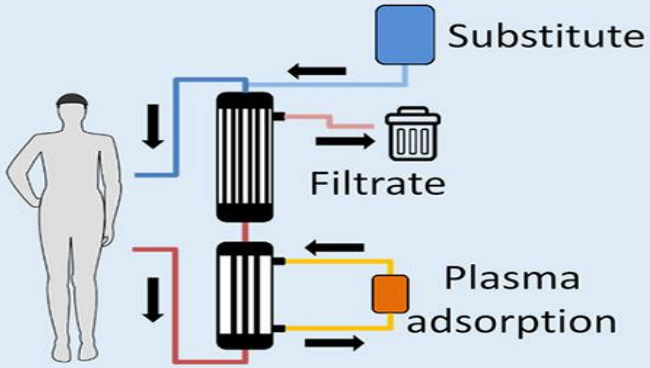

COVID-19
AKI
COVID-19
AKI
COVID-19
AKI
COVID-19
AKI
COVID-19
AKI
ESRD
RFR
Baseline GFR
Age
Hypertension
Diabetes
CVD
COPD
AKI TO
CKD
PROGRESSION
GFR (mL/min/1.73 m²)
180
160
140
120
100
80
60
40
20
0
100
50
0
Nephron Mass (%)

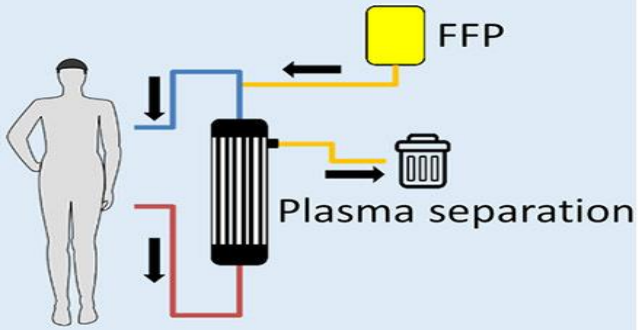
Extra-Corporeal Blood Purification

Extracorporeal blood purification techniques (BPTs) consist of different approaches and methods, most of which have *their origin* in renal replacement therapy (RRT).

Extracorporeal Blood Purification







Convection Therapies

- Continuous Renal Replacement Therapy (CRRT)
- High Volume Hemofiltration (HVHF)
- High Cut-Off Membranes (HCO)

Adsorption Therapies

- Immobilized Polymyxin B (PMX)
- Hemoadsorption (e.g. CytoSorb)

Combination Therapies

- Coupled Plasma Filtration Adsorption (CPFA)
- Combined filtration and Adsorption (e.g. oXiris)

Other Therapies

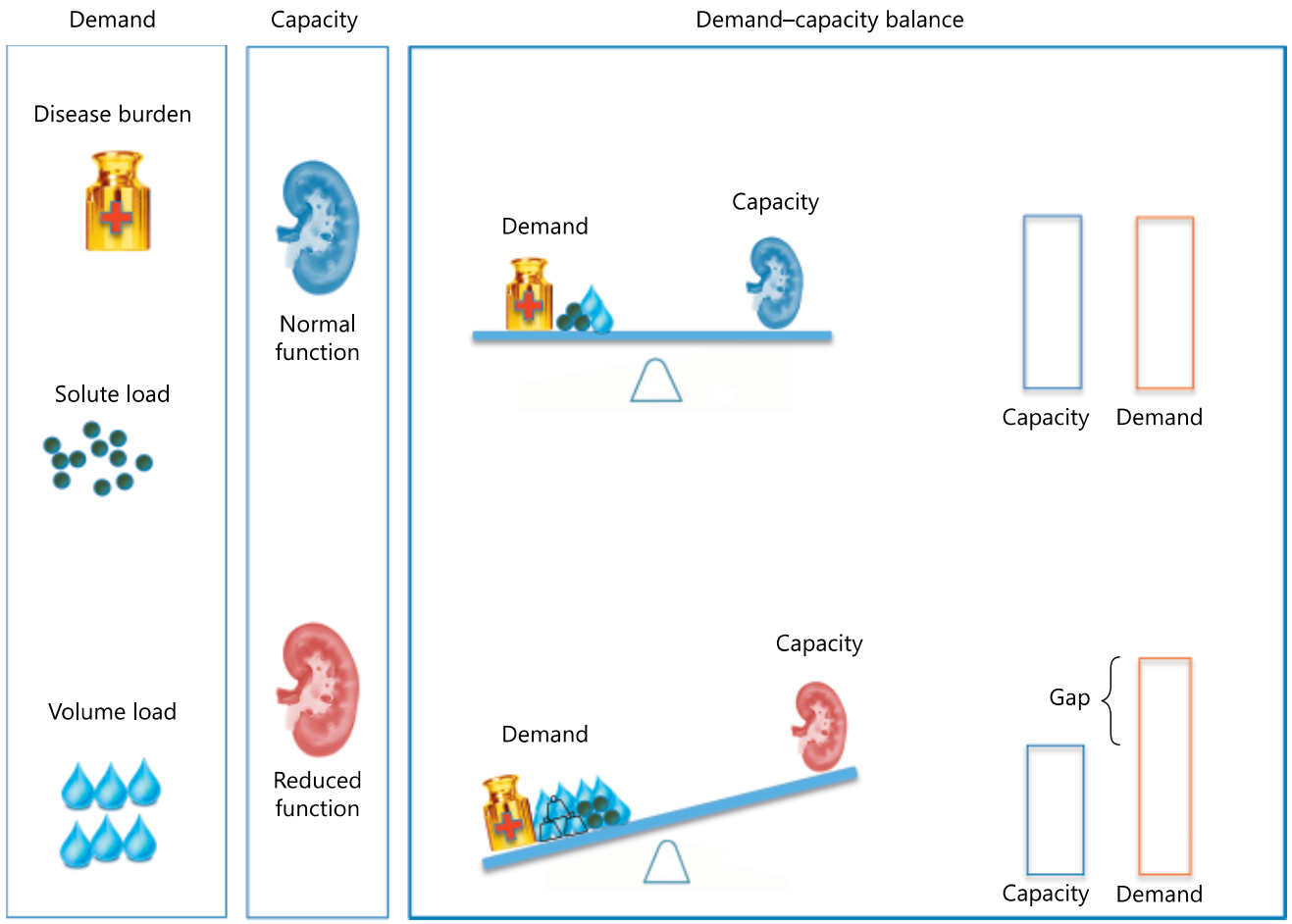
- Plasma Exchange
- Renal Assist Device (RAD)
- Selective Cytapheretic Device (SCD)

Modality

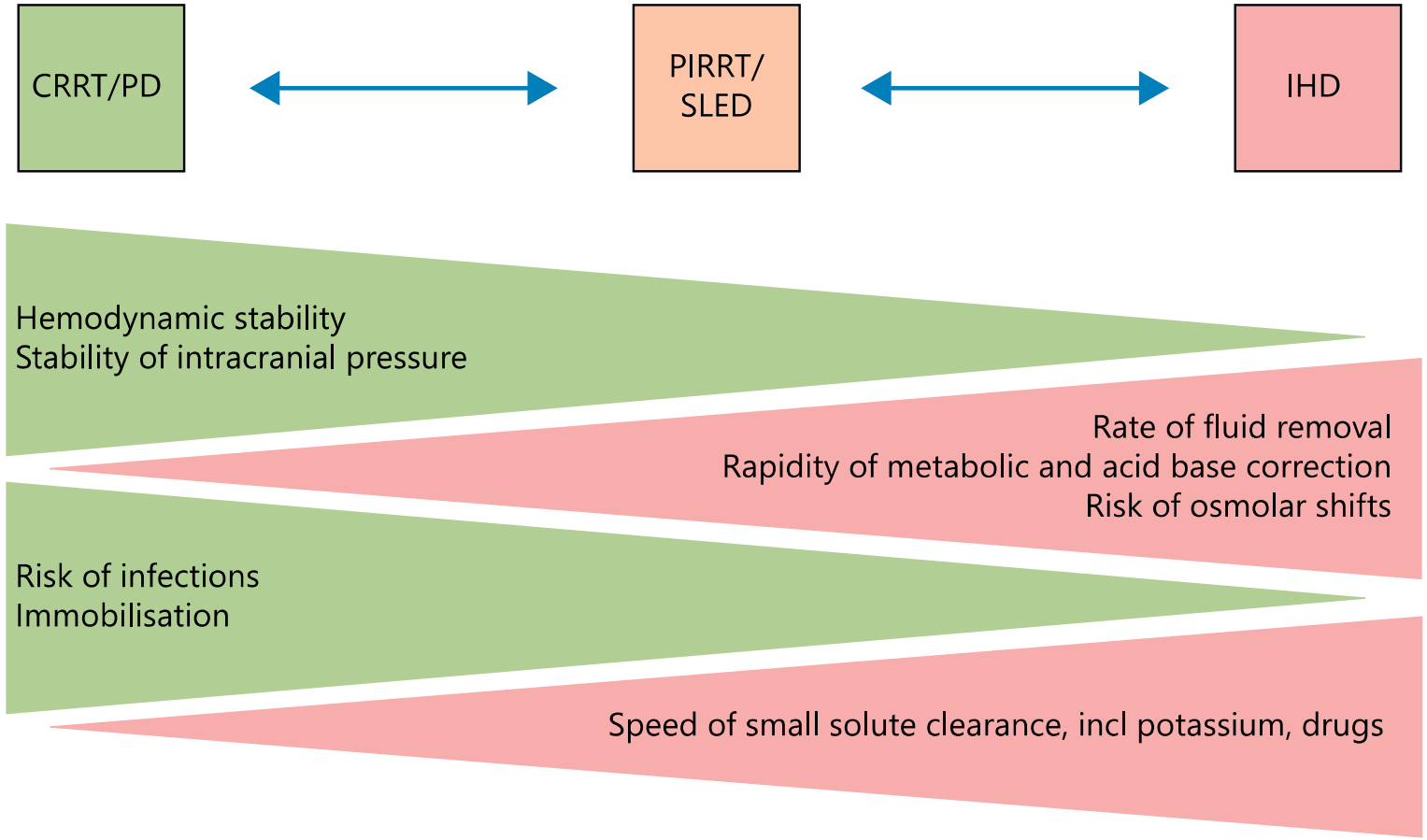
Modality	Advantages in COVID-19 AKI	Disadvantages in COVID-19 AKI
IHD	Widely available Allows treatment of several patients with the same machine in a given day Higher blood flow may reduce risk of clotting	Less effective in reaching daily fluid balance goals Can lead to or exacerbate haemodynamic instability Usually requires a dedicated HD nurse or other staff in addition to an ICU nurse (increasing staff exposure to the isolation environment)
PIRRT: IHD or CRRT	Less likely than other modalities to exacerbate haemodynamic instability Allows treatment of several patients with the same machine in a given day Option for higher blood flow, which may reduce risk of circuit clotting	Not as widely available as other modalities (i.e. hospital protocols are not widely established) Given the procoagulant nature of COVID-19, systemic anticoagulation may be necessary Challenges and uncertainty of drug dosing, especially for antimicrobial and/or COVID-19 therapeutics
CRRT	Achieves steady-state control of small solutes and acid-base status Least likely to exacerbate haemodynamic instability Easy to achieve net negative fluid balance and achieve fluid balance targets with greater haemodynamic stability Can often be performed by the patient's bedside in the ICU, limiting staff contact with the isolation environment	Not as widely available as other modalities outside of resource-rich settings or tertiary centres Requires one machine per patient per day Requires ICU settings and may require 1:1 nursing ratio depending on institutional policies Given the procoagulable nature of COVID-19, anticoagulation is recommended and may require systemic therapeutic anticoagulation Increased frequency circuit clotting may lead to a lower delivered dose, inability to achieve fluid balance targets and increased resource utilization (which may have supply chain impacts)
PD	Widely available No circuit clotting concerns No venous access required Less likely to exacerbate haemodynamic instability Less nursing exposure with the use of automated cycler	May be more challenging in patients in prone positions Risk of peri-catheter leaks Protocols and policies for acute PD are not available at all sites. Requires technical expertise to place catheters May require rapid implementation of training regimen for renal nurses and clinicians

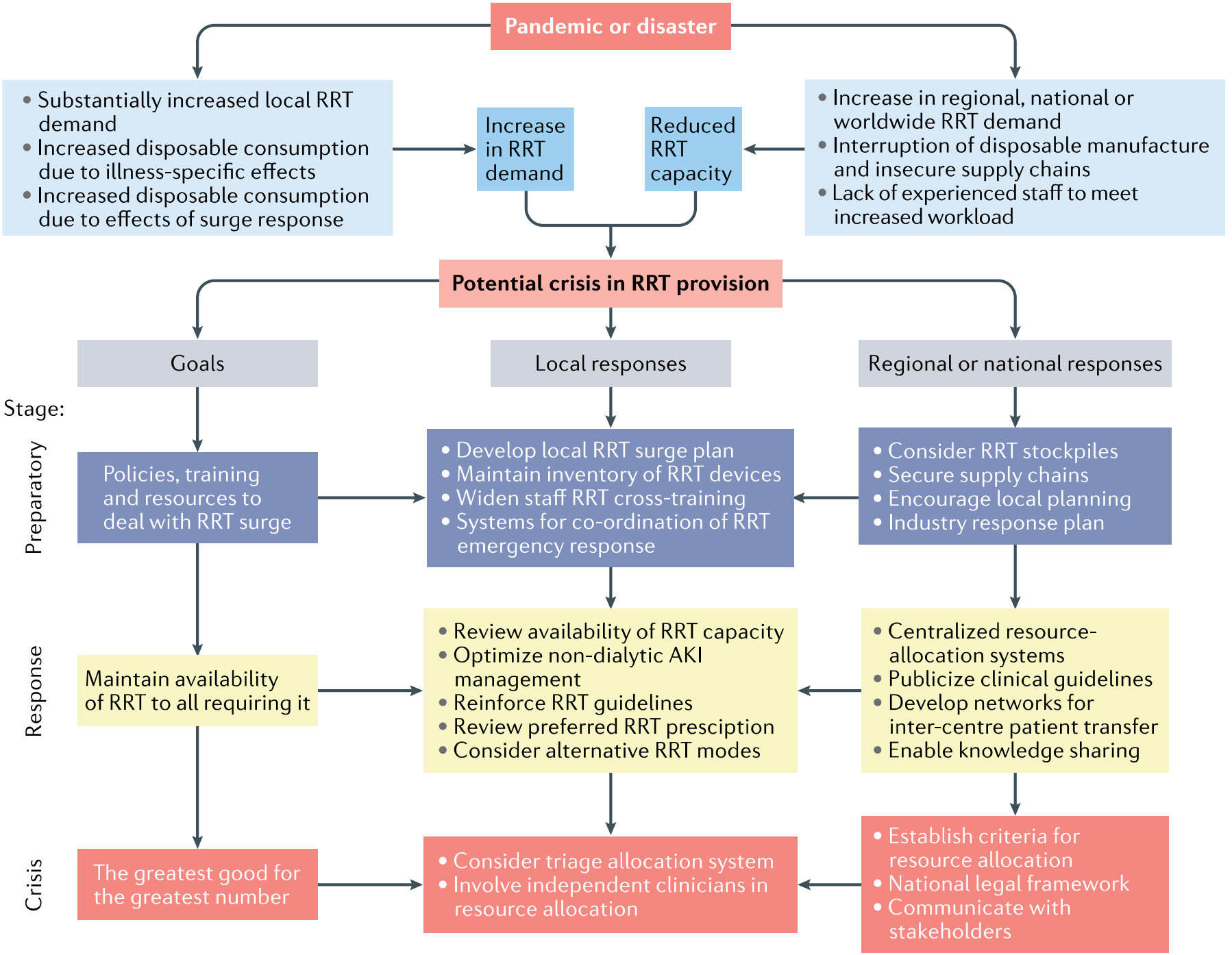
Demand and capacity

"a conceptual model"



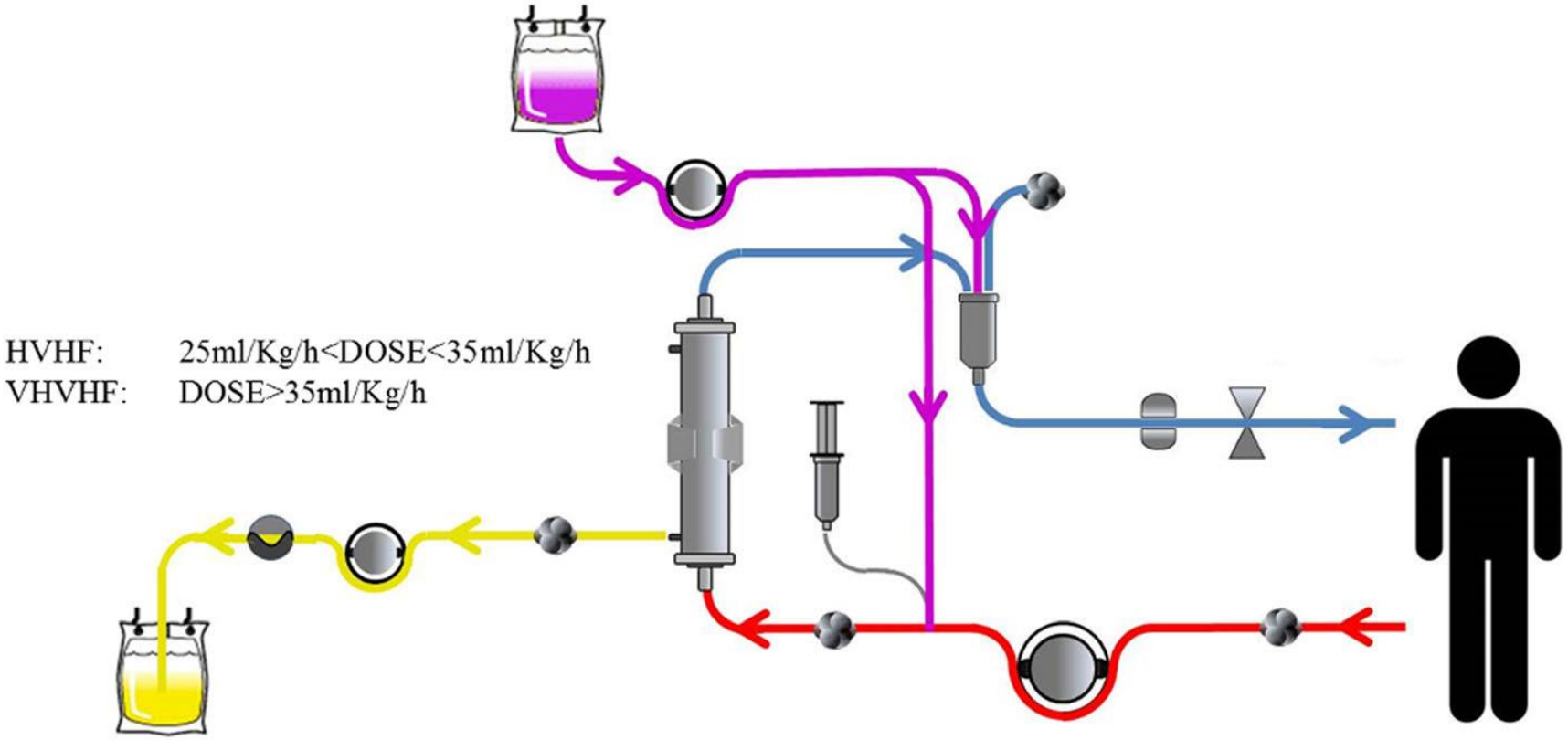
Different RRT Modalities



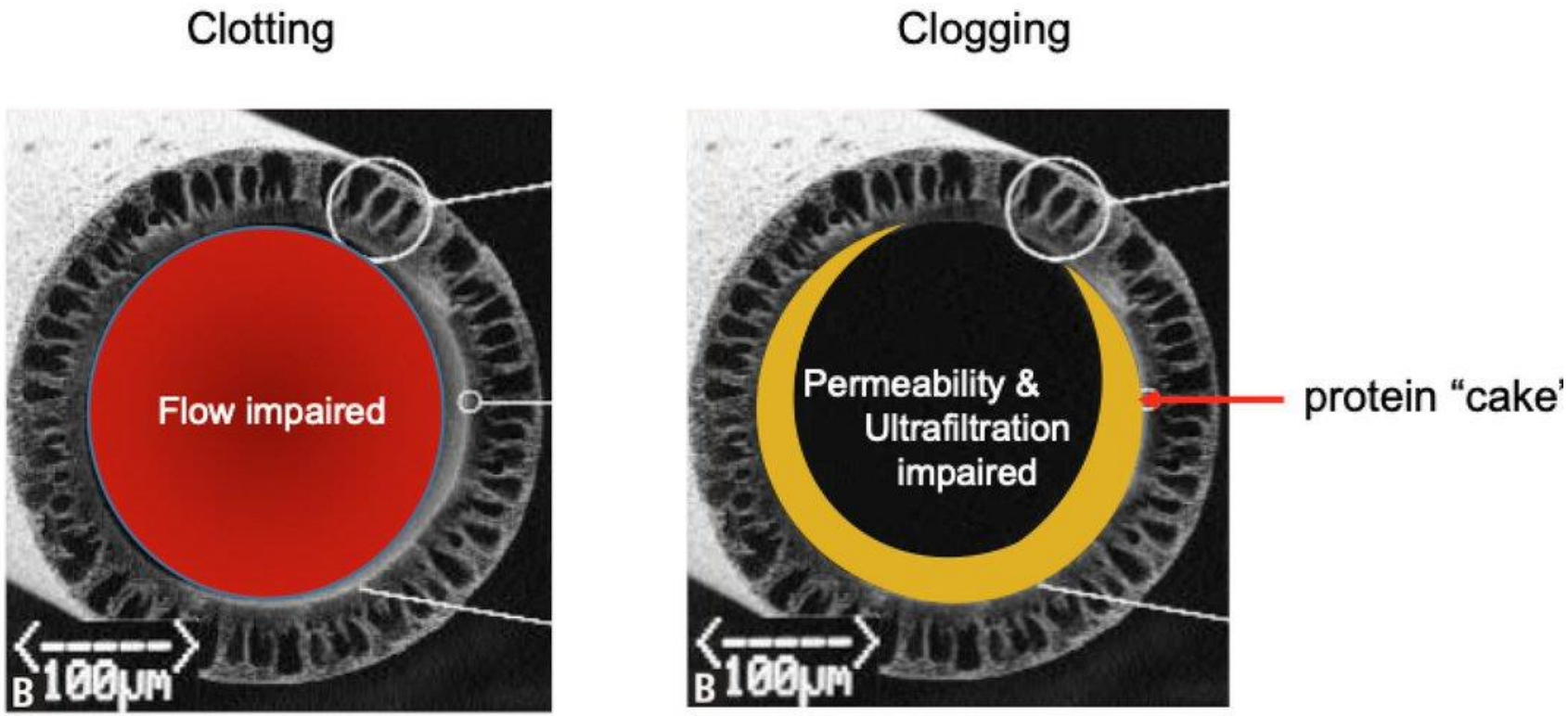

Pandemic or disaster
• Substantially increased local RRT demand
• Increased disposable consumption due to illness-specific effects
• Increased disposable consumption due to effects of surge response
Increase in RRT demand
Reduced RRT capacity
• Increase in regional, national or worldwide RRT demand
• Interruption of disposable manufacture and insecure supply chains
• Lack of experienced staff to meet increased workload
Potential crisis in RRT provision
Goals
Local responses
Regional or national responses
Stage:
Preparatory
Policies, training and resources to deal with RRT surge
• Develop local RRT surge plan
• Maintain inventory of RRT devices
• Widen staff RRT cross-training
• Systems for co-ordination of RRT emergency response
• Consider RRT stockpiles
• Secure supply chains
• Encourage local planning
• Industry response plan
Response
Maintain availability of RRT to all requiring it
• Review availability of RRT capacity
• Optimize non-dialytic AKI management
• Reinforce RRT guidelines
• Review preferred RRT presciption
• Consider alternative RRT modes
• Centralized resource-allocation systems
• Publicize clinical guidelines
• Develop networks for inter-centre patient transfer
• Enable knowledge sharing
Crisis
The greatest good for the greatest number
• Consider triage allocation system
• Involve independent clinicians in resource allocation
• Establish criteria for resource allocation
• National legal framework
• Communicate with stakeholders

Aggressive medical management of electrolyte and acid-base disturbances or fluid overload might *negate the need for RRT or forestall RRT initiation*, thereby enabling improved allocation of finite RRT resources

HVHF/VHVHF/PHVHF

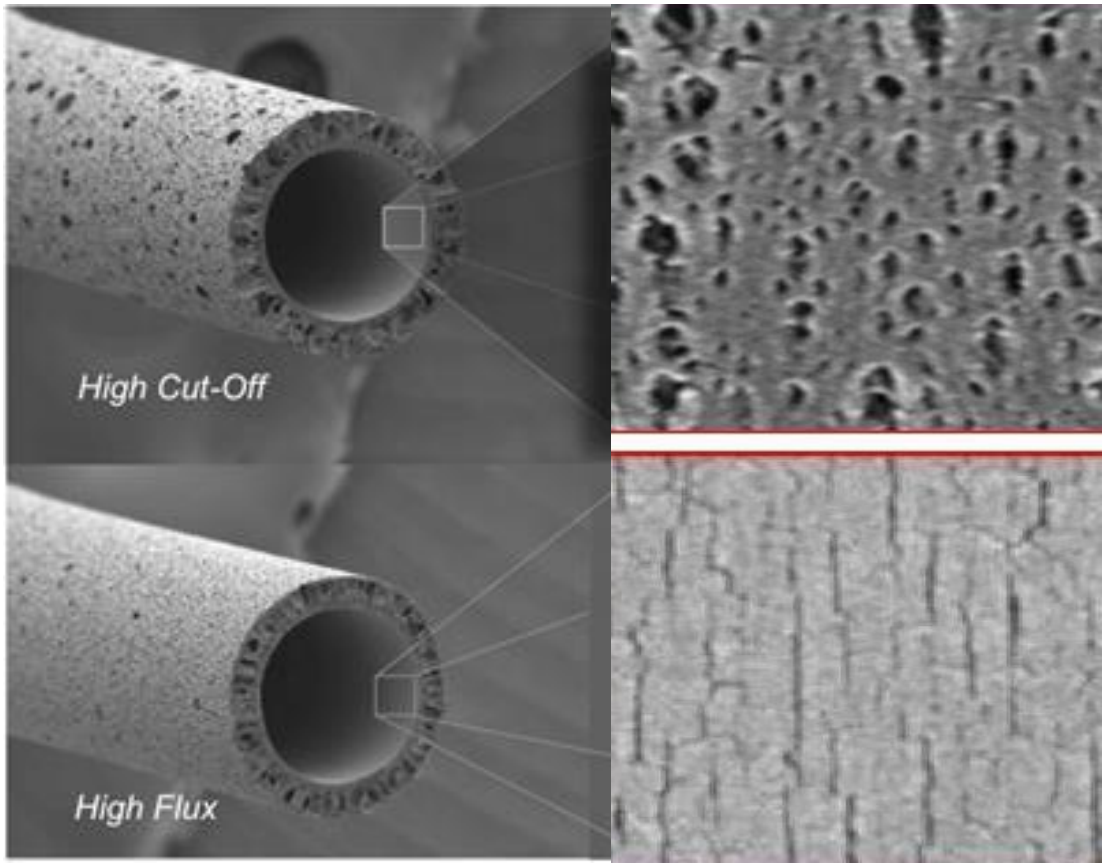


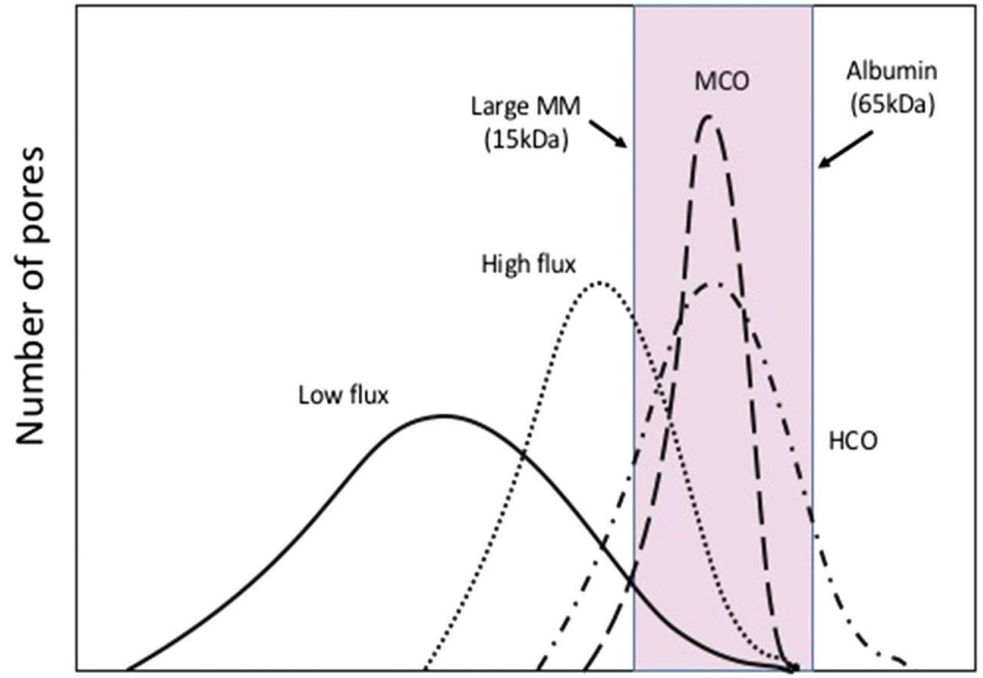
Clotting *vs* Clogging

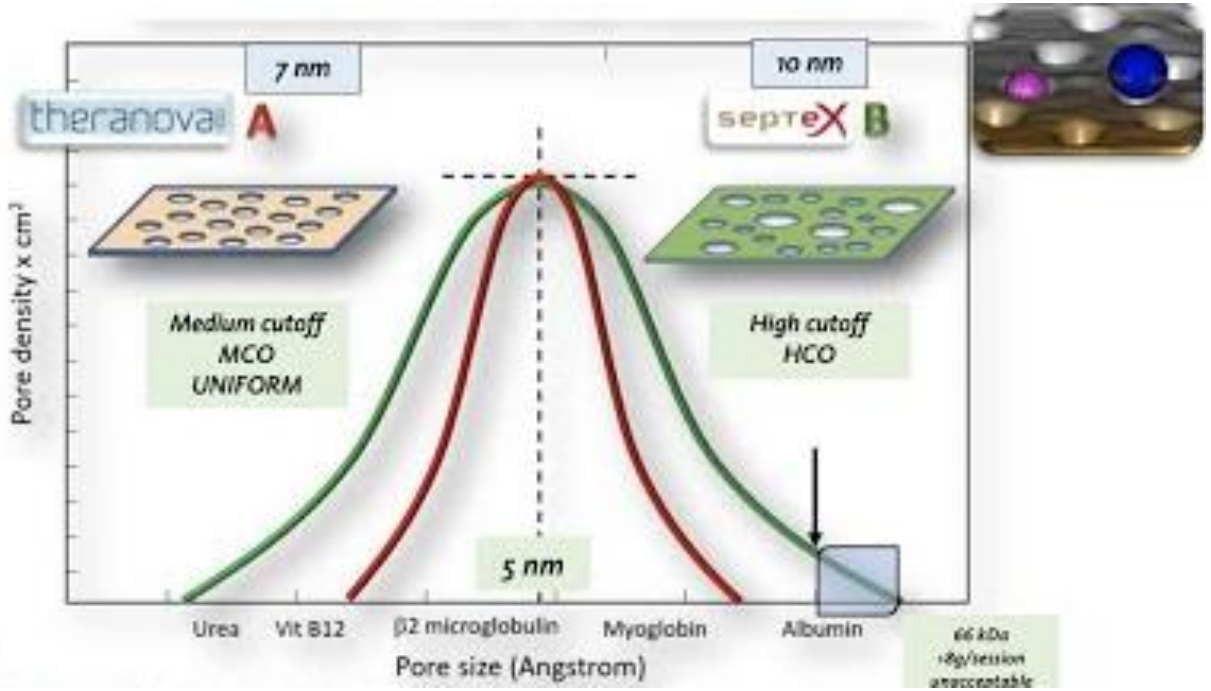


High prevalence of clogging and clotting in COVID-19

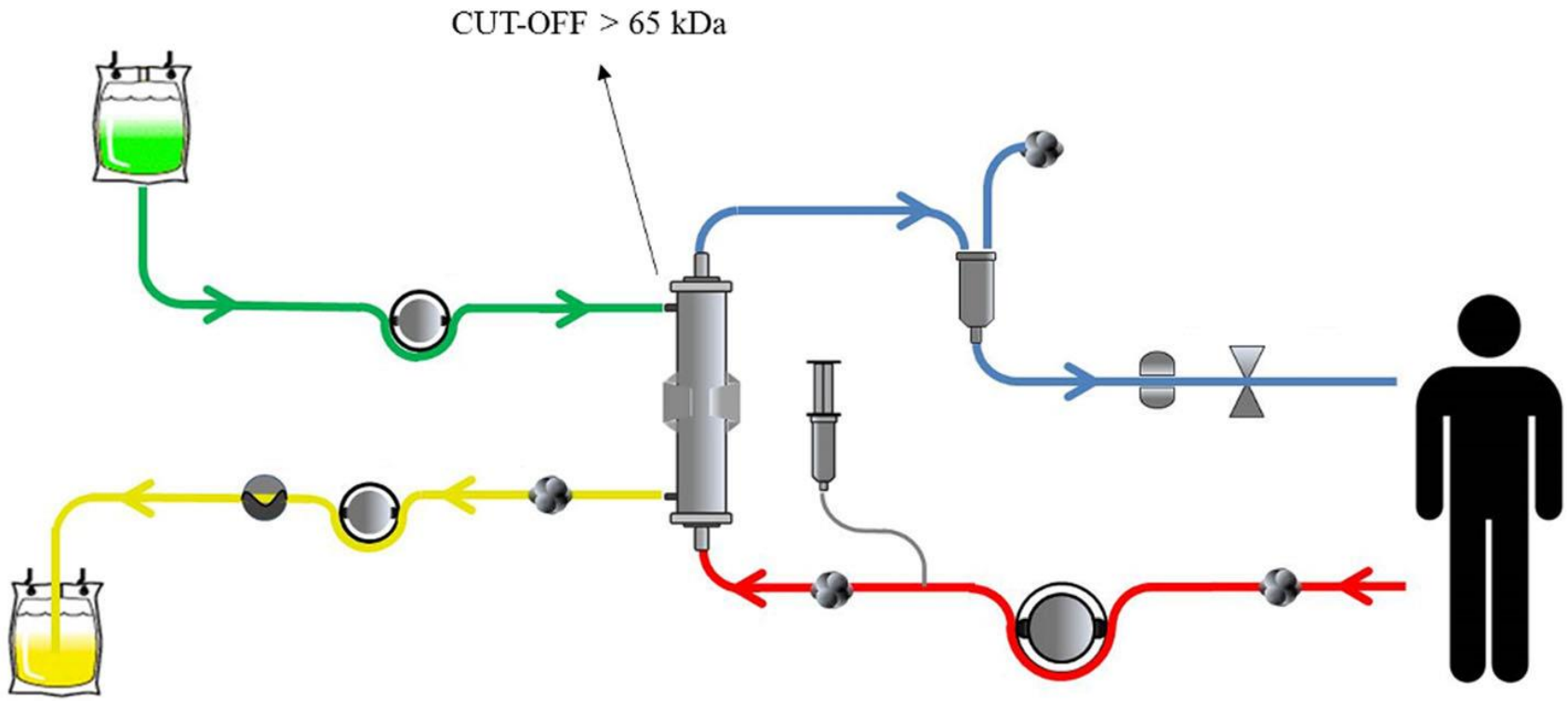
High Flux vs HCOM



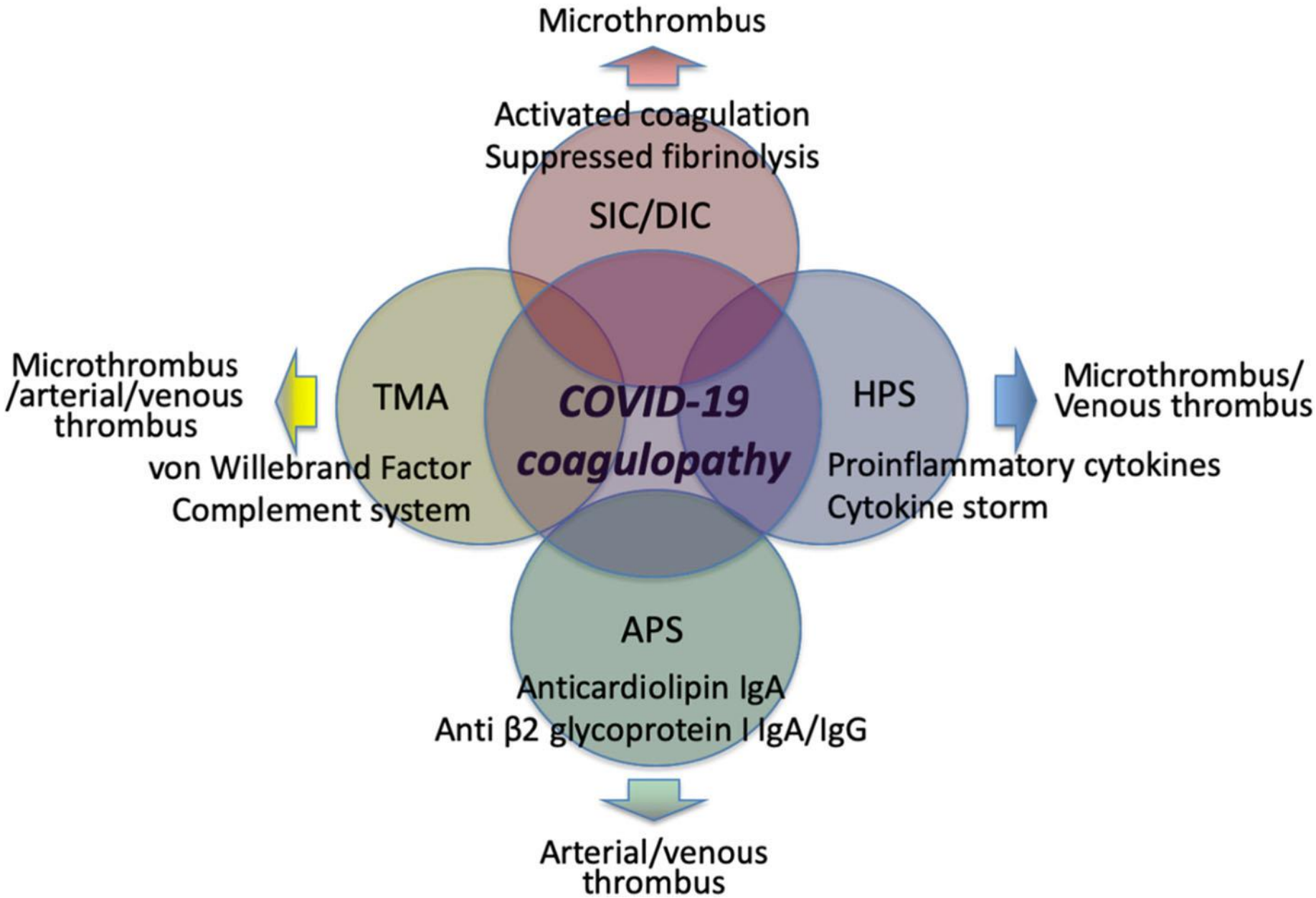


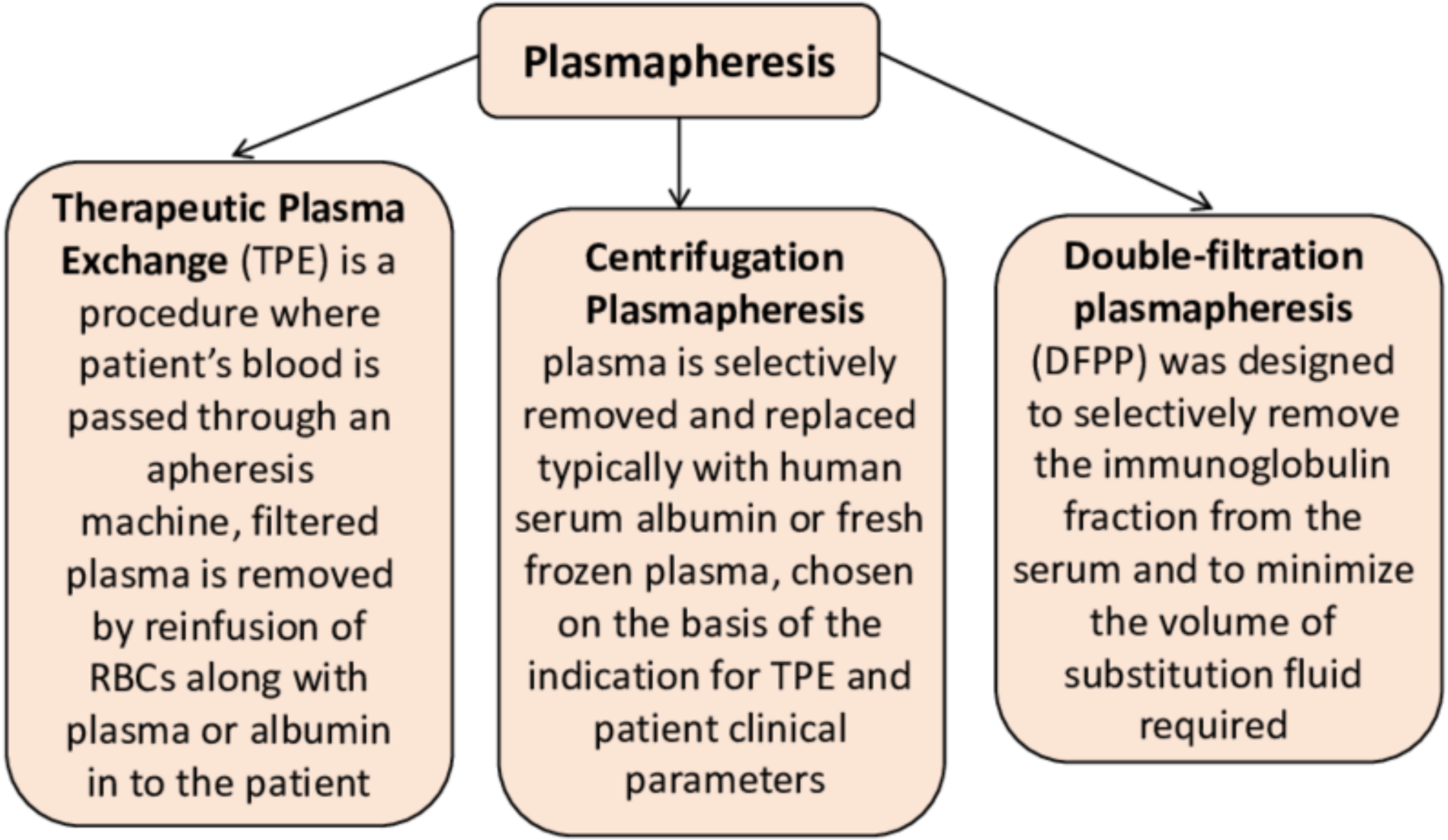


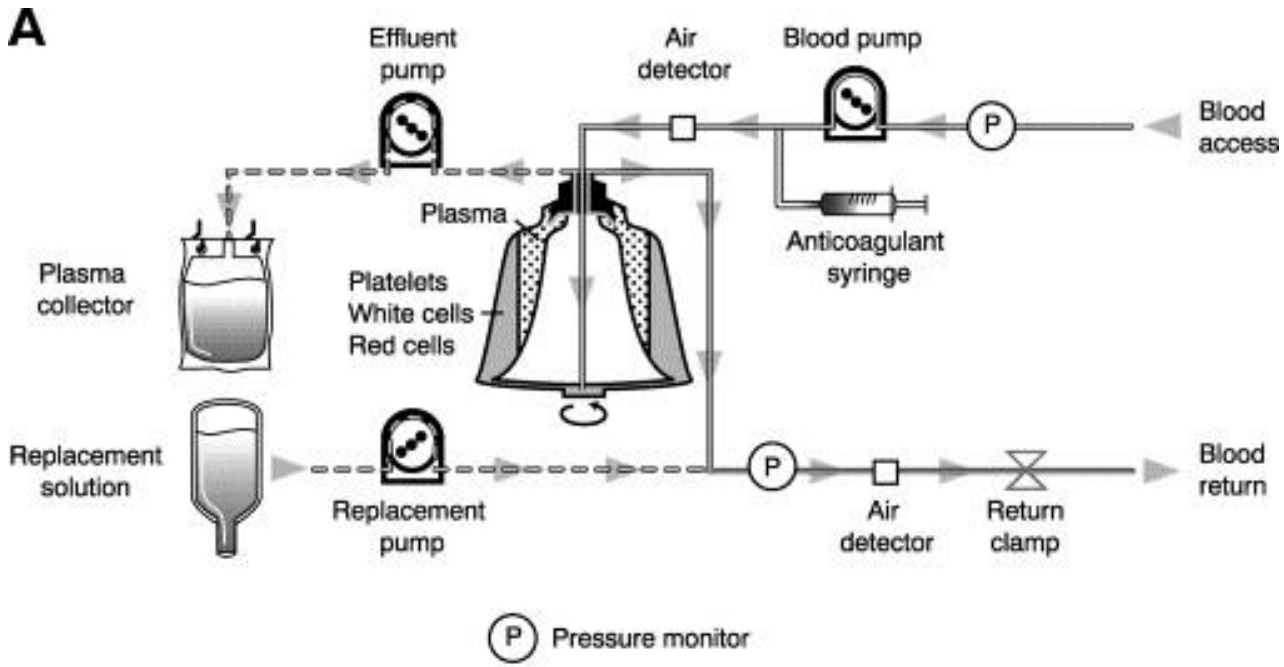
HCOM



Plasmapheresis


Microthrombus
Activated coagulation
Suppressed fibrinolysis
SIC/DIC
Microthrombus
/arterial/venous
thrombus
TMA
von Willebrand Factor
Complement system
COVID-19
coagulopathy
HPS
Proinflammatory cytokines
Cytokine storm
Microthrombus/
Venous thrombus
APS
Anticardiolipin IgA
Anti β2 glycoprotein I IgA/IgG
Arterial/venous
thrombus


Plasmapheresis
Therapeutic Plasma Exchange (TPE) is a procedure where patient's blood is passed through an apheresis machine, filtered plasma is removed by reinfusion of RBCs along with plasma or albumin in to the patient
Centrifugation Plasmapheresis plasma is selectively removed and replaced typically with human serum albumin or fresh frozen plasma, chosen on the basis of the indication for TPE and patient clinical parameters
Double-filtration plasmapheresis (DFPP) was designed to selectively remove the immunoglobulin fraction from the serum and to minimize the volume of substitution fluid required



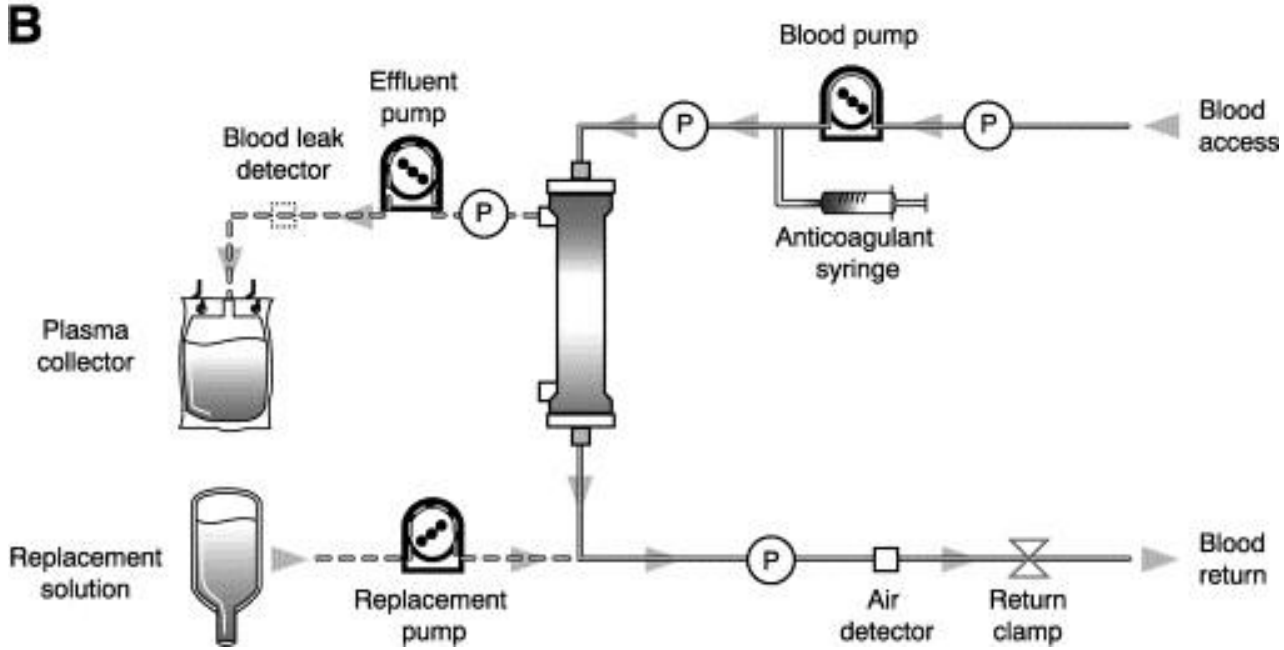
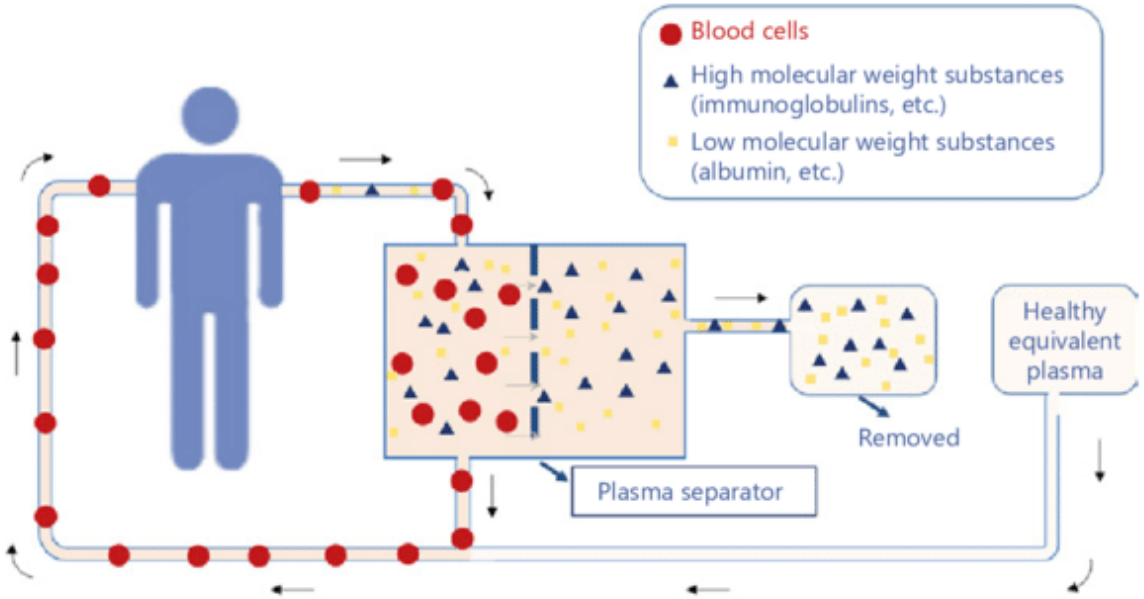


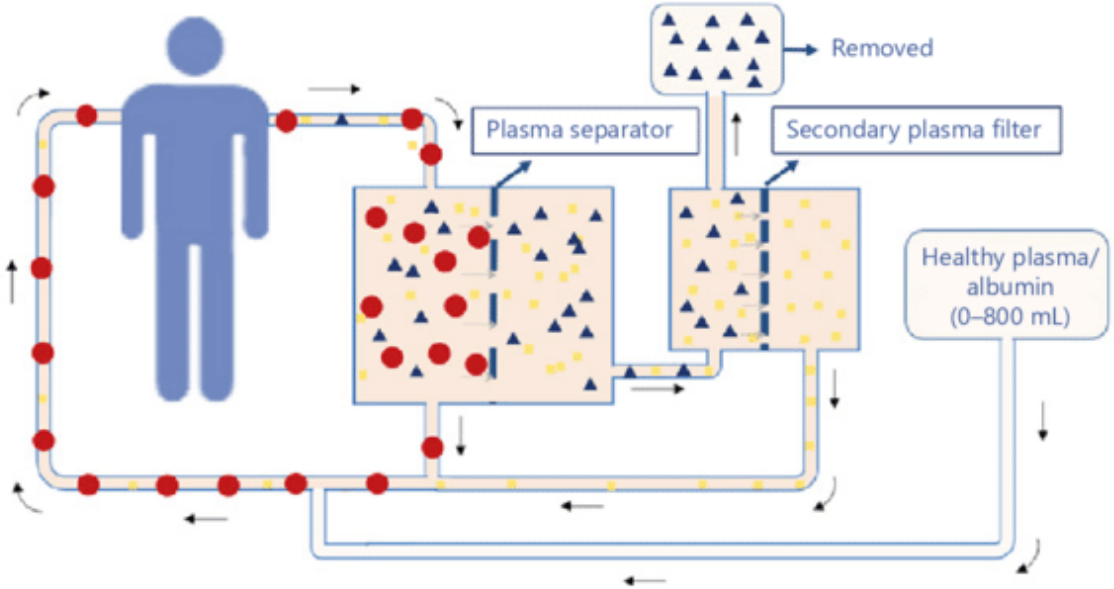
Table 2. Operational contrasts between centrifuge and membrane apheresis procedures

Characteristic	Centrifuge Therapeutic Plasma Exchange	Membrane Therapeutic Plasma Exchange
Mechanism	Centrifugal force	Capillary membrane filter
Blood flow (ml/min)	10–150	150
Plasma extraction (%)	80	30
Plasma removal (ml/min)	Variable	30
Anticoagulation	Citrate	Heparin
Separation	Specific gravity	Size
Blood volume in circuit (ml)	Approximately 180	125
Molecular weight cutoff (D)	N/A	3 million
Sterilization	γ Irradiation or ethylene oxide	Ethylene oxide
Fluid replacement	Albumin, fresh frozen plasma	Albumin, fresh frozen plasma

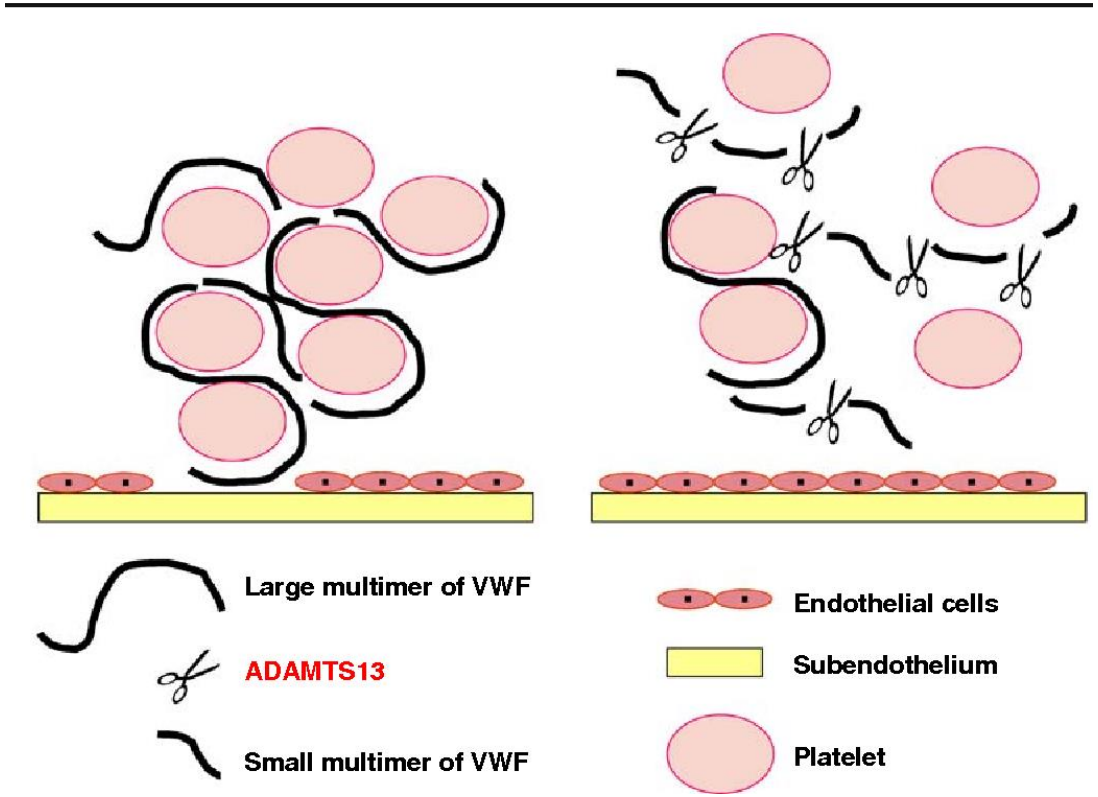
N/A, not applicable.

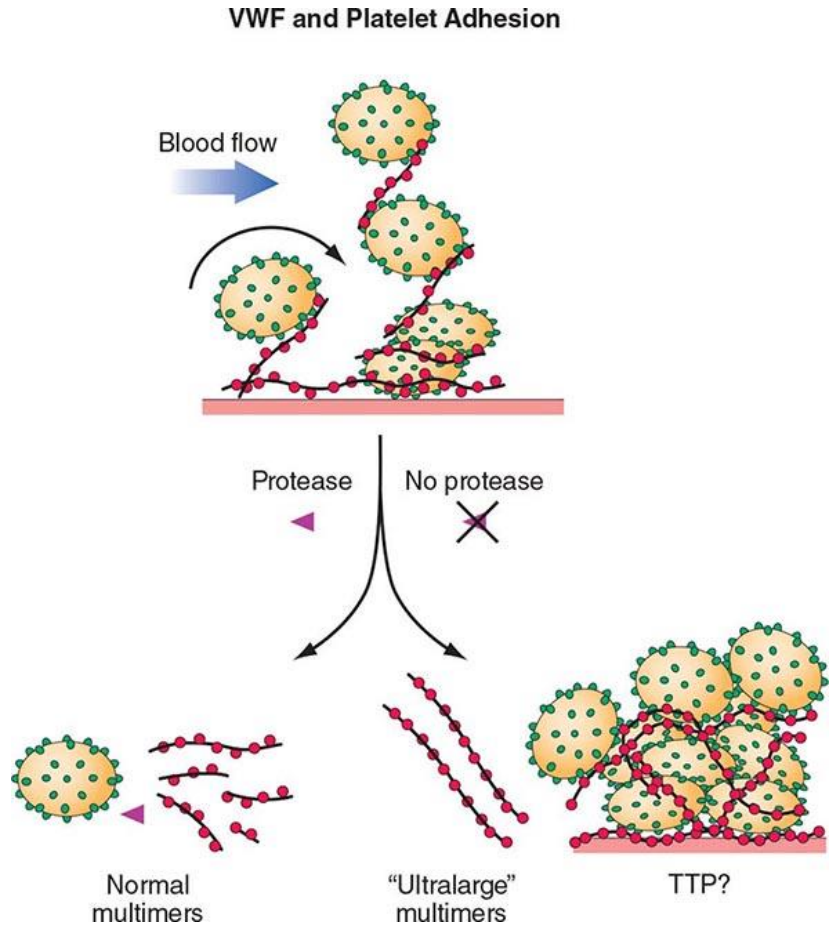

Blood cells
High molecular weight substances (immunoglobulins, etc.)
Low molecular weight substances (albumin, etc.)
Healthy equivalent plasma
Removed
Plasma separator

TPE

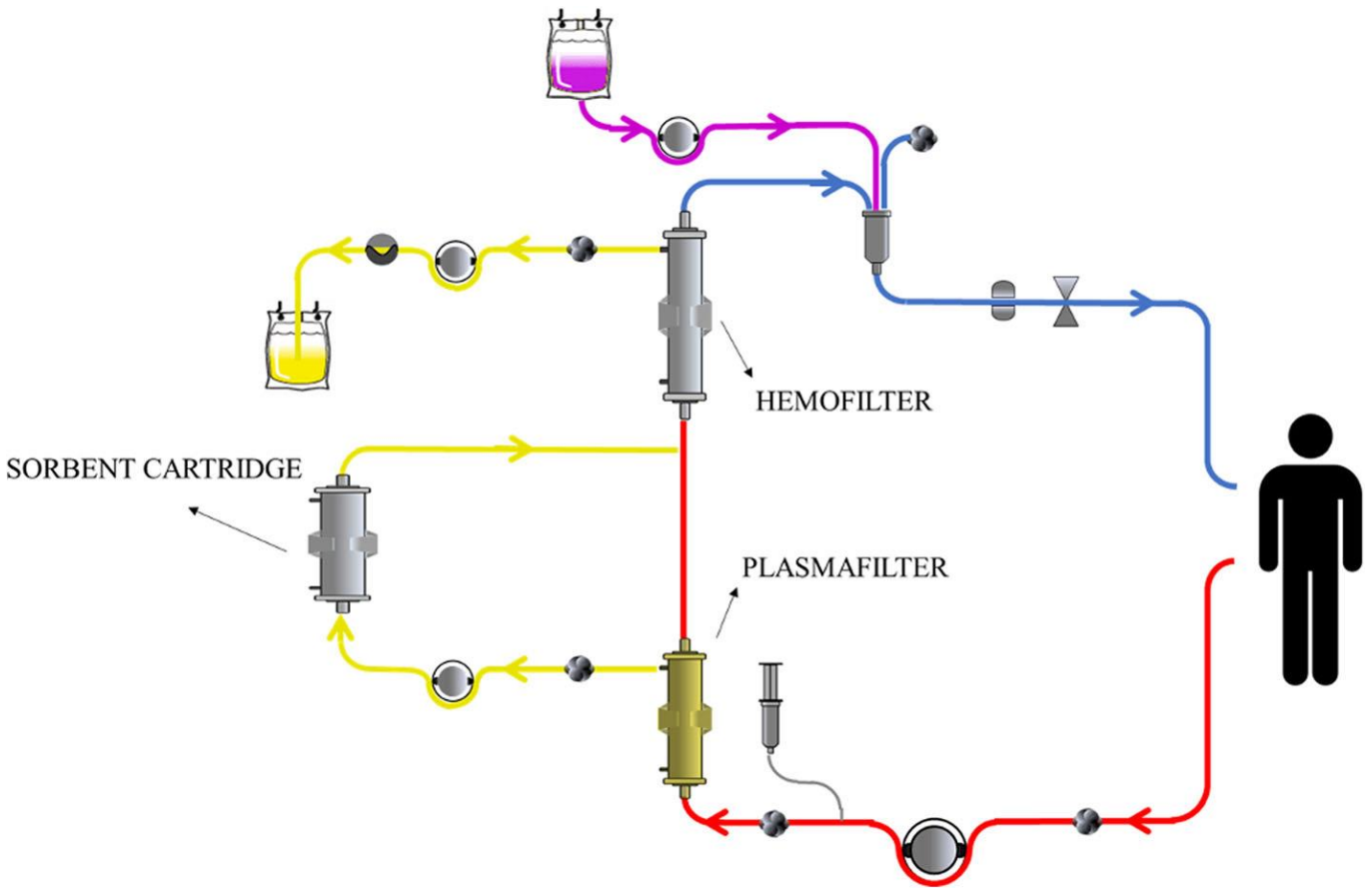

Removed
Plasma separator
Secondary plasma filter
Healthy plasma/ albumin (0–800 mL)

DFPP


Large multimer of VWF
ADAMTS13
Small multimer of VWF
Endothelial cells
Subendothelium
Platelet

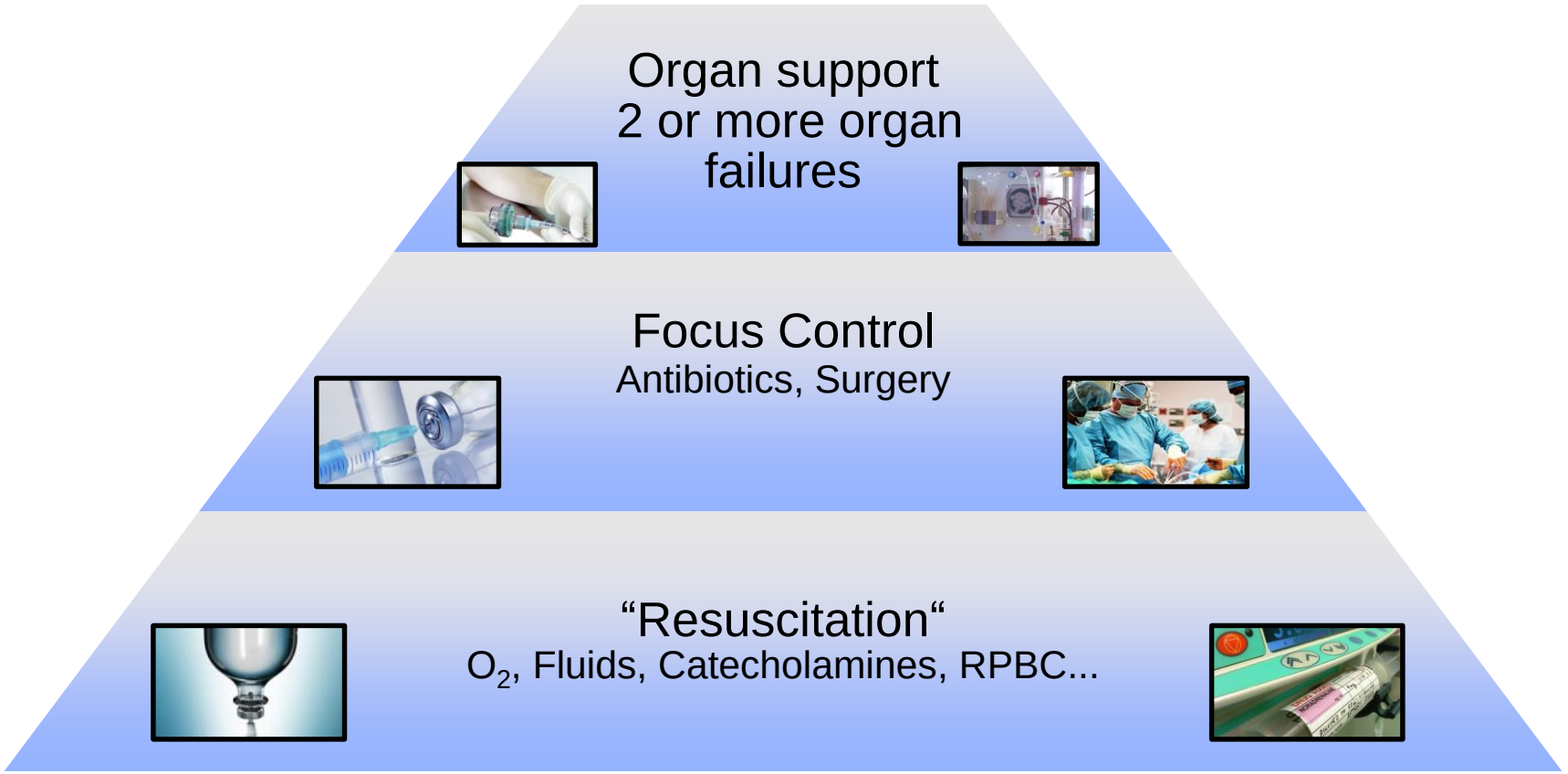

VWF and Platelet Adhesion
Blood flow
Protease
No protease
Normal multimers
"Ultralarge" multimers
TTP?

Coupled Plasma Filtration Adsorption



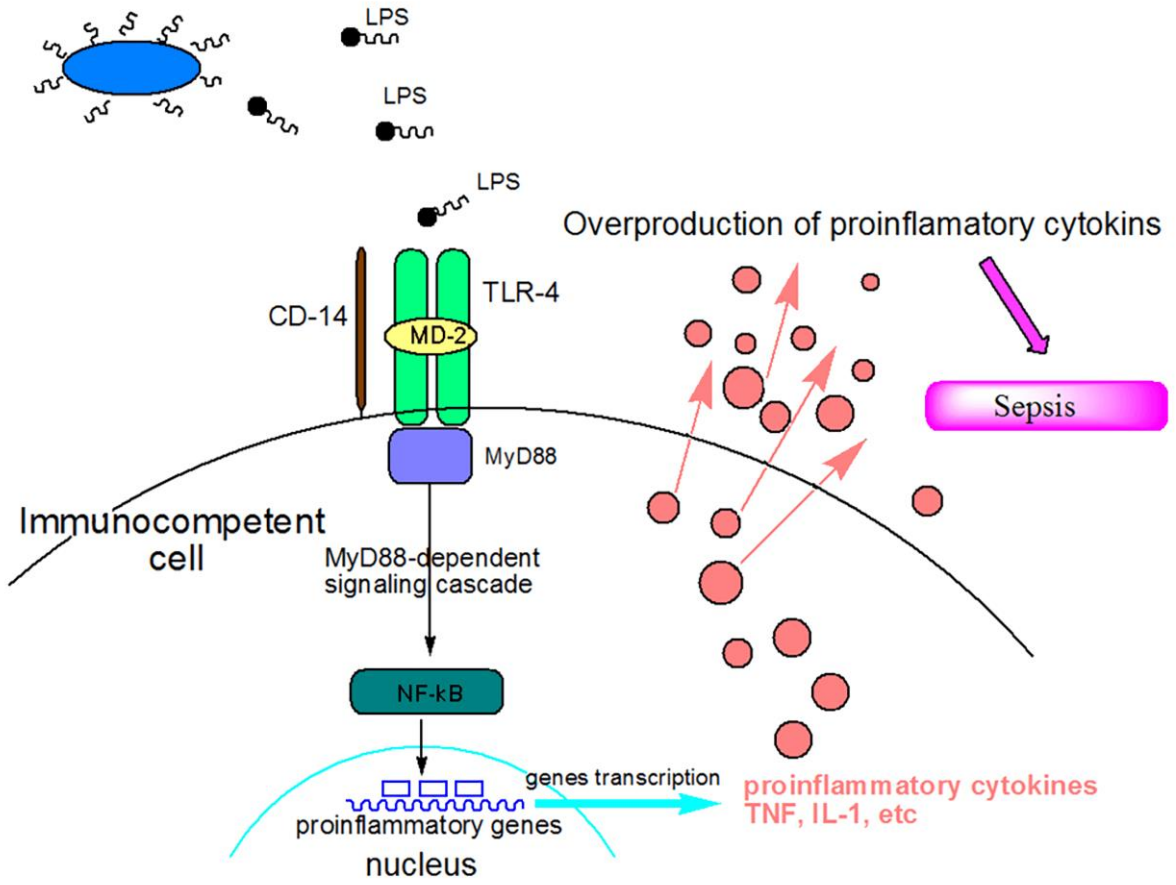
Adsorption Techniques

Rules of sepsis therapy



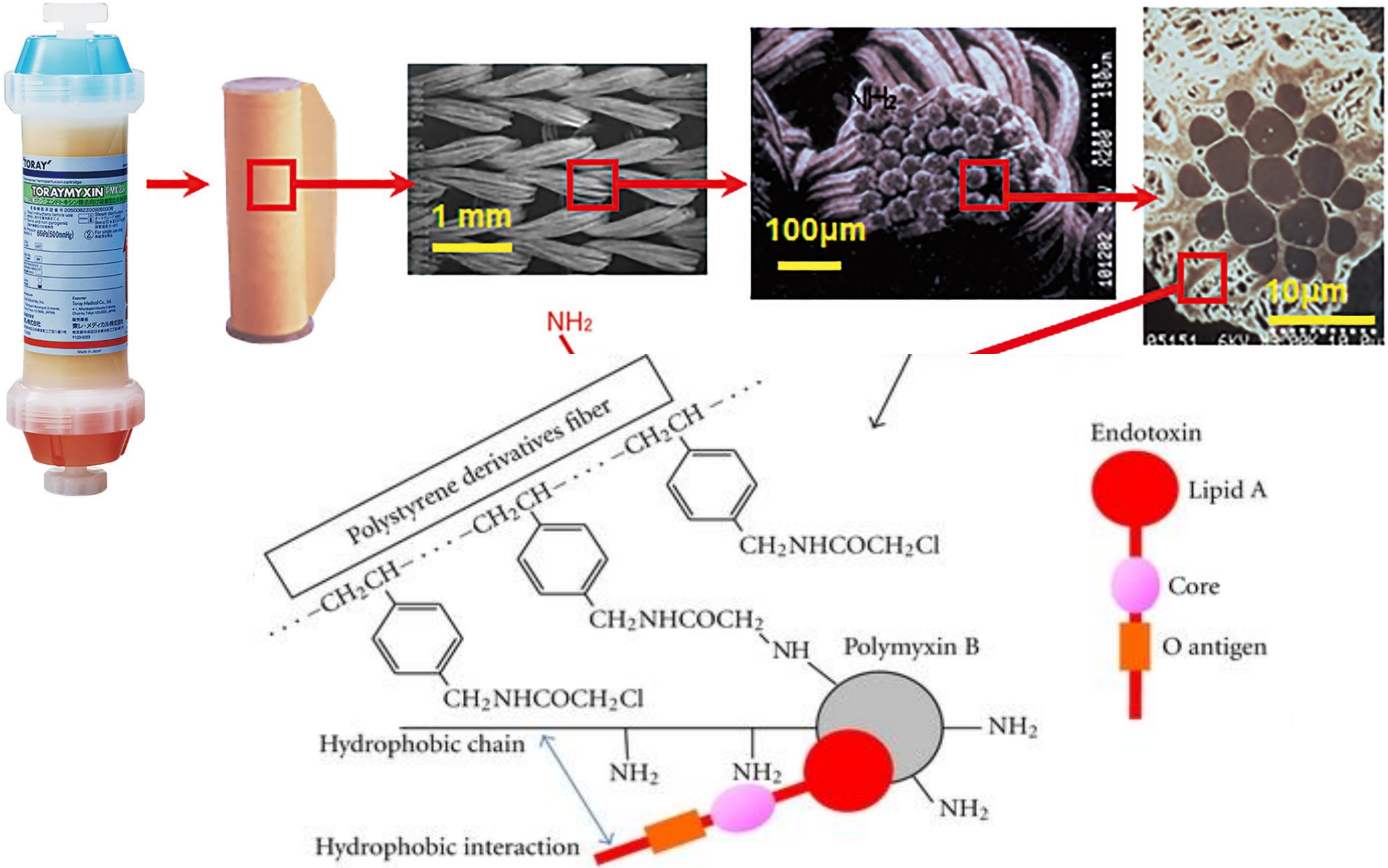
According to : Sepsis: From Pathophysiology to Individualized Patient Care , Ildikó László, Domonkos Trásy, Zsolt Molnár, and János Fazakas, Journal of Immunology Research Volume 2015

lipopolysaccharide (LPS) as a sepsis inducer



LPS is opsonized and recognized by monocytes, through the CD14 >>> leading to endothelial cell activation


100711
1022014
2010. 07. 23
2012. 07. 23
NDC 63323-367-11 306711
POLYMYXIN B
FOR INJECTION, USP
500,000 units per vial
Each vial contains Polymyxin B Sulfate equivalent to 500,000 polymyxin B units
Rx only
Sterile
Lyophilized


TORAY
TORAYMYXIN
1 mm
100μm
10μm
NH2
Polystyrene derivatives fiber
CH2NHCOCH2Cl
Polymyxin B
Hydrophobic chain
Hydrophobic interaction
Endotoxin
Lipid A
Core
O antigen

Intensive Care Med
https://doi.org/10.1007/s00134-018-5463-7

ORIGINAL

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

Abstract

Purpose: The EUPHRATES trial examined the impact of polymyxin B hemoperfusion (PMX) on mortality in patients with septic shock and endotoxemia, defined as EAA ≥ 0.60. No difference was found in 28-day all-cause mortality. However, the trial showed that in some patients with septic shock the burden of endotoxin activity was extreme (EAA ≥ 0.9). In a post hoc analysis, we evaluated the impact of PMX use in patients with septic shock and endotoxin activity measured between 0.6–0.89.

Methods: Post-hoc analysis of the EUPHRATES trial for the 194 patients with EAA ≥ 0.6–0.89 who completed two treatments (PMX or sham). The primary end point was mortality at 28 days adjusted for APACHE II score and baseline mean arterial pressure (MAP). Additional end points included changes in MAP, cumulative vasopressor index (CVI), median EAA reduction, ventilator-free days (VFD), dialysis-free days (DFD) and hospital length of stay. Subpopulations analyzed were site and type of infection and those with norepinephrine dose > 0.1 mcg/kg/min at baseline.

Results: At 28 days, 23 patients of 88 (26.1%) in the PMX group died versus 39 of 106 (36.8%) in the sham group [risk difference 10.7%, OR 0.52, 95% CI (0.27, 0.99), $P = 0.047$]. When unadjusted for baseline variables, $P = 0.11$. The 28-day survival time in the PMX group was longer than for the sham group [HR 0.56 (95% CI 0.33, 0.95) $P = 0.03$]. PMX treatment compared with sham showed greater change in MAP [median (IQR) 8 mmHg (− 0.5, 19.5) vs. 4 mmHg (− 4.0, 11) $P = 0.04$] and VFD [median (IQR) 20 days (0.5, 23.5) vs. 6 days (0, 20), $P = 0.004$]. There were no significant differences in other end points. There was a significant difference in mortality in PMX-treated patients with no bacterial growth on culture [PMX, 6/30 (20%) vs. sham, 13/31 (41.9%), $P = 0.005$]. The median EAA change in the population was − 12.9% (range: increase 49.2%–reduction 86.3%). The mortality in the above median EAA change group was PMX: 6/38 (15.7%) vs. sham 15/49 (30.6%), $P = 0.08$.

Conclusions: These hypothesis-generating results, based on an exploratory post hoc analysis of the EUPHRATES trial, suggest measurable responses in patients with septic shock and an EAA ≥ 0.6 to 0.89 on changes in mean arterial pressure, ventilator-free days and mortality.

Trial registration: Clinicaltrials.gov Identifier: NCT01046669. Funding Spectral Medical Incorporated.

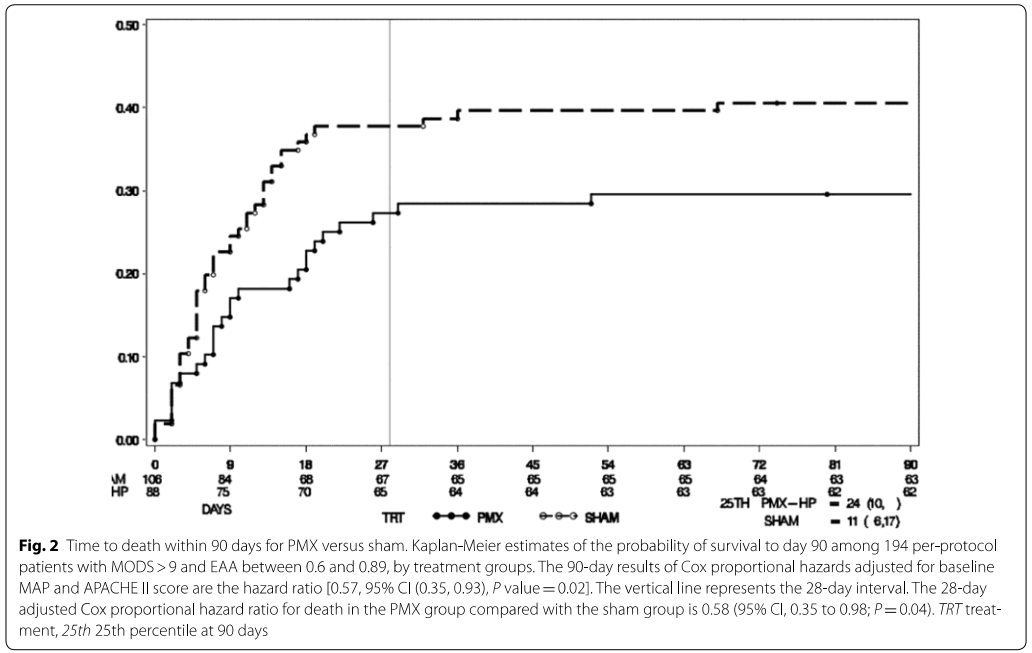
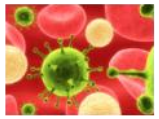


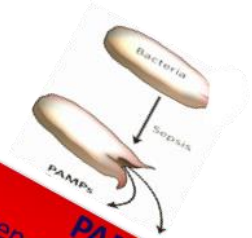
Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE II score are the hazard ratio [0.57, 95% CI (0.35, 0.93), *P* value = 0.02]. The vertical line represents the 28-day interval. The 28-day adjusted Cox proportional hazard ratio for death in the PMX group compared with the sham group is 0.58 (95% CI, 0.35 to 0.98; $P = 0.04$). *TRT* treatment, *25th* 25th percentile at 90 days

Cytokine Adsorption

Infection



bacterial
viral
fungal



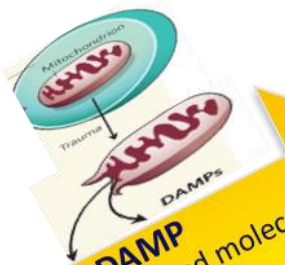
PAMP
Pathogen associated molecular pattern
Cell membrane , LPS, RNA/ DNA etc.

pancreatitis

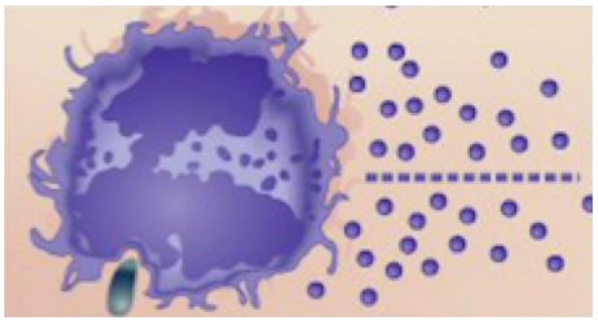
trauma

surgery

Sterile inflammation



DAMP
Damage associated molecular pattern
HMGB1, ATP, DNA fragmennts etc



Immune cell activation and release of inflammatory mediators

IL-6, IL-1ß, TNF-a
IL-10, NO, Selectin
etc

Central nervous system

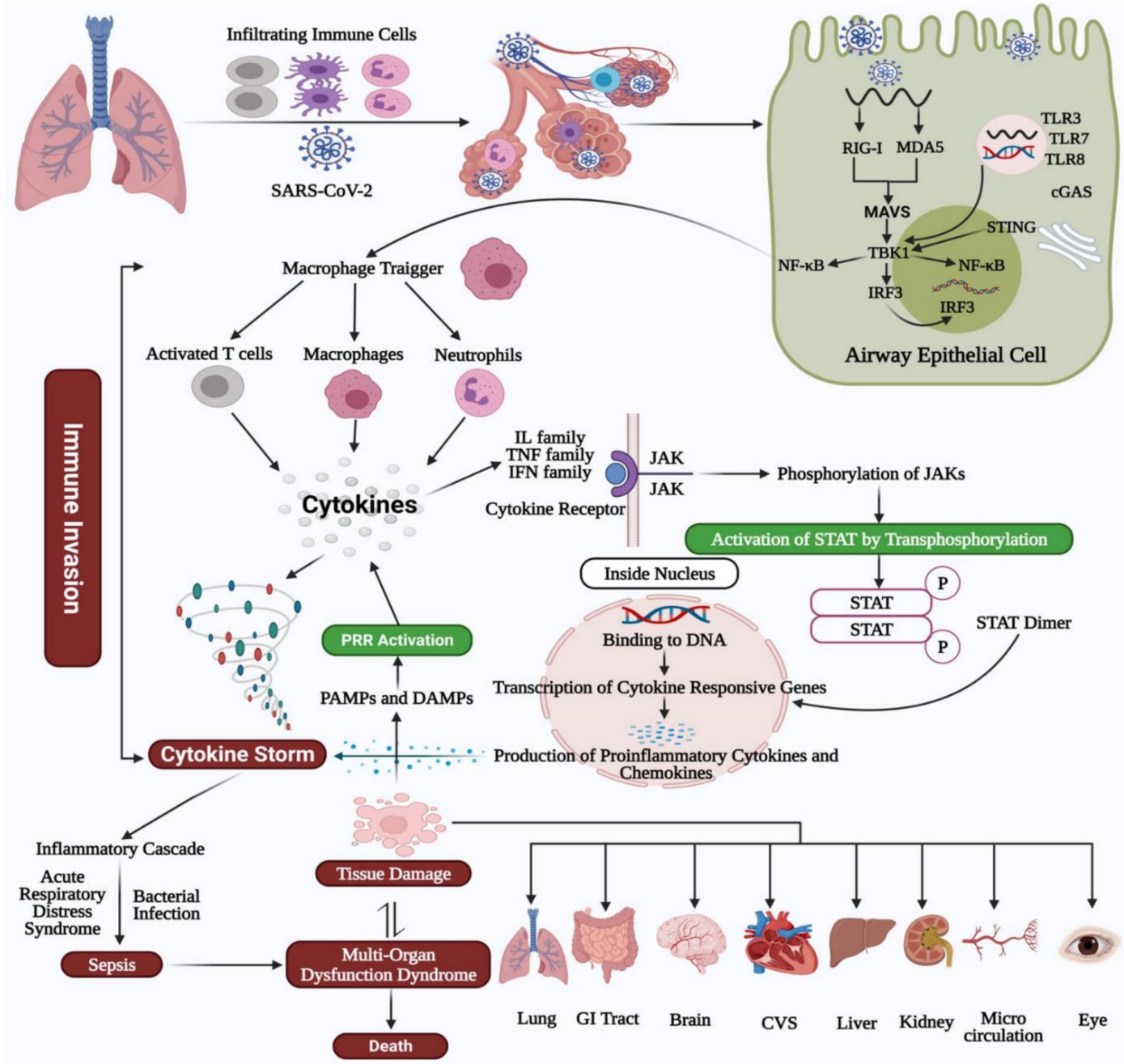
Respiratory organs

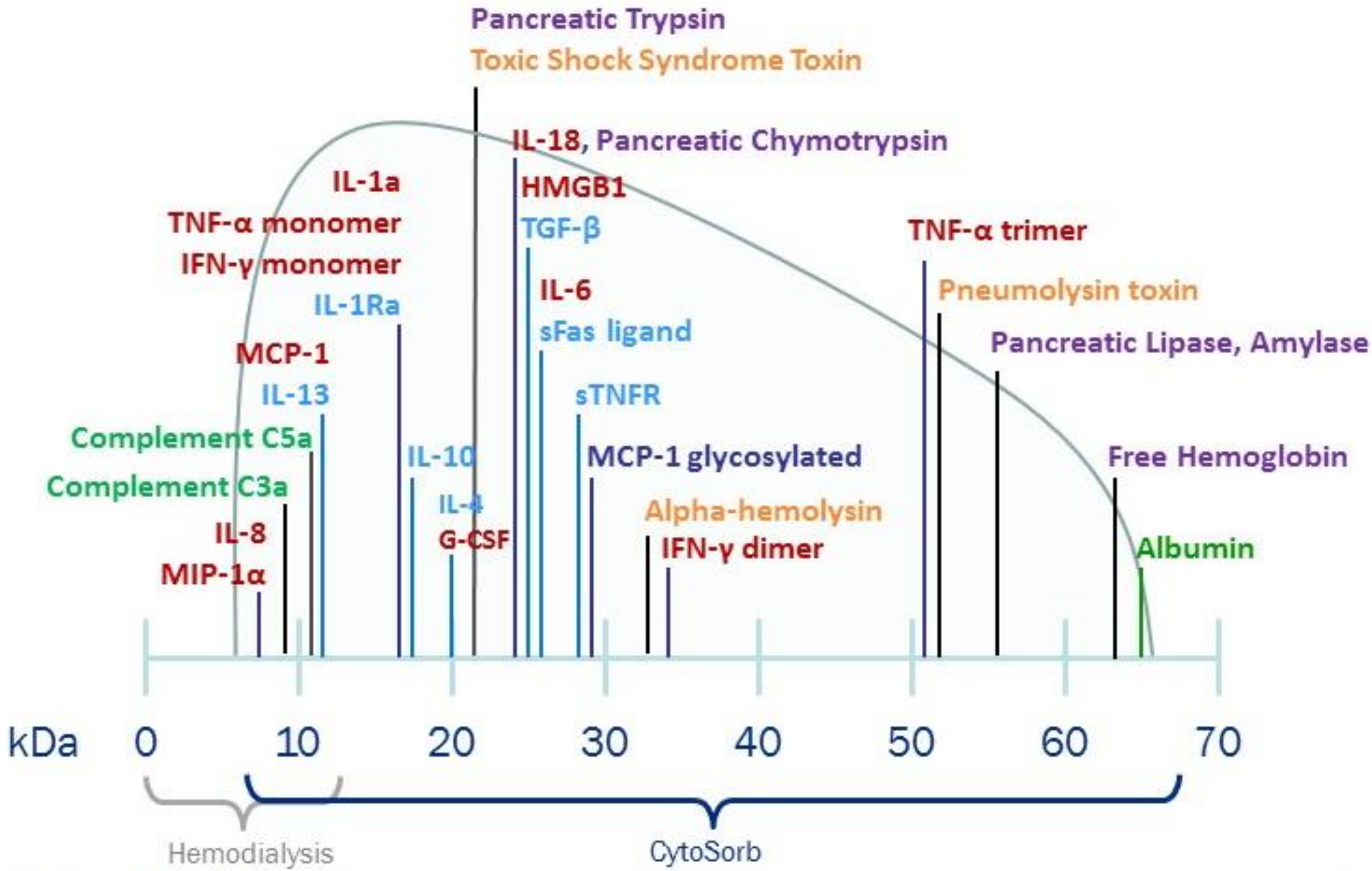
Cardiovascular system

Gastro-intestinal tract

Urinary tract

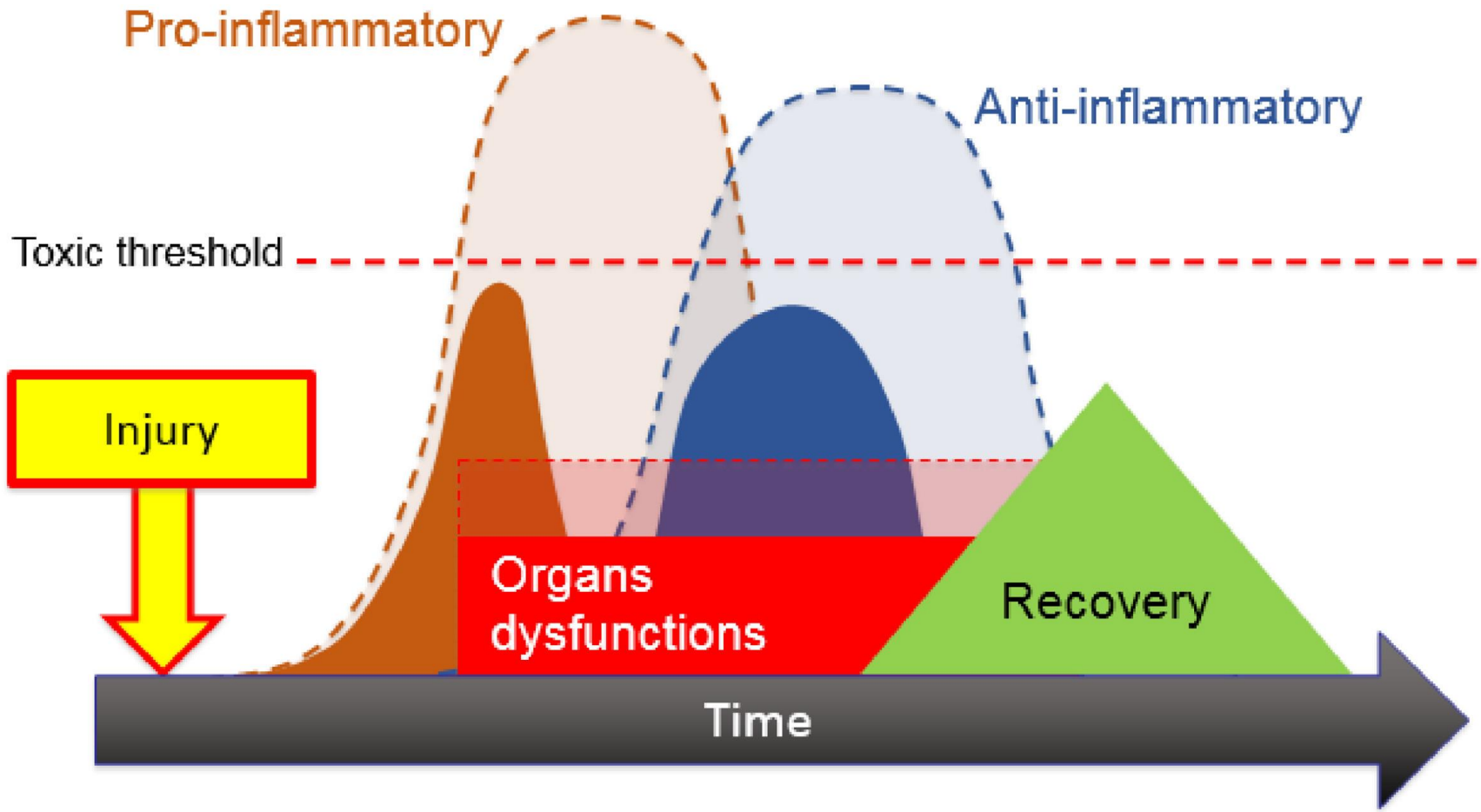
M O D S


Infiltrating Immune Cells
SARS-CoV-2
TLR3
TLR7
TLR8
cGAS
RIG-I
MDA5
MAVS
STING
TBK1
NF-κB
NF-κB
IRF3
IRF3
Airway Epithelial Cell
Macrophage Traigger
Activated T cells
Macrophages
Neutrophils
Immune Invasion
IL family
TNF family
IFN family
Cytokines
JAK
JAK
Cytokine Receptor
Phosphorylation of JAKs
Activation of STAT by Transphosphorylation
Inside Nucleus
STAT
STAT
P
P
STAT Dimer
Binding to DNA
PRR Activation
PAMPs and DAMPs
Transcription of Cytokine Responsive Genes
Cytokine Storm
Production of Proinflammatory Cytokines and Chemokines
Inflammatory Cascade
Acute Respiratory Distress Syndrome
Bacterial Infection
Tissue Damage
Sepsis
Multi-Organ Dysfunction Dyndrome
Death
Lung
GI Tract
Brain
CVS
Liver
Kidney
Micro circulation
Eye

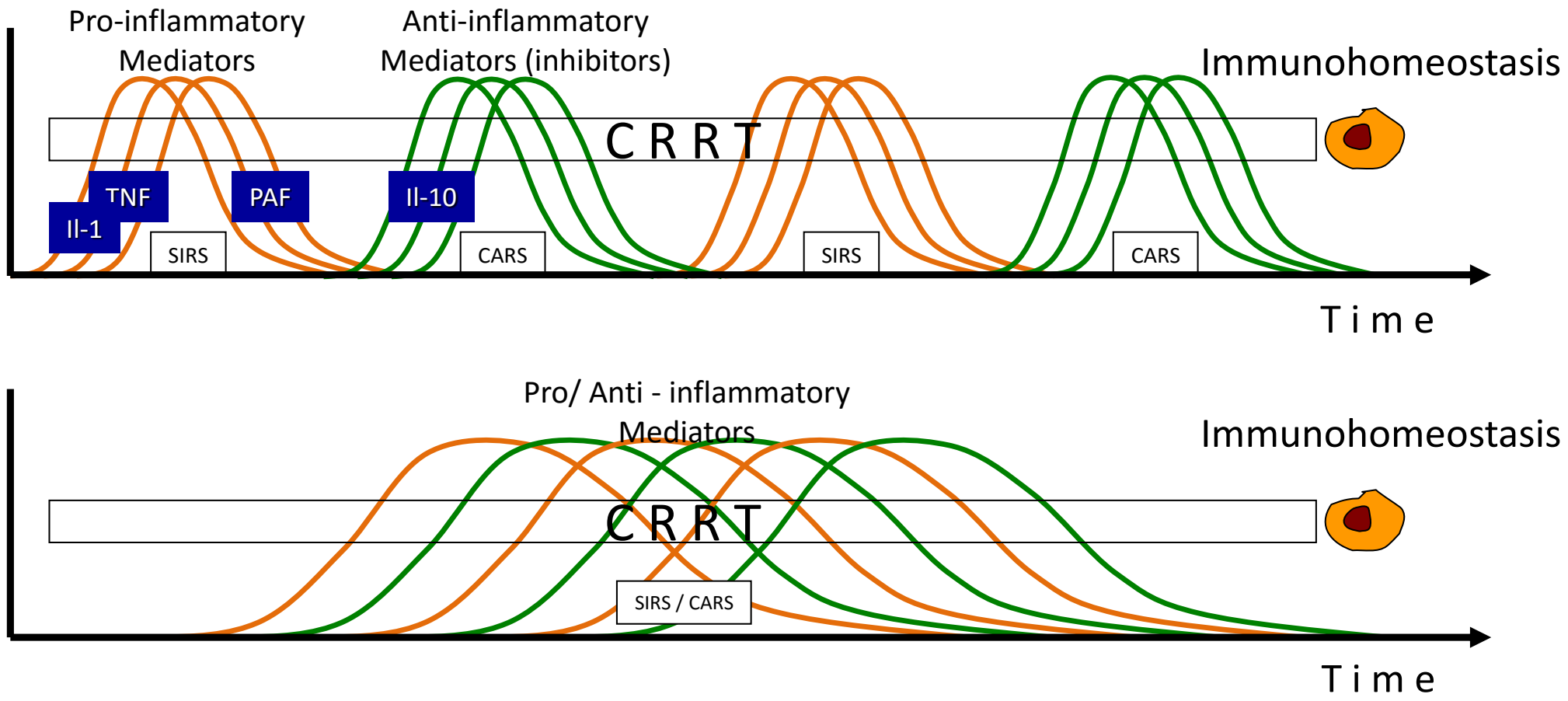

Pancreatic Trypsin
Toxic Shock Syndrome Toxin
IL-18, Pancreatic Chymotrypsin
IL-1a
HMGB1
TNF-α monomer
TGF-β
TNF-α trimer
IFN-γ monomer
IL-6
Pneumolysin toxin
IL-1Ra
sFas ligand
Pancreatic Lipase, Amylase
MCP-1
IL-13
sTNFR
Complement C5a
IL-10
MCP-1 glycosylated
Free Hemoglobin
Complement C3a
IL-4
Alpha-hemolysin
IL-8
G-CSF
IFN-γ dimer
Albumin
MIP-1α
kDa
0
10
20
30
40
50
60
70
Hemodialysis
CytoSorb

Hemadsorption using the Adsorber column is a non-selective and concentration-dependent method by which a spectrum of cytokines and inflammatory mediators are adsorbed from the bloodstream

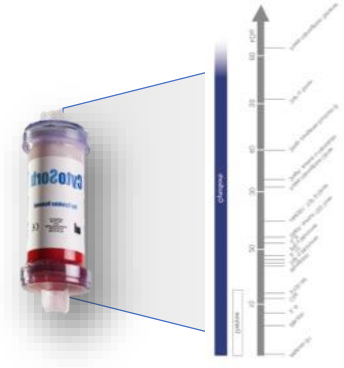
mediators like IL-1β, IL-6, IL-8, IL-10, and TNF-α

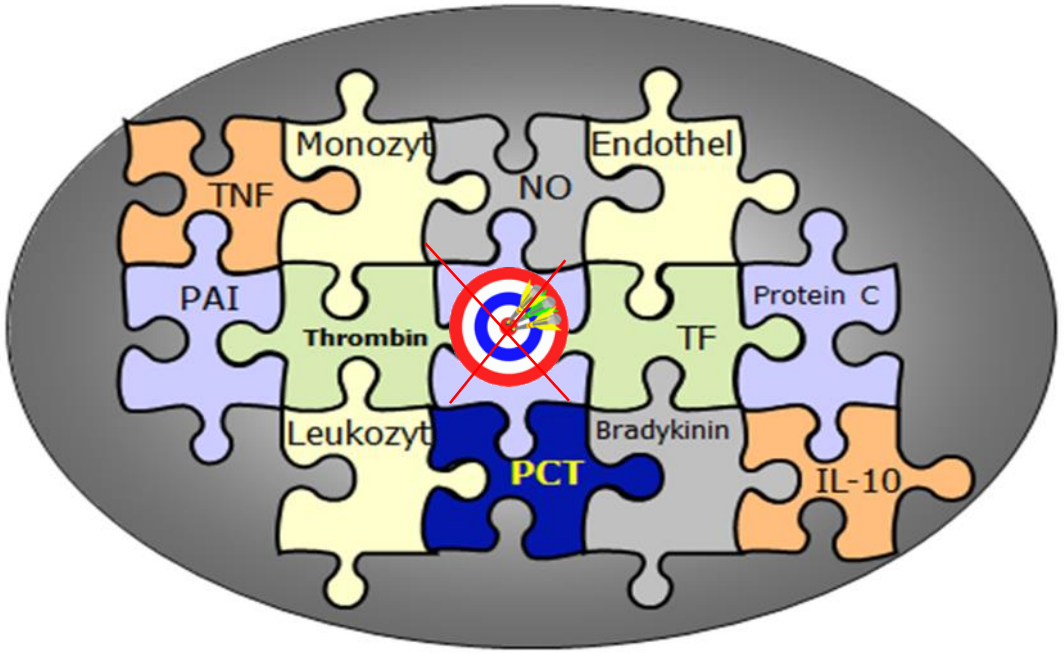

Pro-inflammatory
Anti-inflammatory
Toxic threshold
Injury
Organs dysfunctions
Recovery
Time

Immuno-dysregulation in sepsis



“The way to go is un-specific“



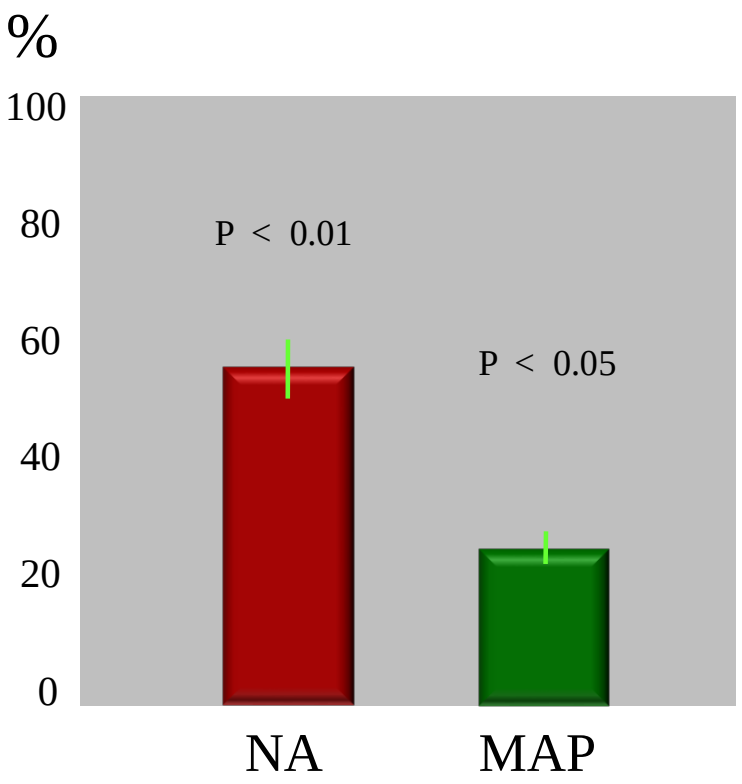


Claudio Ronco :
The way to go is unspecific !
(ISICEM 2016)

Hemodynamics and Biological Effects

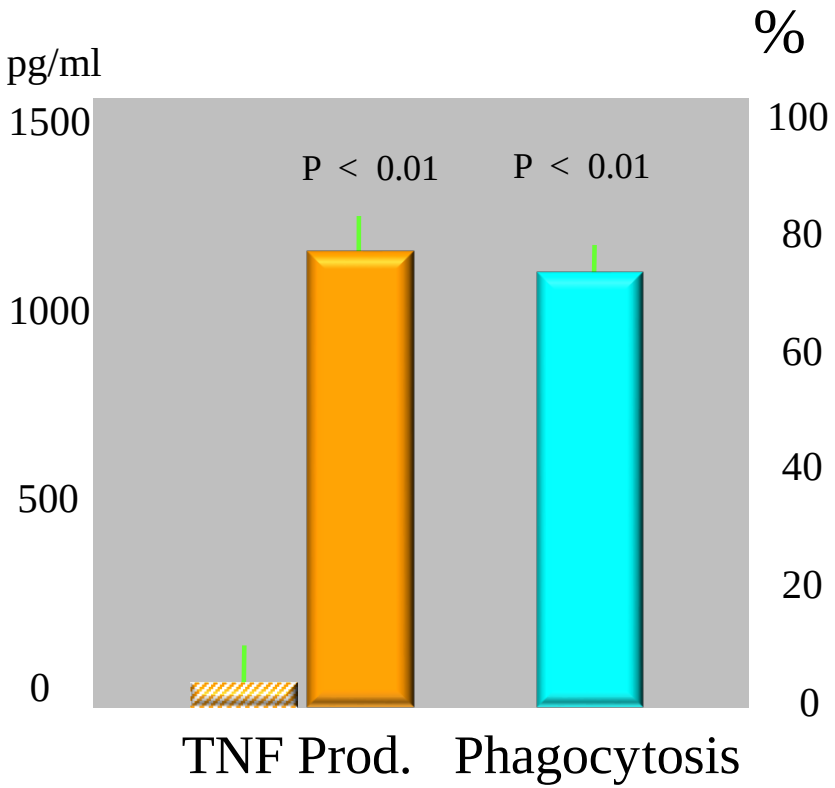
D- Norepinephrine Dose and D+ MAP

at 10 hours of treatment versus baseline

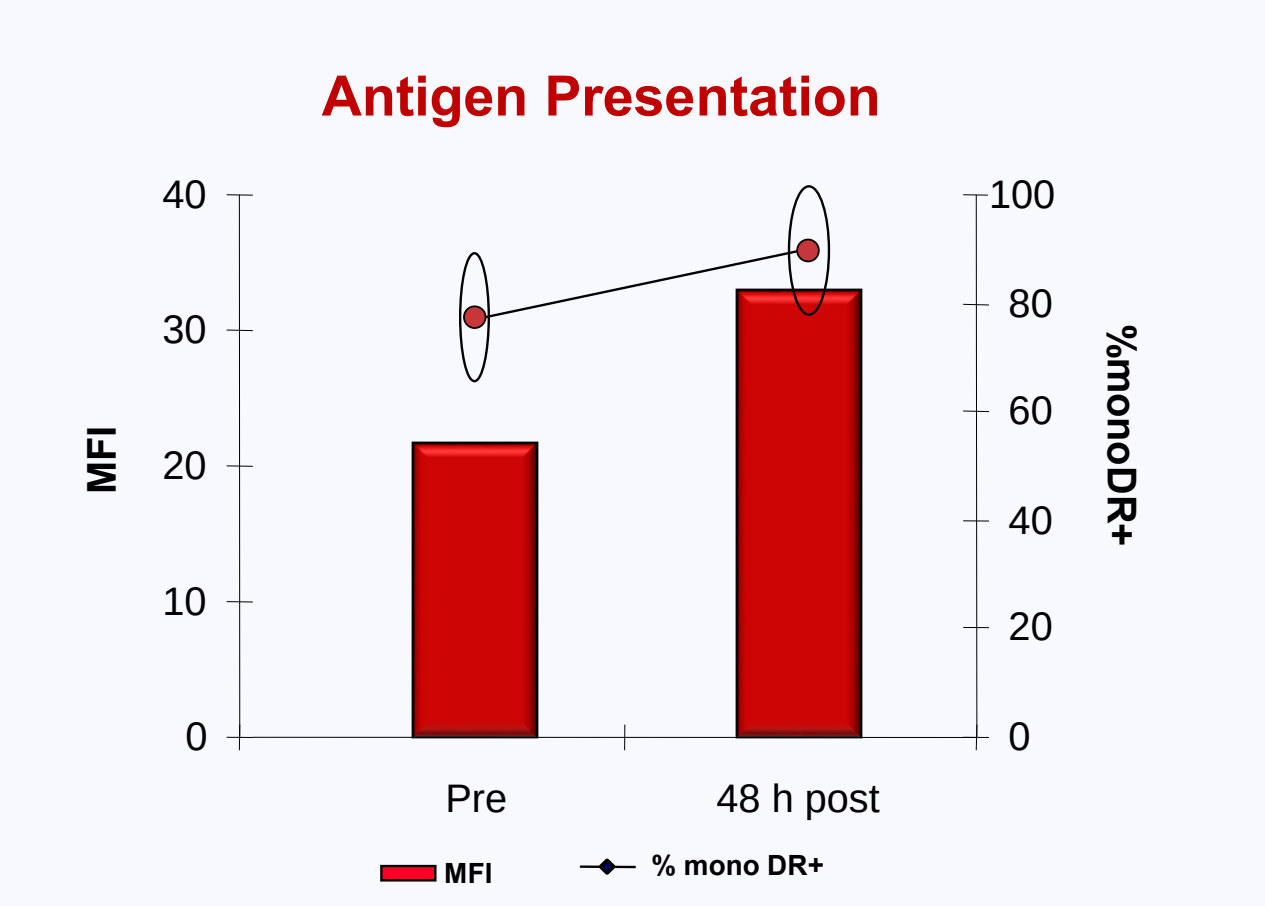


D Monocyte TNF production and Phagocytic Capacity

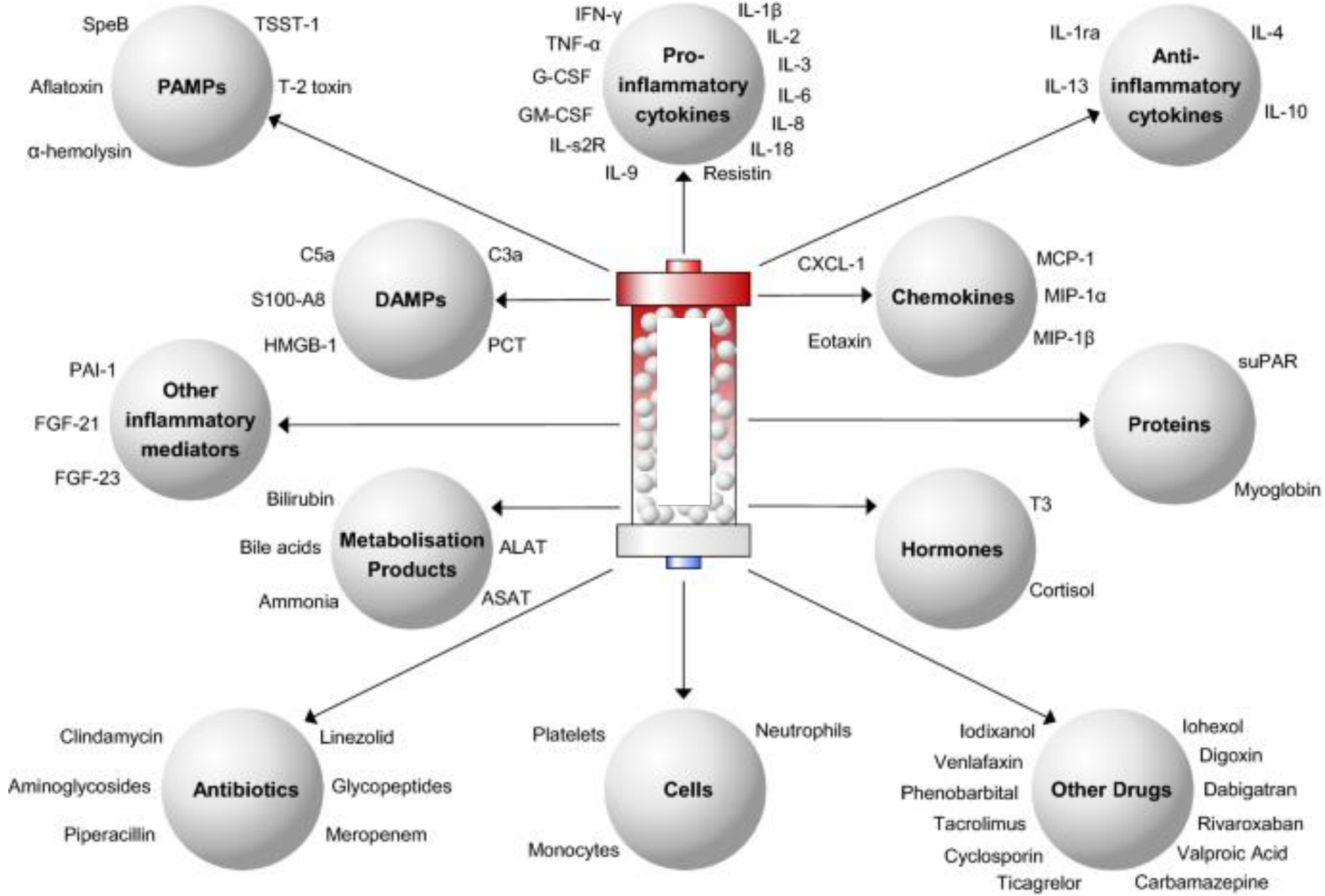
at 10 hours of treatment versus baseline



Increase in the HLA-DR expression *presentation of Ag improves*



Remove the Cytks, it is clear !
WHO declares (EUA)


SpeB
TSST-1
Aflatoxin
PAMPs
T-2 toxin
α-hemolysin
IFN-γ
IL-1β
TNF-α
IL-2
G-CSF
Pro-inflammatory cytokines
IL-3
GM-CSF
IL-6
IL-s2R
IL-8
IL-18
IL-9
Resistin
IL-1ra
IL-4
IL-13
Anti-inflammatory cytokines
IL-10
C5a
C3a
S100-A8
DAMPs
HMGB-1
PCT
CXCL-1
MCP-1
MIP-1α
Chemokines
Eotaxin
MIP-1β
PAI-1
Other inflammatory mediators
FGF-21
FGF-23
suPAR
Proteins
Myoglobin
Bilirubin
Bile acids
Metabolisation Products
ALAT
Ammonia
ASAT
T3
Hormones
Cortisol
Clindamycin
Linezolid
Aminoglycosides
Antibiotics
Glycopeptides
Piperacillin
Meropenem
Platelets
Neutrophils
Cells
Monocytes
Iodixanol
Iohexol
Venlafaxin
Digoxin
Phenobarbital
Other Drugs
Dabigatran
Tacrolimus
Rivaroxaban
Cyclosporin
Valproic Acid
Ticagrelor
Carbamazepine

Dynamic Scoring
=> defined parameters & tresholds

- **Parameters:**

⇒ **blood lactate & changes /6 hrs**

⇒ **catecholamine demand & changes/6 hrs**

⇒ **initial volume demand & needed boli/6 hrs**

⇒ **2nd catecholamine or/and hydrocortison use**

- **Tresholds:**

⇒ **lactate 2 mmol, vasopressor 0.1µg/kg, 30 ml/kg initial volume are our defined tresholds.**

⇒ **Each parameter with this values signs for 1 pt, dynamic increasing means additional point, decreasing means 0**

CytoScore

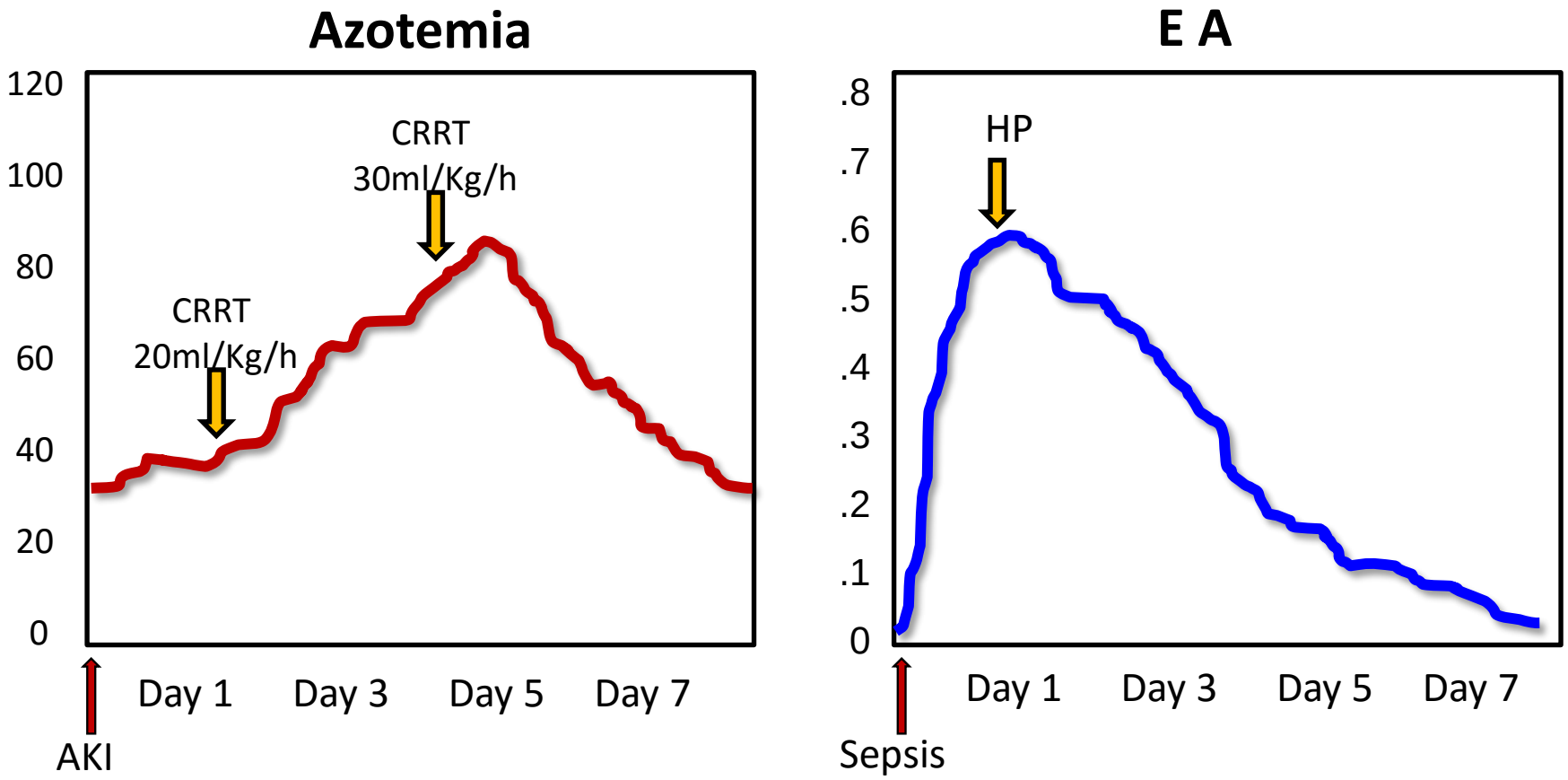
parameters				
lactate mmol/l	< 2	-	≥ 2	
lactat-change 6h	decreased	increased	increased > 50%	
NA µg/kg/min (MAP=65)	< 0.1	-	≥ 0.1	
vasopressor demand change / 6 h	decreased	increased	increased > 50%	
2. catecholamine	-	-	yes	
hydrocortisone applicated	-	-	yes	
Volume bolus 30 ml/kgbw	-	< 2 boli	≥ 2 boli	
	0	1	2	
	APACHE II	Cytosorb treatment		Score
		Yes ?	No	
	special indications: no score needed			

Kinetics of Cytk

- ***we don't know how much is produced ?***
- ***we don't know how much is metabolized ?***
- ***we don't know how much is eliminated by the kidneys ?***
- ***we don't know how much we need to remove by the cartridge ?***

- ***>>> we know that around 12 hrs starts to show a plateau in adsorption*** **>>> may suggest more frequent**

Dynamic Prescription



adjuvant therapy for critically ill patients with COVID-19

impasse !

Table 1 | **Potential mechanisms of kidney damage and treatment strategies in COVID-19**

Pathway[a]	Mechanism of kidney damage	Suggested treatment strategy
Cytokine damage		
Cytokine release syndrome	Direct cytokine lesion	Cytokine removal using various approaches: direct haemoperfusion using a neutro-macroporous sorbent; plasma adsorption on resin after separation from whole blood; CKRT with hollow fibre filters with adsorptive properties; high-dose CKRT with MCO or HCO membranes
Increased cytokine generation owing to ECMO, invasive mechanical ventilation and/or CKRT		
Haemophagocytic syndrome		
Organ crosstalk		
Cardiomyopathy and/or viral myocarditis	Cardiorenal syndrome type 1	LVAD, arteriovenous ECMO
Alveolar damage	Renal medullary hypoxia	Venovenous ECMO
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome	Venovenous ECMO, extracorporeal CO_2 removal, CKRT
Rhabdomyolysis	Tubular toxicity	CKRT using a HCO or MCO membrane
Systemic effects		
Positive fluid balance	Renal compartment syndrome	Continuous ultrafiltration and diuretics
Endothelial damage, third-space fluid loss and hypotension	Renal hypoperfusion	Vasopressors and fluid expansion
Rhabdomyolysis	Tubular toxicity	CKRT using a HCO or MCO membrane
Endotoxins	Septic AKI	Endotoxin removal using polysterene fibres functionalized with polymyxin-B

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ECMO, extracorporeal membrane oxygenation; HCO, high cut-off; LVAD, left ventricular assist device; MCO, medium cut-off. [a]The pathways and mechanisms are interconnected and treatment strategies will influence different aspects simultaneously.

Hindawi
Critical Care Research and Practice
Volume 2021, Article ID 7769516, 10 pages
https://doi.org/10.1155/2021/7769516

Review Article

The Use of CytoSorb Therapy in Critically Ill COVID-19 Patients: Review of the Rationale and Current Clinical Experiences

Juan Carlos Ruiz-Rodríguez,[1] **Zsolt Molnar**,[2,3,4,5] **Efthymios N. Deliargyris**,[6] **and Ricard Ferrer**[1]

[1]*Department of Intensive Care, Hospital Universitari Vall d'Hebron, Shock Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain*
[2]*CytoSorbents Europe GmbH, Berlin, Germany*
[3]*Institute for Translational Medicine, School of Medicine, University of Pécs, Pécs, Hungary*
[4]*Department of Anesthesiology and Intensive Therapy, Poznan University of Medical Sciences, Poznan, Poland*
[5]*Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary*
[6]*CytoSorbents Corporation, Monmouth Junction, NJ, USA*

Correspondence should be addressed to Ricard Ferrer; r.ferrer@vhebron.net

Academic Editor: Samuel A. Tisherman

The COVID-19 pandemic has led to the biggest global health crisis of our lifetime. There is accumulating evidence that a substantial number of critically ill COVID-19 patients exhibit a dysregulated host response manifesting as cytokine storm or cytokine release syndrome, which in turn contributes to the high observed rates of mortality. Just as in other hyperinflammatory conditions, extracorporeal cytokine removal may have potential beneficial effects in this subgroup of COVID-19 patients. The CytoSorb blood purification device is the most extensively investigated cytokine removal platform with considerable evidence suggesting that early intervention can provide rapid hemodynamic stabilization and improvement in vital organ functions. The purpose of this review is to provide an overview of the pathophysiological background of hyperinflammation in COVID-19 and to summarize the currently available evidence on the effects of hemoadsorption in these patients.

1. Background

The COVID-19 pandemic has led to the biggest global health crisis of our lifetime, particularly in intensive care units (ICUs) [1]. The disease has caused not only high infectivity and fatality but also universal economic burden and heavy financial losses [2]. As per the latest World Health Organization (WHO) consensus data (website accessed 27.04.2021), there have been more than 146 million cases and over 3 million casualties reported worldwide [3].

There is accumulating evidence that a substantial number of critically ill COVID-19 patients frequently exhibit viral RNAemia together with a dysregulated immune response [4] with hyperinflammation manifesting as a cytokine storm or as cytokine release syndrome (CRS), which in turn contributes to the high observed rates of mortality [5, 6]. The cytokine profile in these COVID-19 cases seems to resemble secondary hemophagocytic lymphohistiocytosis (sHLH), a severe hyperinflammatory syndrome, which in nearly 30% of cases stem from a viral infection as the underlying condition [5, 7–9]. Reports from China and Italy showing elevated ferritin levels, a recognized hallmark of HLH, further corroborate the mechanistic similarities with severe COVID-19 cases [10].

The above mechanism supports the hypothesis that extracorporeal cytokine removal may have beneficial effects in COVID-19 patients similar to those seen in other hyperinflammatory conditions [11]. In addition, the high mortality observed with severe COVID-19 disease may at least in part be explained by a differential response of these

Received: 3 March 2021 | Revised: 8 June 2021 | Accepted: 9 June 2021
DOI: 10.1111/aor.14024

MAIN TEXT ARTICLE

Artificial Organs WILEY

Blood purification with CytoSorb in critically ill COVID-19 patients: A case series of 26 patients

Amir Ahmad Nassiri[1] | **Monir Sadat Hakemi**[2] | **Mir Mohammad Miri**[3] | **Reza Shahrami**[4] | **Azadeh Ahmadi Koomleh**[1] | **Tahereh Sabaghian**[1]

[1]Division of Nephrology, Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Nephrology ward, Shariati Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[3]Anesthesiology and Critical Care Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Intensive Care Department, NIOC Tehran Hospital, Tehran, Iran

Correspondence
Amir Ahmad Nassiri, Shahid Beheshti University of Medical Sciences, Division of Nephrology, Department of Internal Medicine, Tehran, Iran.
Email: nassirimorad@yahoo.com

Abstract

Severe forms of the coronavirus disease 2019 (COVID-19) can progress to sepsis-like complications accompanied by "cytokine storm" for which the most effective treatment has not yet been established. Our study describes the results of CytoSorb hemoadsorption in COVID-19 patients treated on the intensive care unit (ICU). In this retrospective study, 26 patients with COVID-19 and acute respiratory distress syndrome (ARDS) were treated with hemoadsorption therapy. Pre-, and post-treatment values (clinical and laboratory) were compared. Data are expressed as mean (confidence intervals, CI), or median [interquartile ranges, IQR], as appropriate. Patients received 2 hemoadsorption treatments. This resulted in a significant decrease in norepinephrine requirements, and inflammatory marker plasma concentrations (procalcitonin, C-reactive protein, ferritin) when comparing pre versus post treatment levels. The PaO_2/FiO_2 and overall organ function (ie, Sequential Organ Failure Assessment—SOFA score) also improved significantly. Patients stayed on the ICU for 9 days and 21 of them survived. To the best of our knowledge, this is one of the largest case series to date reporting early experiences on extracorporeal hemoadsorption therapy in SARS-CoV-2 positive patients with hyperinflammation and moderate ARDS. Treatment proved to be effective, technically feasible and well- tolerated.

KEYWORDS
COVID-19, CytoSorb, hemoadsorption, hemodynamic, hyperinflammation, lung function

1 | INTRODUCTION

In December 2019, China became the center of an outbreak of the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], which has since spread globally, resulting in the ongoing pandemic coronavirus disease 2019 (COVID-19). Clinical symptoms of the disease include fever, myalgia, fatigue, headache, dry cough, expectoration, hemoptysis and diarrhea, while some patients go on to develop severe sepsis-like complications such as acute respiratory distress syndrome (ARDS) (40.3%), acute renal failure (18.3%), cardiac injury (59.6%) and shock (11.9%).[1]

Table 1: Overview of the currently available literature.

Author	Study title details	Type of study	Country	Number of patients	Improvement in hemodynamics	Improvement in oxygenation	Control of inflammatory response	Reference number from manuscript
Alharthy A	Continuous Renal Replacement Therapy with the Addition of CytoSorb® Cartridge in Critically Ill Patients with COVID-19 plus Acute Kidney Injury: a Case-Series. Artificial Organs 2021; 45(5):E101-112	Retrospective case series	Saudi Arabia	50		Yes	Yes	31
Berlot G	Effects of Tocilizumab Versus Hemoadsorption Combined with Tocilizumab in Patients with SARS-CoV-2 Pneumonia: Preliminary Results. Int *J* Artif organs 2021; epub	Retrospective case series	Italy	2		Yes	Yes	51
Rieder M et al.	Cytokine Adsorption in Patients with Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation. Crit Care 2020; 24: 435	Randomized control trial—Interim analysis	Germany	4 vs 4			Yes	55
Rampino T et al.	Hemoperfusion with CytoSorb as Adjuvant Therapy in Critically Ill Patients with SARS-CoV2 Pneumonia. Blood Purif 2020; epub	Retrospective case series	Italy	5 of 9 consecutive pts treated with CytoSorb		Yes	Yes	56
Lebreton G et al.	Longitudinal Cytokine Profiling in Severe COVID-19 Patients on ECMO and Hemoadsorption. AJRCCM 2021; 203(11): 1433–5	Prospective case series	France	11 consecutive patients on CytoSorb compared to 11 noncontemporaneous pts			Yes	57
Ferrer R	Regain control of Inflammation – IL6 Blockers or CytoSorb (or both)? Presented at "the trinity of COVID-19: Immunity, Inflammation and Intervention Webinar," May 20th 2020.	Webinar presentation of retrospective patients	Spain	7		Yes	Yes	59
Moazami N	CytoSorb: First Clinical Experience in the USA. Presented at the "EuroELSO Virtual ECMO Day," June 25th 2020	Webinar presentation of retrospective patients	USA	10 vs 10	Yes		Yes	65
Nassiri AA	Blood Purification with CytoSorb in Critically Ill COVID-19 Patients: A Case Series of 26 Patients. Artif Org 2021; epub	Retrospective case series	Iran	26	Yes	Yes	Yes	66

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the final results of this assessment.

RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55).

CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

The members of the writing committee (Peter Horby, F.R.C.P., Wei Shen Lim, F.R.C.P., Jonathan R. Emberson, Ph.D., Marion Mafham, M.D., Jennifer L. Bell, M.Sc., Louise Linsell, D.Phil., Natalie Staplin, Ph.D., Christopher Brightling, F.Med.Sci., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Christopher Green, D.Phil., Timothy Felton, Ph.D., David Chadwick, Ph.D., Kanchan Rege, F.R.C.Path., Christopher Fegan, M.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Edmund Juszczak, M.Sc., J. Kenneth Baillie, M.D., Ph.D., Richard Haynes, D.M., and Martin J. Landray, F.R.C.P.) assume responsibility for the overall content and integrity of this article.

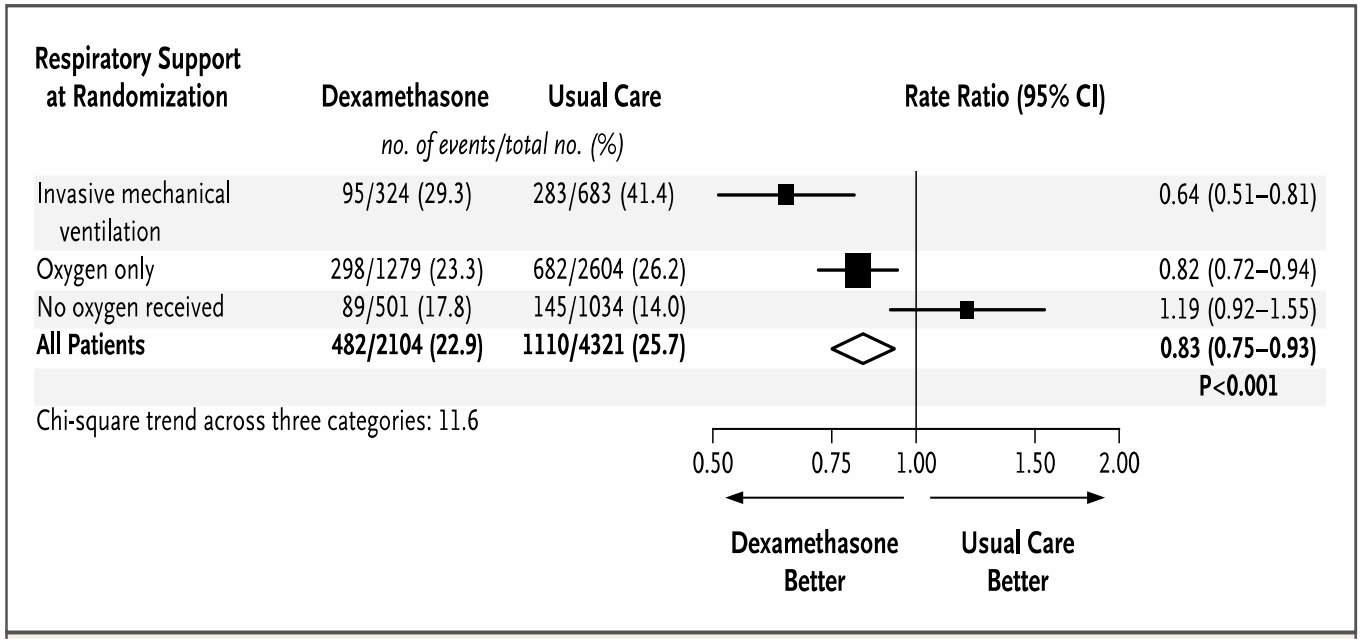
The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Drs. Horby and Landray at RECOVERY Central Coordinating Office, Richard Doll Bldg., Old Road Campus, Roosevelt Dr., Oxford OX3 7LF, United Kingdom, or at recoverytrial@ndph.ox.ac.uk.

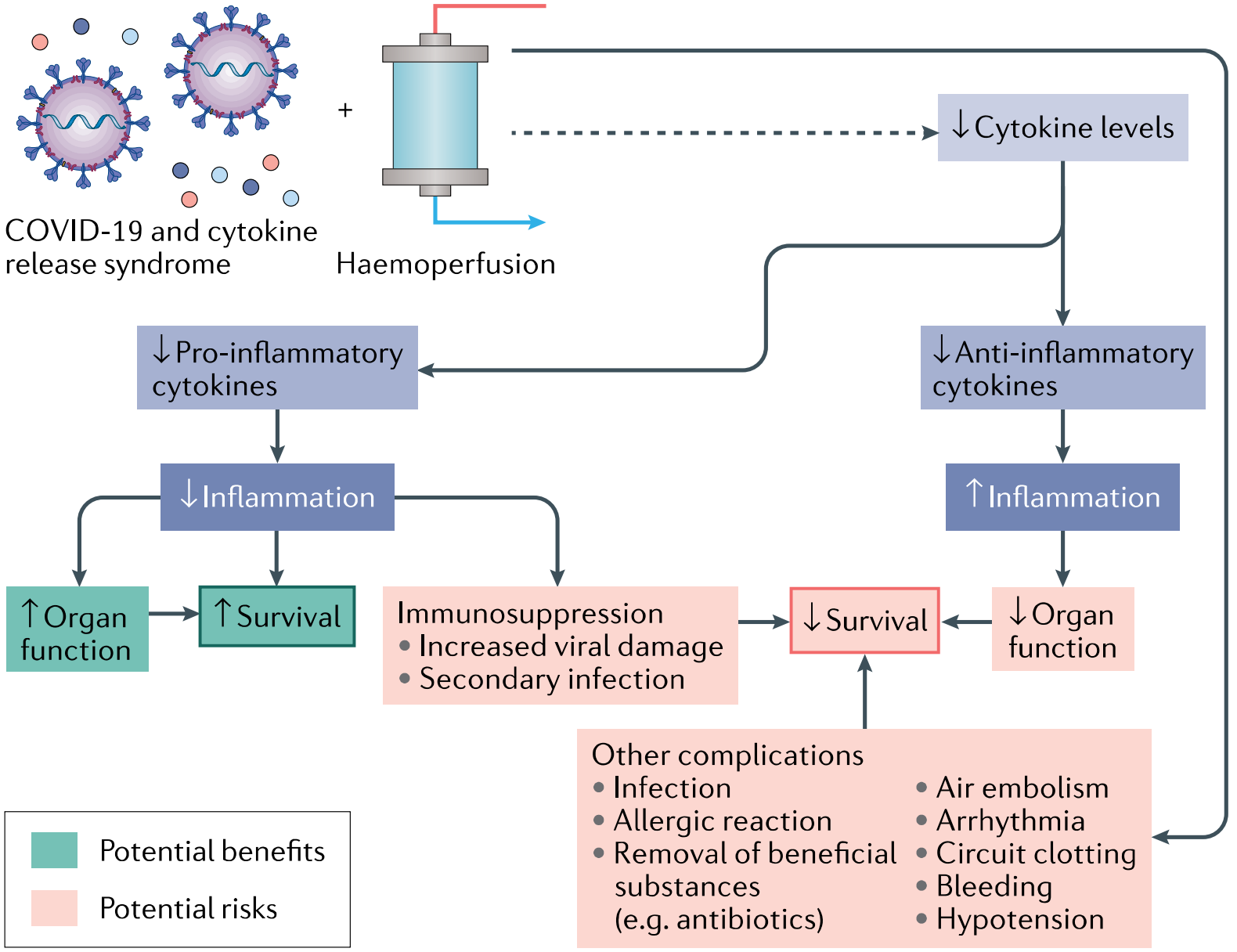
*A complete list of collaborators in the RECOVERY trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Horby, Lim, and Emberson and Drs. Haynes and Landray contributed equally to this article.

A preliminary version of this article was published on July 17, 2020, at NEJM.org.

N Engl J Med 2021;384:693-704.
DOI: 10.1056/NEJMoa2021436




COVID-19 and cytokine release syndrome
+
Haemoperfusion
↓Cytokine levels
↓Pro-inflammatory cytokines
↓Anti-inflammatory cytokines
↓Inflammation
↑Inflammation
↑Organ function
↑Survival
Immunosuppression
• Increased viral damage
• Secondary infection
↓Survival
↓Organ function
Other complications
• Infection
• Allergic reaction
• Removal of beneficial substances (e.g. antibiotics)
• Air embolism
• Arrhythmia
• Circuit clotting
• Bleeding
• Hypotension
Potential benefits
Potential risks

… whether haemo-perfusion can alter cytokine, endotoxin or pathogen levels sufficiently to have a *biological impact* is *unclear*

A trial that evaluated 97 patients with severe sepsis or septic shock and acute lung injury or ARDS showed that haemoperfusion removed IL-6 from the blood but did not lower circulating IL-6 levels

PLOS ONE

RESEARCH ARTICLE

The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial

Dirk Schädler[1☯]*, Christine Pausch[2☯], Daniel Heise[3], Andreas Meier-Hellmann[4], Jörg Brederlau[5], Norbert Weiler[1], Gernot Marx[6], Christian Putensen[7], Claudia Spies[8], Achim Jörres[9], Michael Quintel[3], Christoph Engel[2], John A. Kellum[10], Martin K. Kuhlmann[11]

1 Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany, **2** Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, **3** Centre of Anaesthesiology, Emergency and Intensive Care Medicine, University Hospital Göttingen, Göttingen, Germany, **4** Department of Anesthesiology and Intensive Care Medicine, HELIOS Klinikum, Erfurt, Germany, **5** Department of Intensive Care Medicine, Helios Hospital Berlin-Buch, Berlin, Germany, **6** Department of Intensive Care and Intermediate Care, RWTH University Hospital Aachen, Aachen, Germany, **7** Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany, **8** Anaesthesiology and Intensive Care Medicine, Campus Charité Mitte and Campus Charité Virchow-Klinikum, Charité - University Medicine Berlin, Berlin, Germany, **9** Department of Medicine I - Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany, **10** Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **11** Department of Nephrology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

☯ These authors contributed equally to this work.
* dirk.schaedler@uksh.de

OPEN ACCESS

Citation: Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, et al. (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. PLoS ONE 12(10): e0187015. https://doi.org/10.1371/journal.pone.0187015

Editor: Kathrin Eller, Medizinische Universitat Graz, AUSTRIA

Received: March 11, 2017

Accepted: October 10, 2017

Published: October 30, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The study was supported by Cytosorbents Corporation, New Jersey, United States. Cytosorbents was involved in study design and data collection. Cytosorbents had no role in analysis, decision to publish or preparation of the manuscript.

Abstract

Objective

We report on the effect of hemoadsorption therapy to reduce cytokines in septic patients with respiratory failure.

Methods

This was a randomized, controlled, open-label, multicenter trial. Mechanically ventilated patients with severe sepsis or septic shock and acute lung injury or acute respiratory distress syndrome were eligible for study inclusion. Patients were randomly assigned to either therapy with CytoSorb hemoperfusion for 6 hours per day for up to 7 consecutive days (treatment), or no hemoperfusion (control). Primary outcome was change in normalized IL-6-serum concentrations during study day 1 and 7.

Results

97 of the 100 randomized patients were analyzed. We were not able to detect differences in systemic plasma IL-6 levels between the two groups (n = 75; p = 0.15). Significant IL-6 elimination, averaging between 5 and 18% per blood pass throughout the entire treatment period was recorded. In the unadjusted analysis, 60-day-mortality was significantly higher in the

Abstract

Objective

We report on the effect of hemoadsorption therapy to reduce cytokines in septic patients with respiratory failure.

Methods

This was a randomized, controlled, open-label, multicenter trial. Mechanically ventilated patients with severe sepsis or septic shock and acute lung injury or acute respiratory distress syndrome were eligible for study inclusion. Patients were randomly assigned to either therapy with CytoSorb hemoperfusion for 6 hours per day for up to 7 consecutive days (treatment), or no hemoperfusion (control). Primary outcome was change in normalized IL-6-serum concentrations during study day 1 and 7.

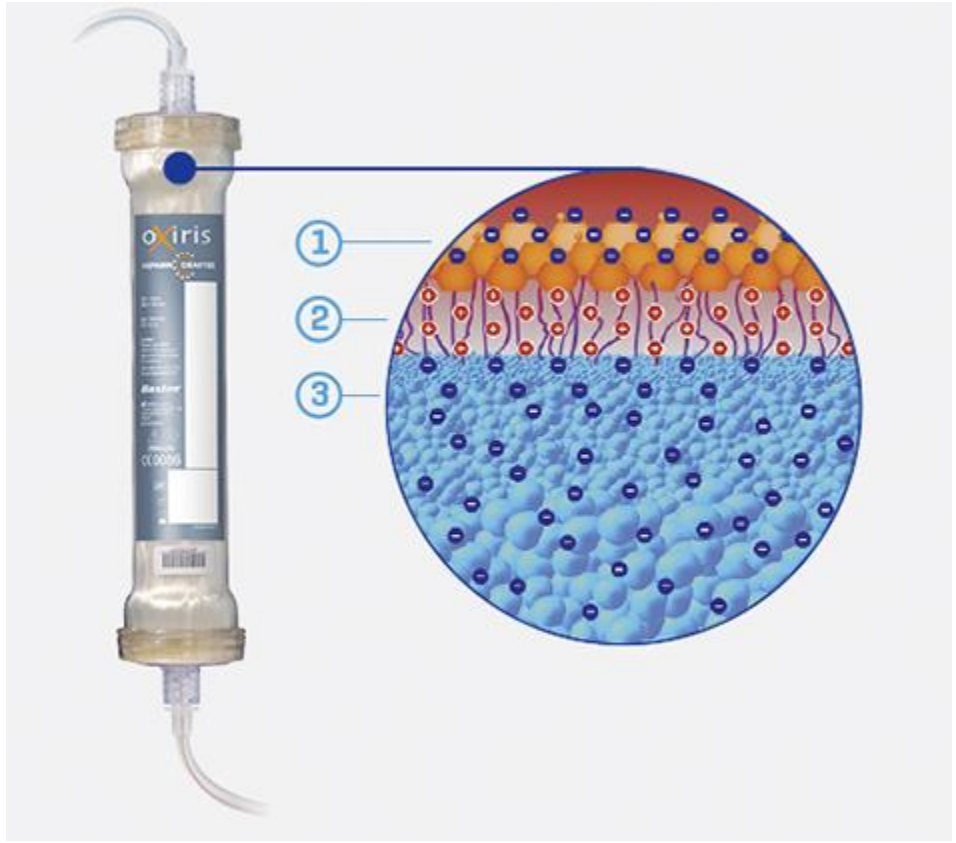
Results

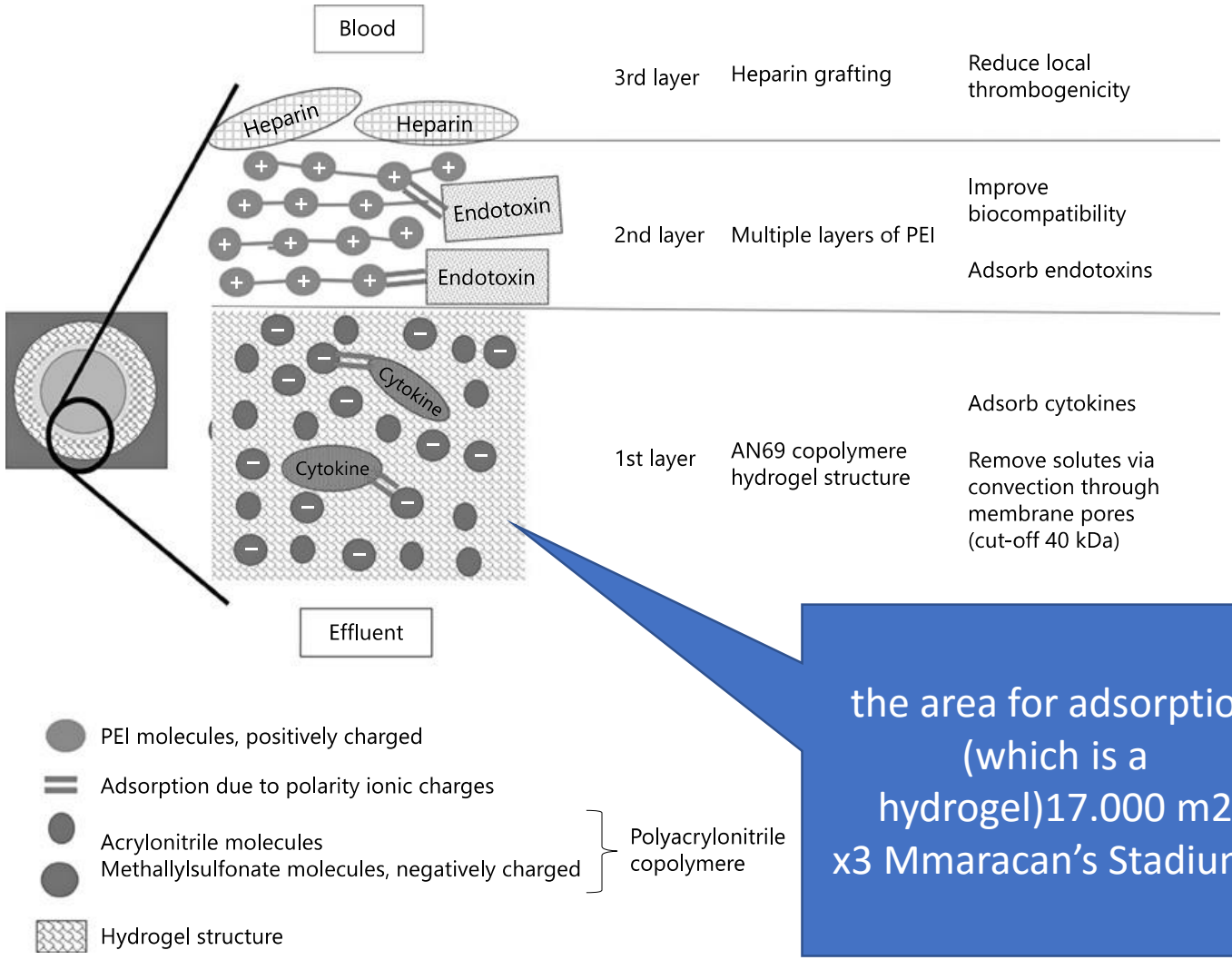
97 of the 100 randomized patients were analyzed. We were not able to detect differences in systemic plasma IL-6 levels between the two groups (n = 75; p = 0.15). Significant IL-6 elimination, averaging between 5 and 18% per blood pass throughout the entire treatment period was recorded. In the unadjusted analysis, 60-day-mortality was significantly higher in the treatment group (44.7%) compared to the control group (26.0%; p = 0.039). The proportion of patients receiving renal replacement therapy at the time of enrollment was higher in the treatment group (31.9%) when compared to the control group (16.3%). After adjustment for patient morbidity and baseline imbalances, no association of hemoperfusion with mortality was found (p = 0.19).

Conclusions

In this patient population with predominantly septic shock and multiple organ failure, hemoadsorption removed IL-6 but this did not lead to lower plasma IL-6-levels. We did not detect statistically significant differences in the secondary outcomes multiple organ dysfunction score, ventilation time and time course of oxygenation.

oXiris


oXiris
1
2
3


Blood
Heparin
Heparin
Endotoxin
Endotoxin
Cytokine
Cytokine
Effluent
3rd layer
Heparin grafting
Reduce local thrombogenicity
2nd layer
Multiple layers of PEI
Improve biocompatibility
Adsorb endotoxins
1st layer
AN69 copolymere hydrogel structure
Adsorb cytokines
Remove solutes via convection through membrane pores (cut-off 40 kDa)
PEI molecules, positively charged
Adsorption due to polarity ionic charges
Acrylonitrile molecules
Methallylsulfonate molecules, negatively charged
Polyacrylonitrile copolymere
Hydrogel structure
the area for adsorption (which is a hydrogel)17.000 m2
x3 Mmaracan's Stadium !

Hemopurifier

a fascinating technique
XC Virus elimination

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

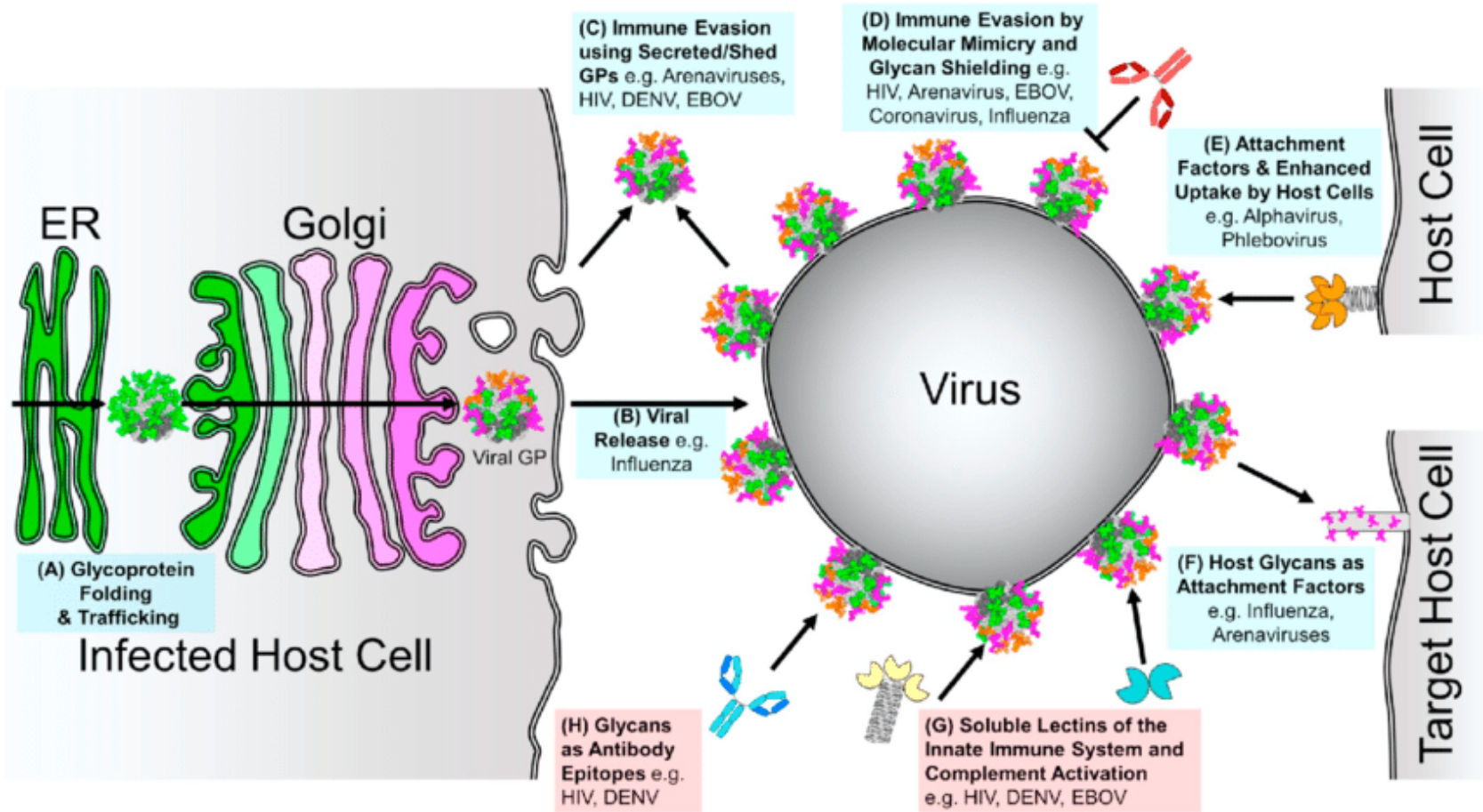
APRIL 9, 2015

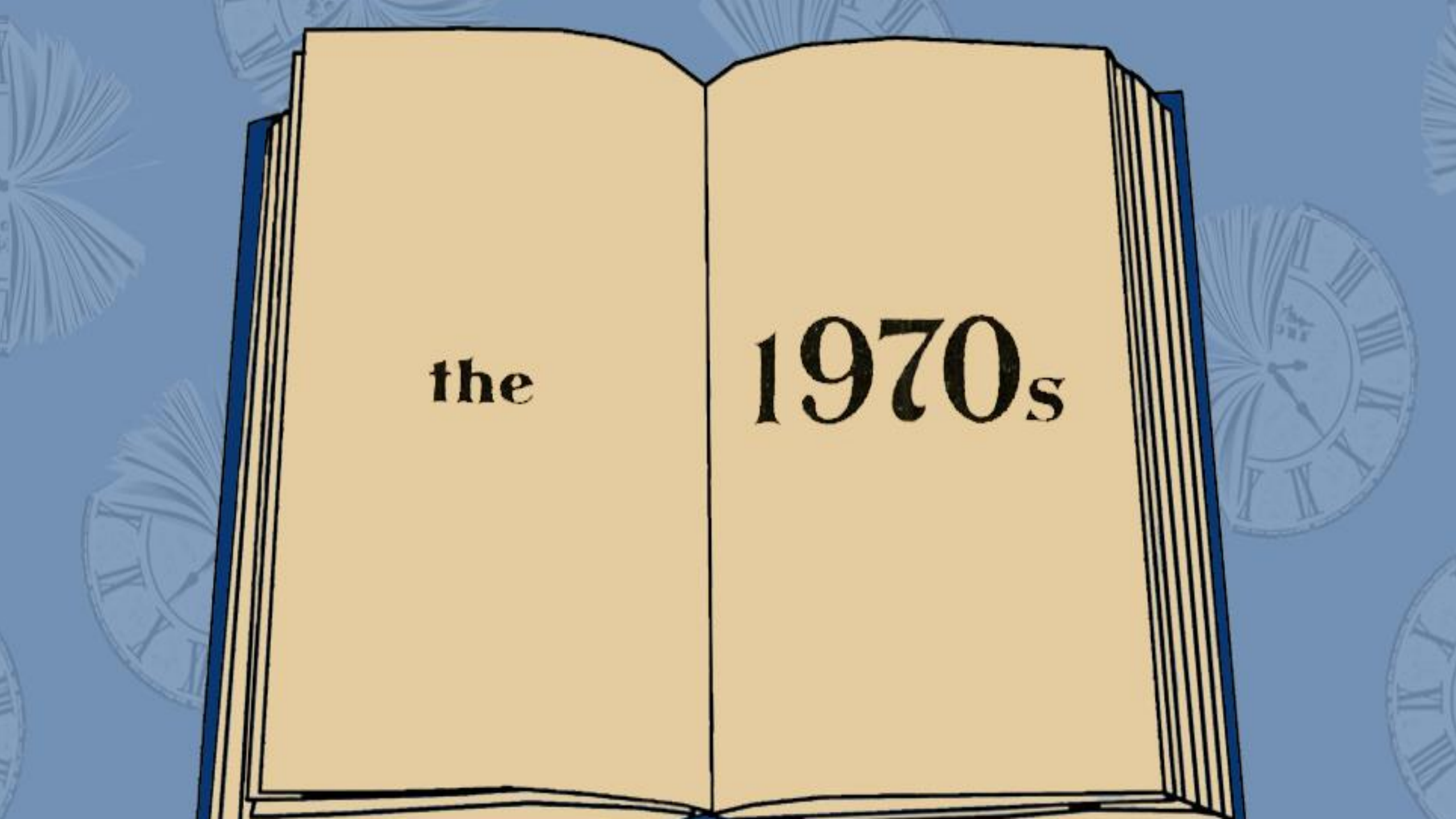
The Next Epidemic — Lessons from Ebola

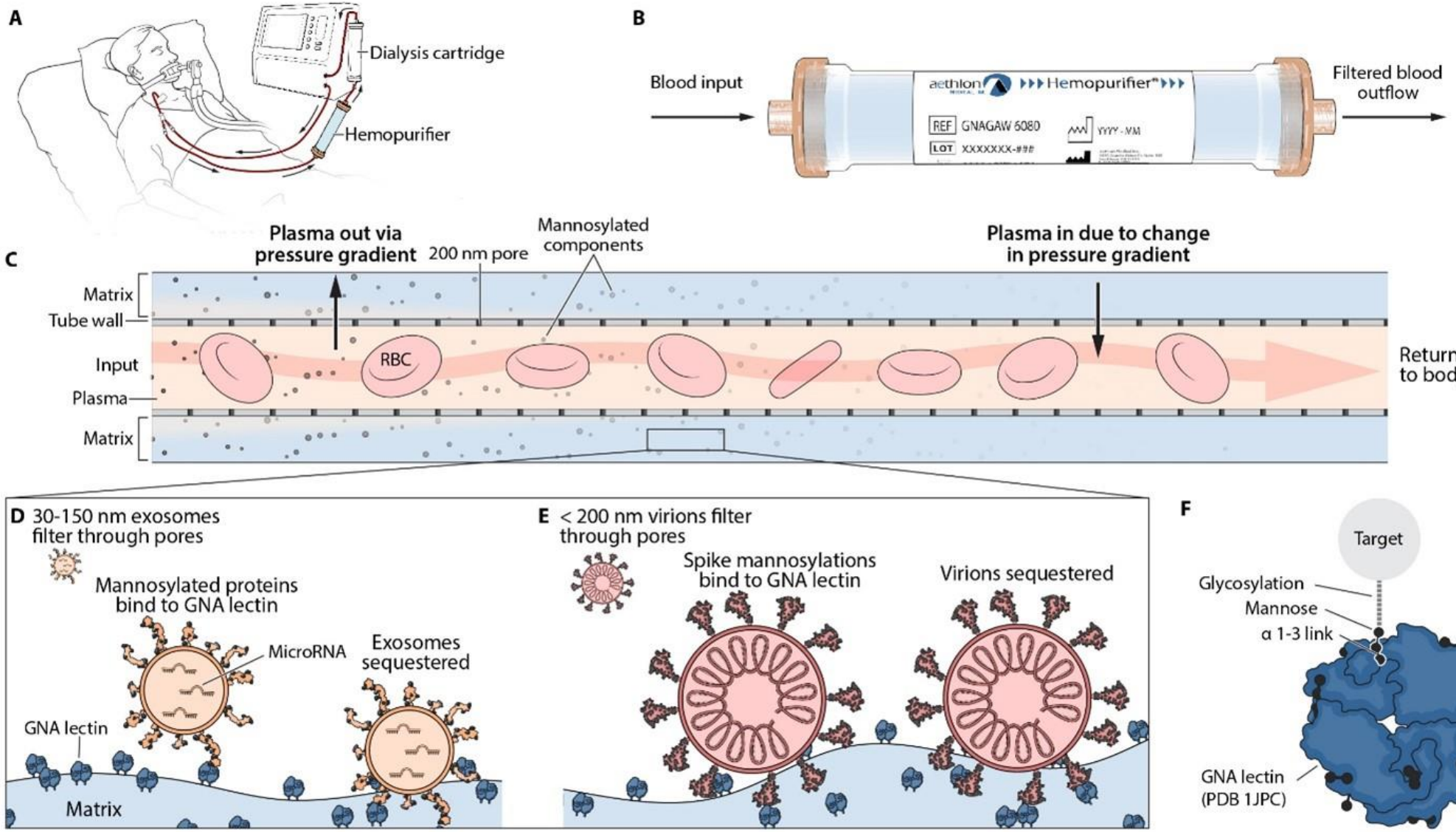
Bill Gates

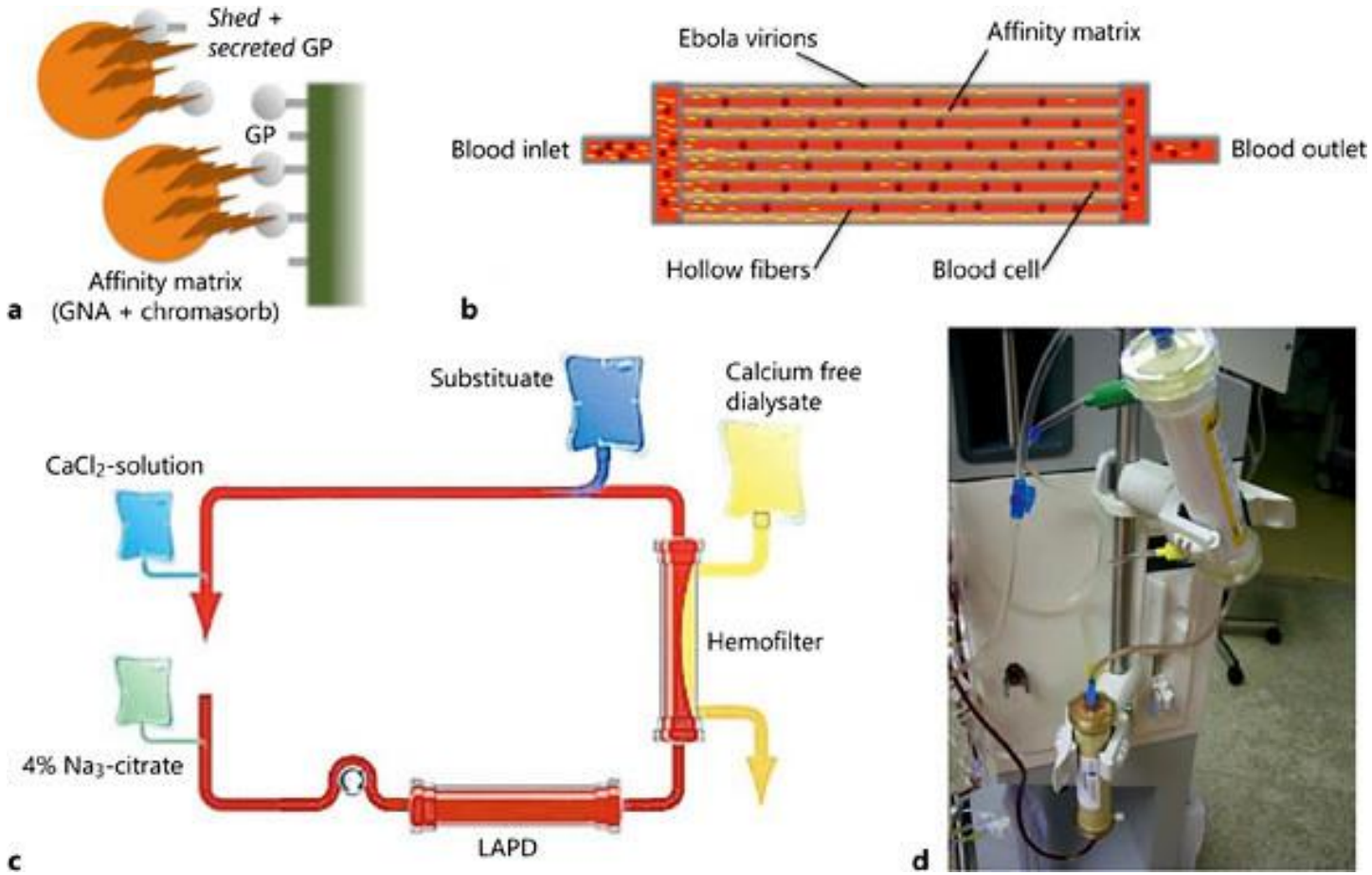
Perhaps the only good news from the tragic Ebola epidemic in Guinea, Sierra Leone, and Liberia is that it may serve as a wake-up call: we must prepare for future epidemics of diseases that may spread

Bio-terrorism could kill >30 million people in a year in future, warns Bill Gate


ER
Golgi
Viral GP
(A) Glycoprotein Folding & Trafficking
Infected Host Cell
(C) Immune Evasion using Secreted/Shed GPs e.g. Arenaviruses, HIV, DENV, EBOV
(B) Viral Release e.g. Influenza
(D) Immune Evasion by Molecular Mimicry and Glycan Shielding e.g. HIV, Arenavirus, EBOV, Coronavirus, Influenza
Virus
(E) Attachment Factors & Enhanced Uptake by Host Cells e.g. Alphavirus, Phlebovirus
Host Cell
(F) Host Glycans as Attachment Factors e.g. Influenza, Arenaviruses
Target Host Cell
(G) Soluble Lectins of the Innate Immune System and Complement Activation e.g. HIV, DENV, EBOV
(H) Glycans as Antibody Epitopes e.g. HIV, DENV


the
1970s


A
Dialysis cartridge
Hemopurifier
B
Blood input
aethlon
Hemopurifier
REF GNAGAW 6080
LOT XXXXXXX-###
Filtered blood outflow
C
Plasma out via pressure gradient
200 nm pore
Mannosylated components
Plasma in due to change in pressure gradient
Matrix
Tube wall
Input
Plasma
Matrix
RBC
Return to body
D 30-150 nm exosomes filter through pores
Mannosylated proteins bind to GNA lectin
MicroRNA
Exosomes sequestered
GNA lectin
Matrix
E < 200 nm virions filter through pores
Spike mannosylations bind to GNA lectin
Virions sequestered
F
Target
Glycosylation
Mannose
α 1-3 link
GNA lectin
(PDB 1JPC)


Shed + secreted GP
GP
Affinity matrix (GNA + chromasorb)
a
Ebola virions
Affinity matrix
Blood inlet
Blood outlet
Hollow fibers
Blood cell
b
Substituate
Calcium free dialysate
$CaCl_2$-solution
Hemofilter
4% Na_3-citrate
LAPD
c
d

Original Paper

Blood Purification

Blood Purif 2018;46:126–133
DOI: 10.1159/000487224

Received: November 14, 2017
Accepted: January 29, 2018
Published online: April 26, 2018

Lectin Affinity Plasmapheresis for Middle East Respiratory Syndrome-Coronavirus and Marburg Virus Glycoprotein Elimination

Benjamin Koch[a] Patricia Schult-Dietrich[b] Stefan Büttner[a] Bijan Dilmaghani[a]
Dario Lohmann[a] Patrick C. Baer[a] Ursula Dietrich[b] Helmut Geiger[a]

[a]Goethe University Hospital, Med. III, Division of Nephrology, Dialysis and Transplantation, Frankfurt, Germany;
[b]Georg-Speyer-Haus, Institute for Tumor Biology and Experimental Therapy, Frankfurt, Germany

Keywords
Middle East respiratory syndrome coronavirus · Marburg virus · Extracorporeal purification · Lectin affinity plasmapheresis

Abstract
Background/Aims: Middle East respiratory syndrome coronavirus (MERS-CoV) and Marburg virus (MARV) are among the World Health Organization's top 8 emerging pathogens. Both zoonoses share nonspecific early symptoms, a high lethality rate, and a reduced number of specific treatment options. Therefore, we evaluated extracorporeal virus and glycoprotein (GP) elimination by lectin affinity plasmapheresis (LAP). ***Methods:*** For both MERS-CoV (pseudovirus) as well as MARV (GPs), 4 LAP devices (Mini Hemopurifiers, Aethlon Medical, San Diego, CA, USA) and 4 negative controls were tested. Samples were collected every 30 min and analyzed for reduction in virus infectivity by a flow cytometry-based infectivity assay (MERS-CoV) and in soluble GP content (MARV) by an immunoassay. ***Results:*** The experiments show a time-dependent clearance of MERS-CoV of up to 80% within 3 h (pseudovirus). Up to 70% of MARV-soluble GPs were eliminated at the same time. Substantial saturation of the binding resins was detected within the first treatment hour. ***Conclusion:*** MERS-CoV (pseudovirus) and MARV soluble GPs are eliminated by LAP in vitro. Considering the high lethality and missing established treatment options, LAP should be evaluated in vivo. Especially early initiation, continuous therapy, and timed cartridge exchanges could be of importance. Video Journal Club 'Cappuccino with Claudio Ronco' at http://www.karger.com/?doi=487224.

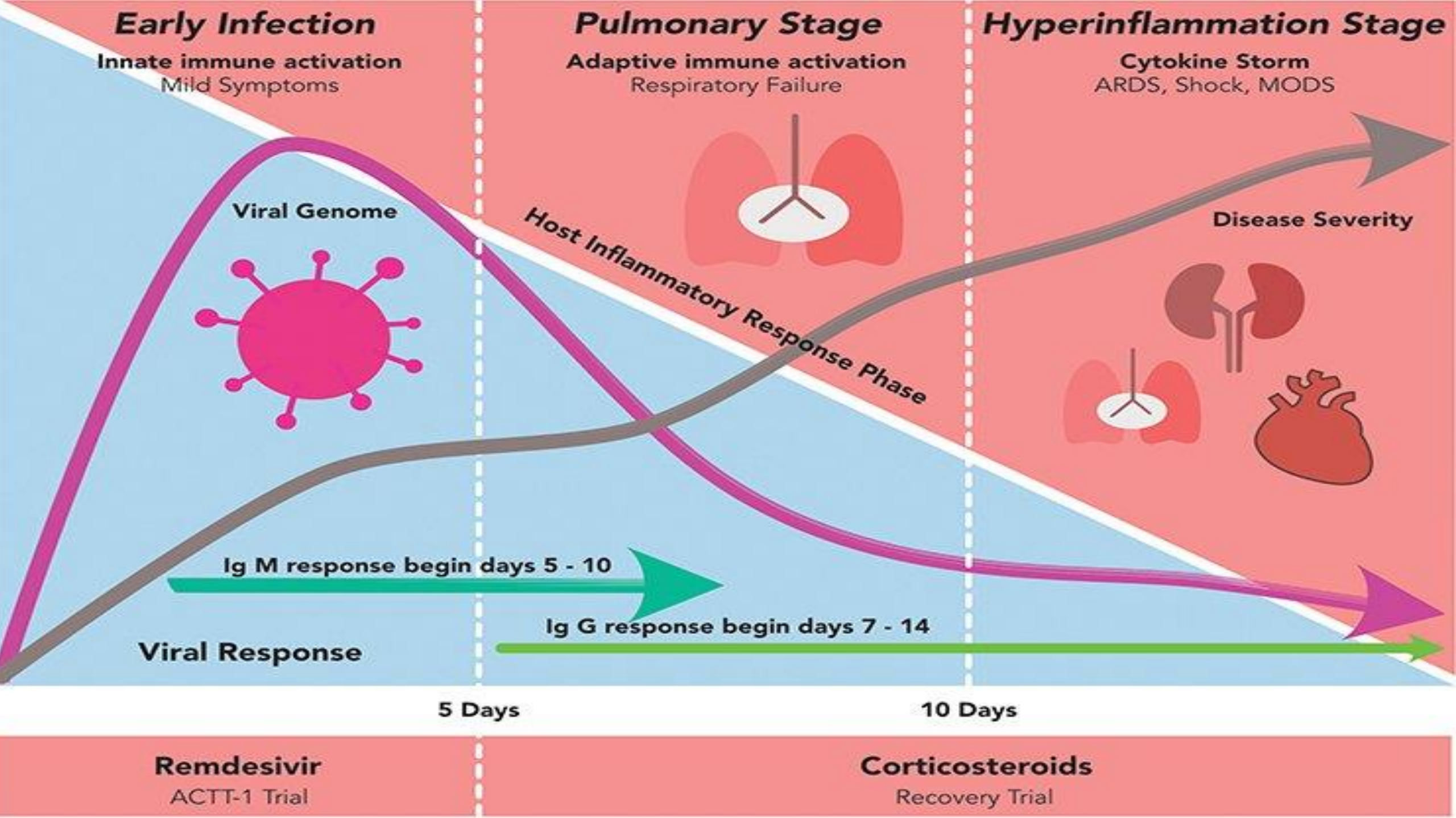
Introduction

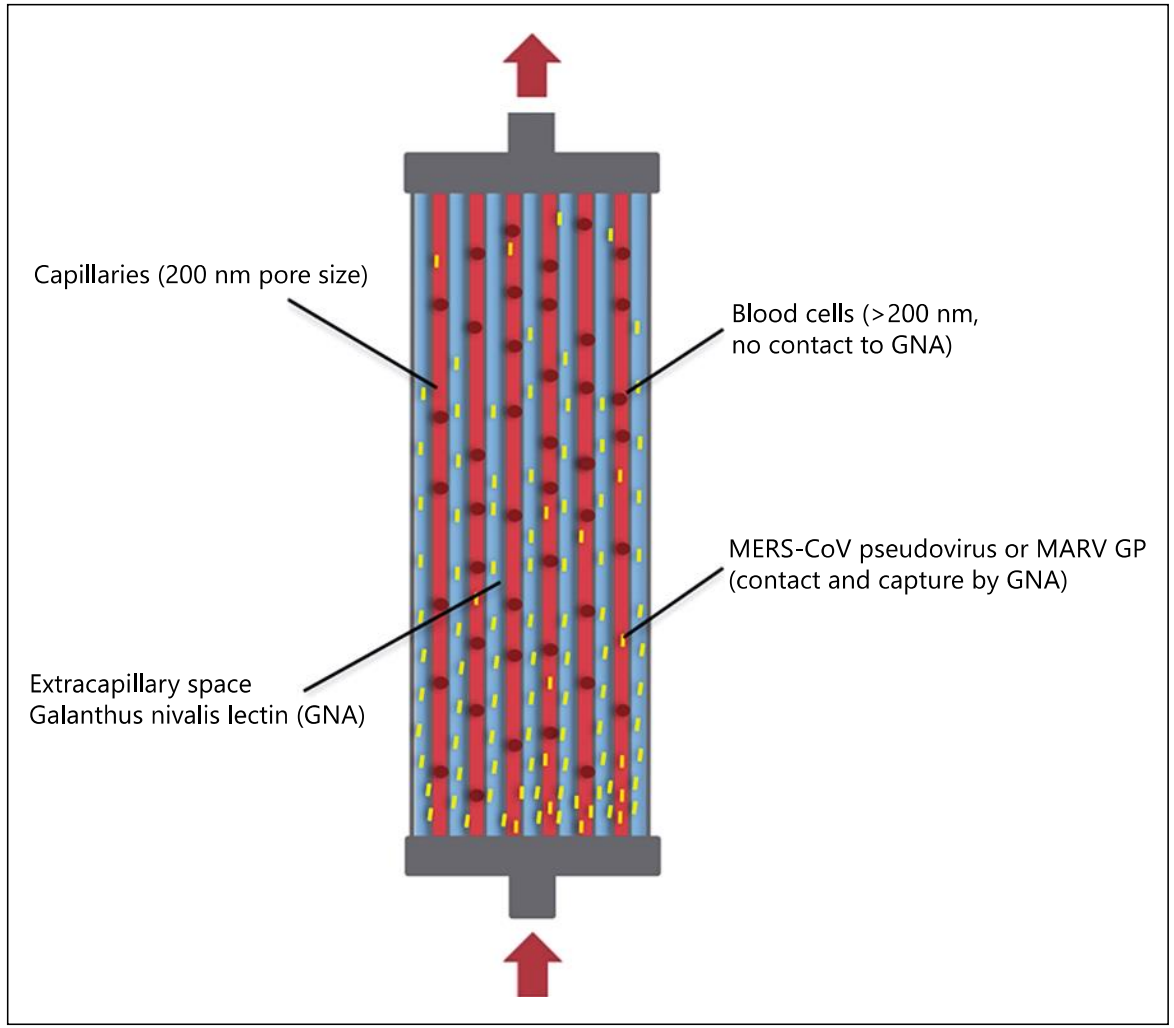
According to Bill Gates' address at the Munich Security Conference 2017, the next 10–15 years could witness a global pandemic taking more than 30 million victims in less than a year [1]. He therefore called for an accelerated development of new vaccines, therapeutics, and diagnostics for emerging pathogens. Among the World Health Organization's top 8 emerging pathogens are Middle East respiratory syndrome coronavirus (MERS-CoV) as well as Marburg virus (MARV) [2]. Besides a zoonotic transmission chain, their common features are nonspecific early symptoms, a high lethality rate, and a reduced number of effective treatment options [3, 4].

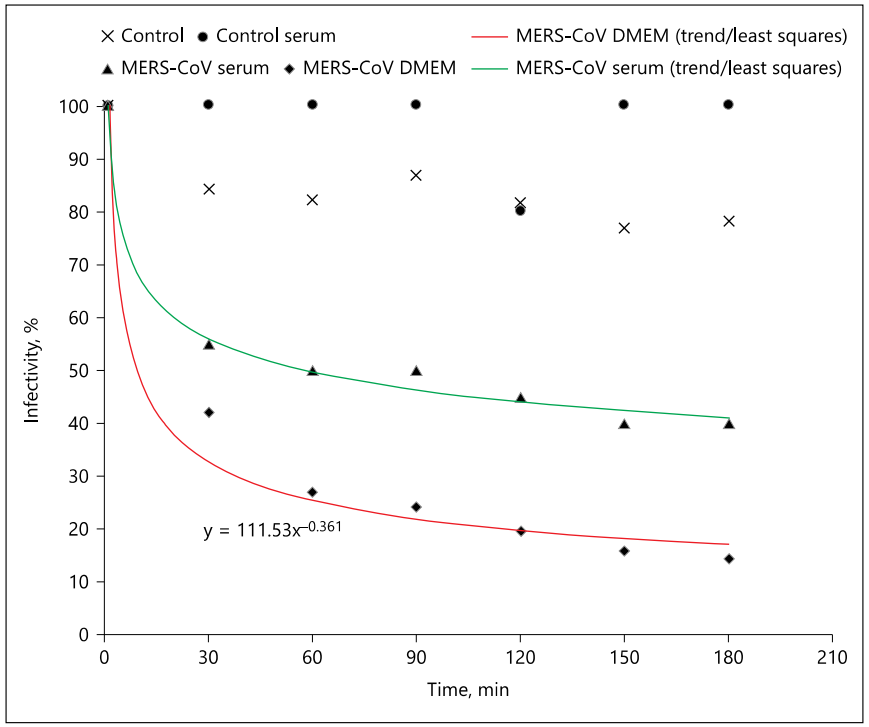
Work was supported in part by a grant from Aethlon Medical Inc., San Diego, USA for a DARPA research project on Dialysis-Like Therapeutics.

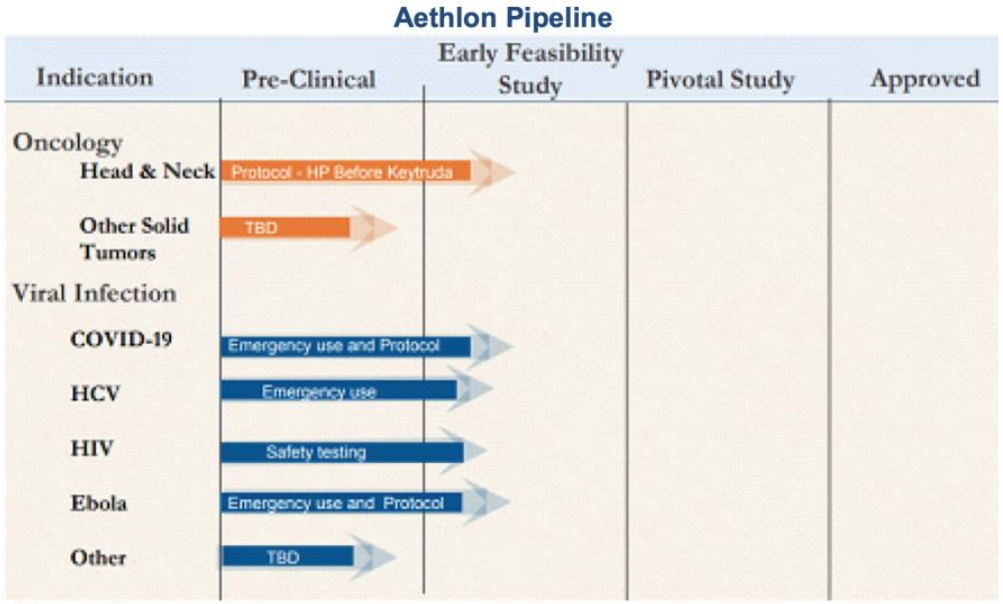
E-Mail karger@karger.com
www.karger.com/bpu

Benjamin Koch, MD
Division of Nephrology, Dialysis and Transplantation
Goethe University Hospital Med. III
Theodor-Stern-Kai 7, DE–60590 Frankfurt (Germany)
E-Mail Benjamin.Koch@kgu.de


Early Infection
Innate immune activation
Mild Symptoms
Pulmonary Stage
Adaptive immune activation
Respiratory Failure
Hyperinflammation Stage
Cytokine Storm
ARDS, Shock, MODS
Viral Genome
Host Inflammatory Response Phase
Disease Severity
Ig M response begin days 5 - 10
Ig G response begin days 7 - 14
Viral Response
5 Days
10 Days
Remdesivir
ACTT-1 Trial
Corticosteroids
Recovery Trial



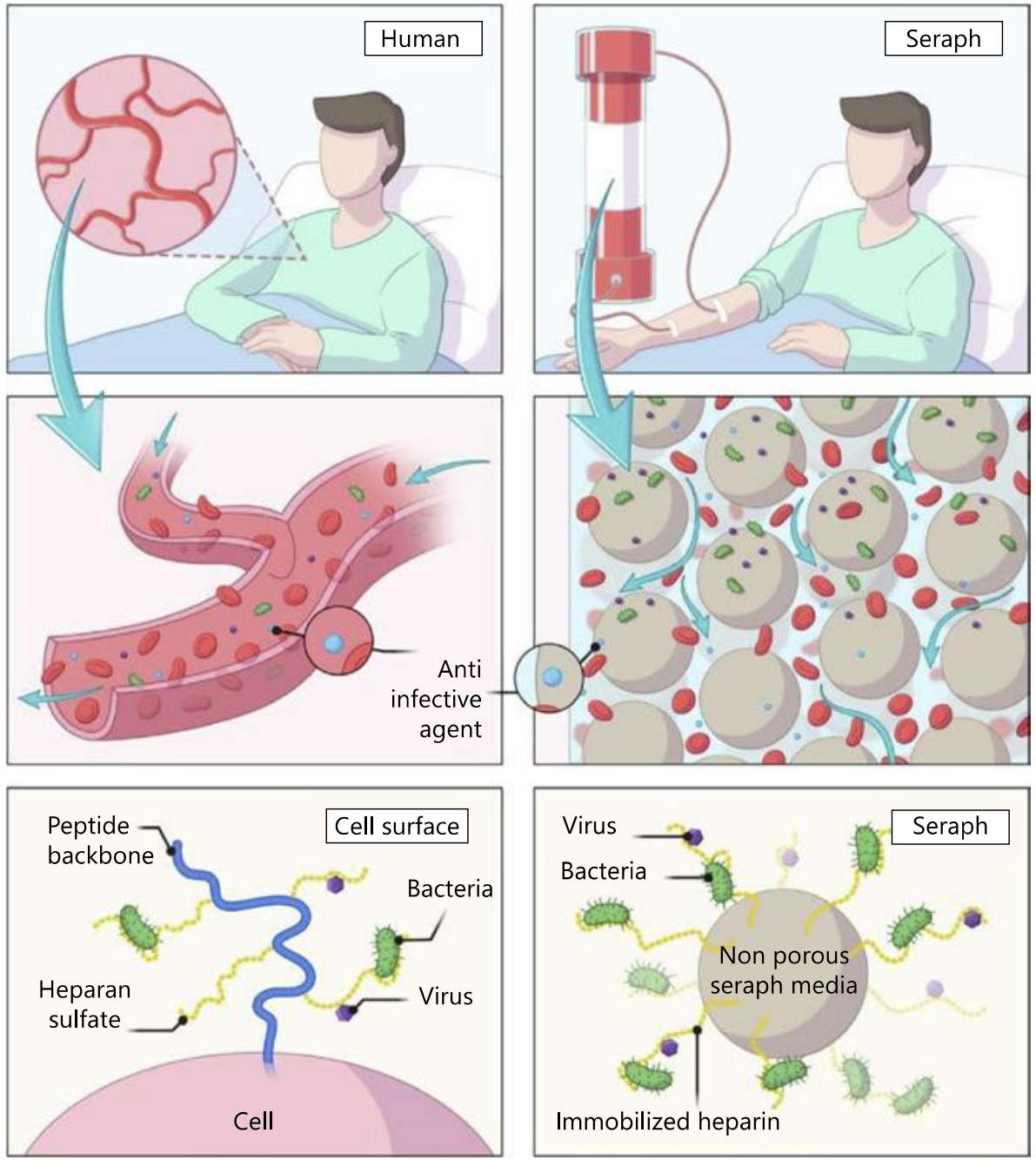


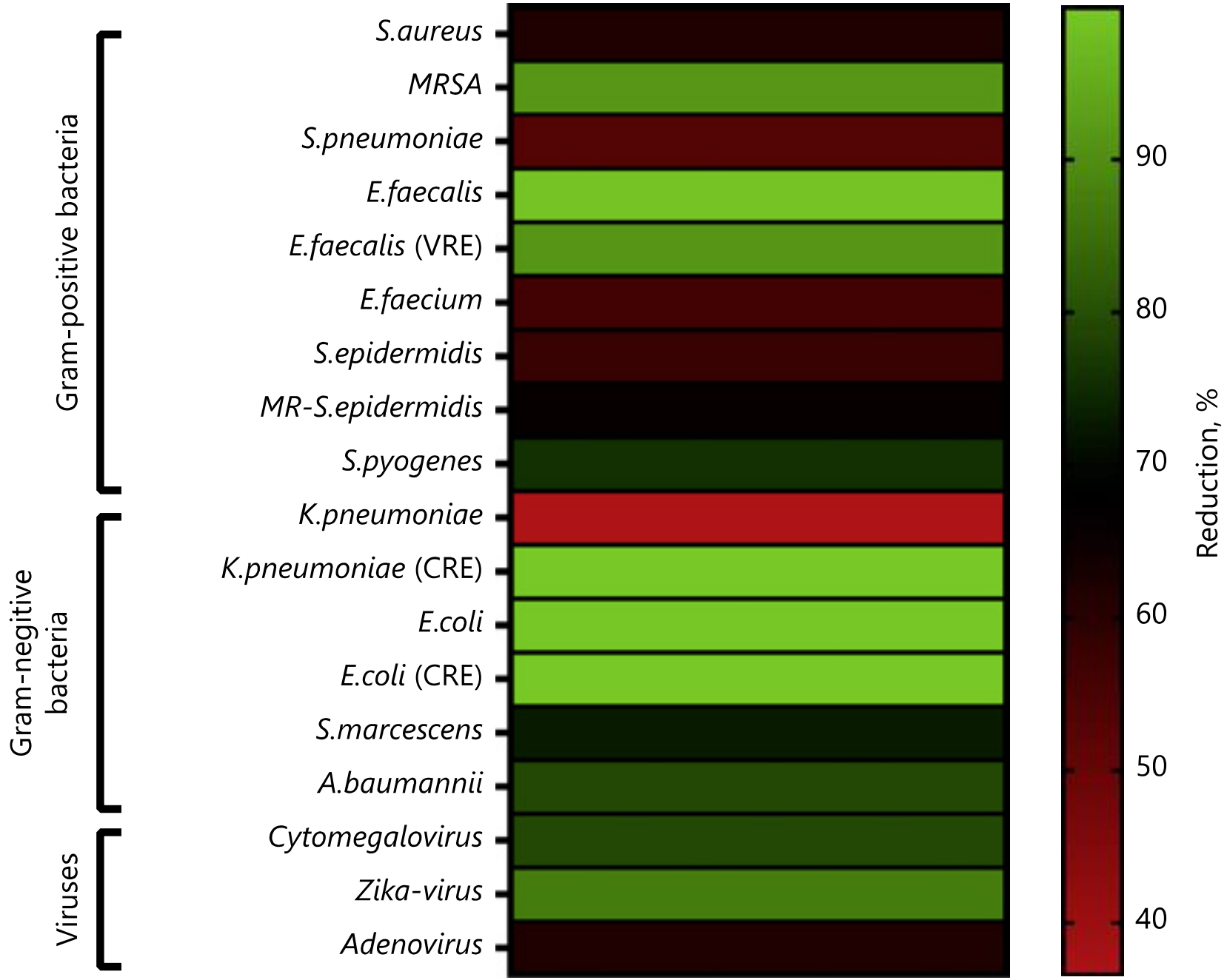


Source: Company reports

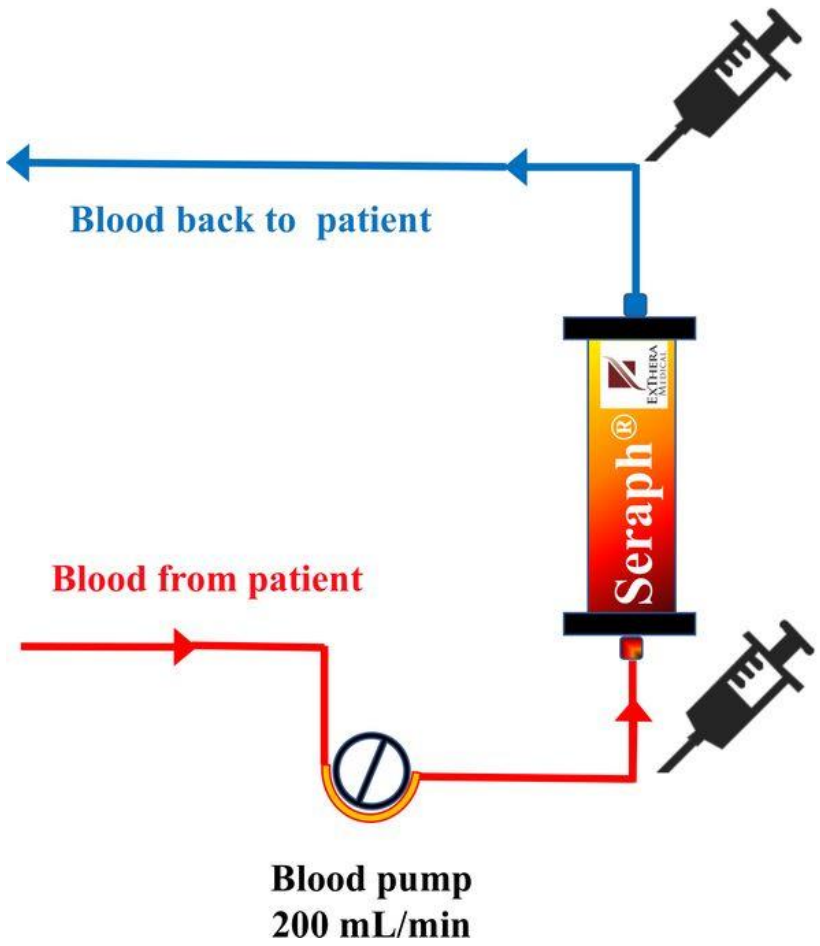
Seraph® 100

using heparin for pathogen removal from the blood


Human
Seraph
Anti
infective
agent
Peptide
backbone
Cell surface
Bacteria
Heparan
sulfate
Virus
Cell
Virus
Bacteria
Seraph
Non porous
seraph media
Immobilized heparin


Gram-positive bacteria
Gram-negitive bacteria
Viruses
S.aureus
MRSA
S.pneumoniae
E.faecalis
E.faecalis (VRE)
E.faecium
S.epidermidis
MR-S.epidermidis
S.pyogenes
K.pneumoniae
K.pneumoniae (CRE)
E.coli
E.coli (CRE)
S.marcescens
A.baumannii
Cytomegalovirus
Zika-virus
Adenovirus
90
80
70
60
50
40
Reduction, %

Seraph 100 Micro-bind Affinity Blood Filter



Treatment time (min)	Time to positivity (hours)
5	Negative blood culture
120	Negative blood culture
240	Negative blood culture

Treatment time (min)	Time to positivity (hours)
5	26
120	28
240	Negative blood culture

What is the rationale to use the Seraph® 100 in COVID-19 patients?

1- elimination of the virus from the blood

2- reduction of proinflammatory cytokines

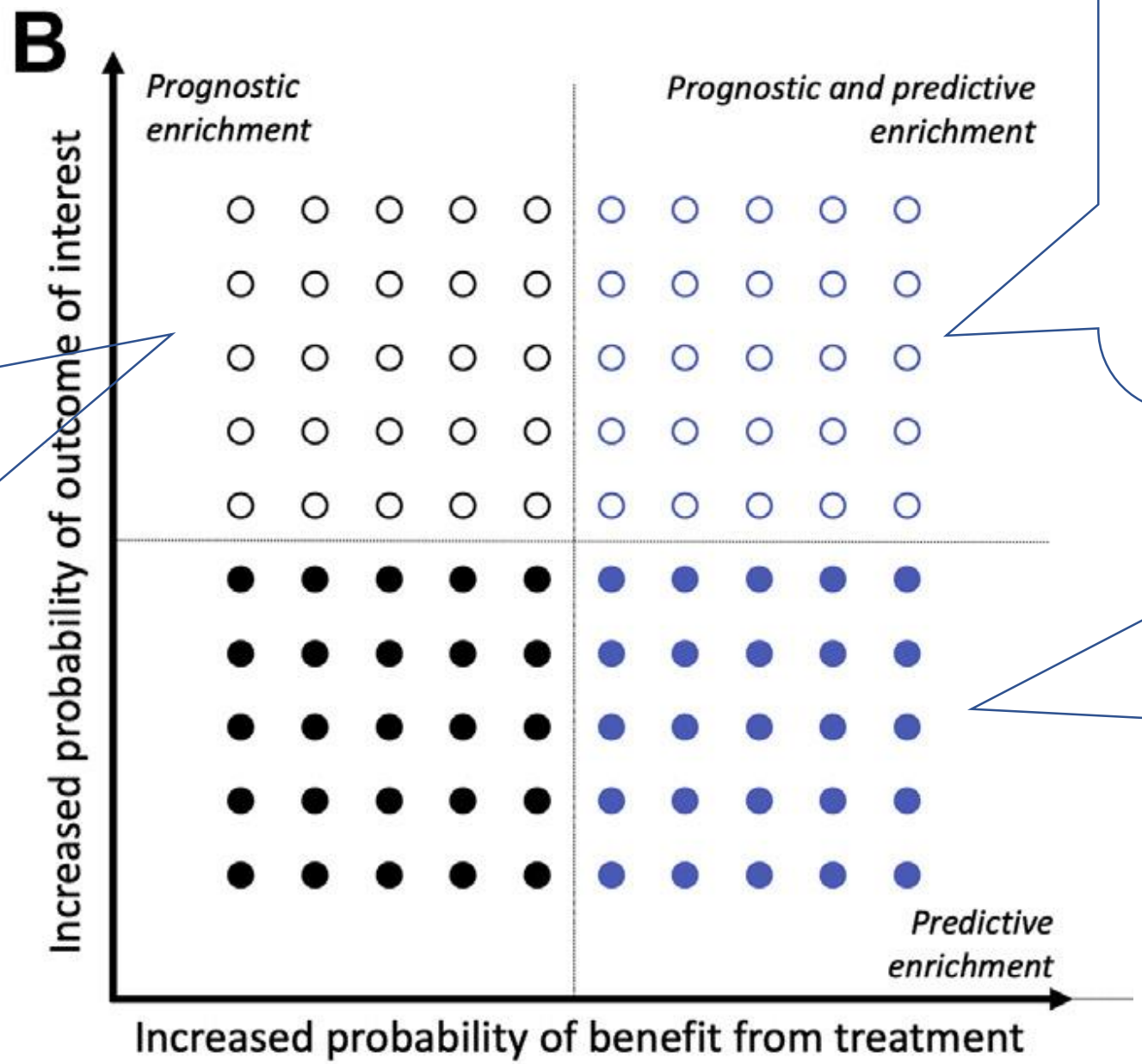
3- improvement in oxygen saturation

In April 2020, the US Food and Drug Administration granted emergency use authorization for certain medical devices to be used in patients with coronavirus disease 2019 (CO- VID-19).
This included extracorporeal blood purification devices.

the Enrichment Strategy

to select pt that might benefit better of the treatment

Outcome
identify patients at higher risk of the outcome of interest
>>>
1-PaO2/FiO2 increment,
2-Ven.t free days,
3-Weaning from NE



Outcome (no mortality)
&
Better selection (with Biomarkers)
to select the correct outcome expected & plausible to be changed in ICU
>>> ***for a better results***

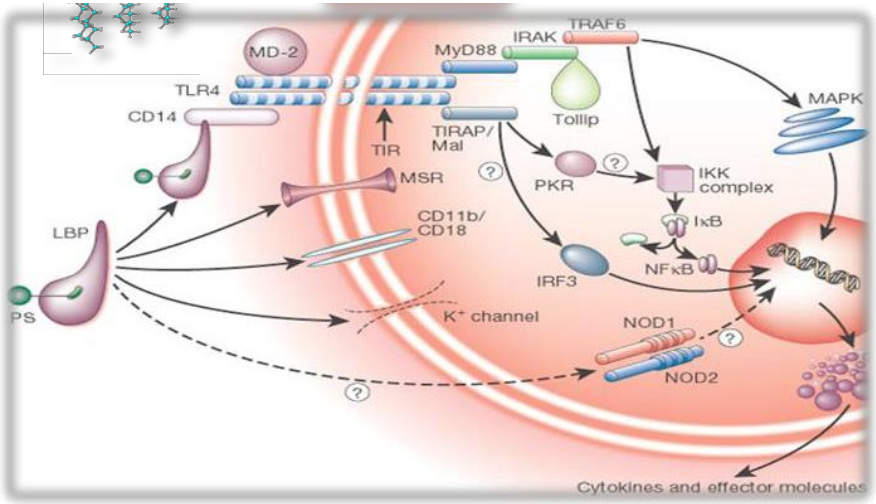
Better selection
Biomarkers can identify patient with better response to treatment
>>>
1-biomarkers of AKI (TIMP2 x IGFBP7, NGAL, KIM-1) or
2-IL-6 or
3-Endotoxin activity


Conclusion

SEPSIS CASCADE

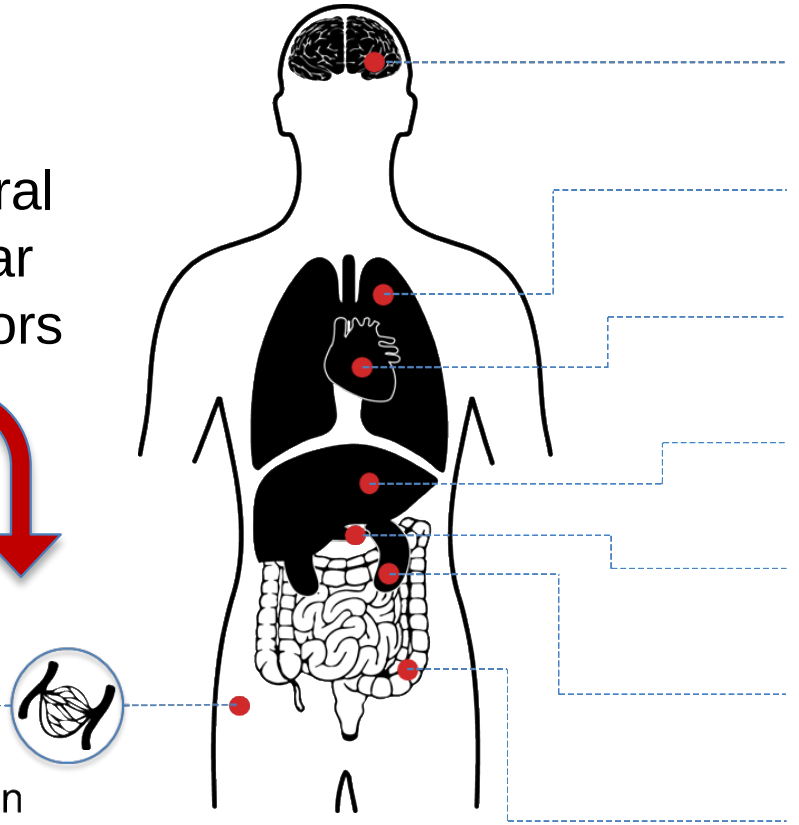
Infection >>> Immuno response >>> Organ Damage

Bacteria/Virus



Humoral
Cellular
Effectors

Endothelial activation



Microcirculation
- Microvascular thrombosis

Central nervous system
- Confusion

Lungs
- ARDS

Cardiovascular system
- Shock

Liver
- Excretory failure

Pancreas
- Hyperglycemia

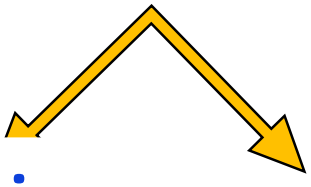
Kidneys
- Oliguria

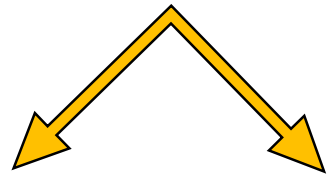
Gastrointestinal tract
- Loss of barrier function

SEPTIC PATIENT and THERAPEUTIC TARGETS

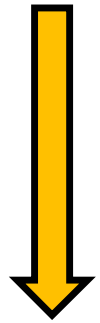
Infection >>> Immuno dysregulation >> Organ Damage

Drugs





Drugs



Source

Bacteria/Endotoxin /Virus removal

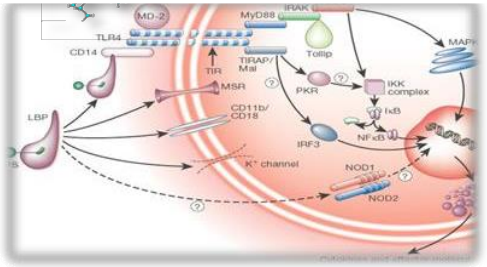
Immuno modulation Cytokine removal

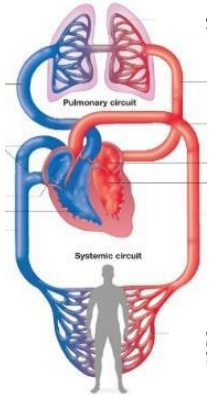
Multiple Organ Support Therapy

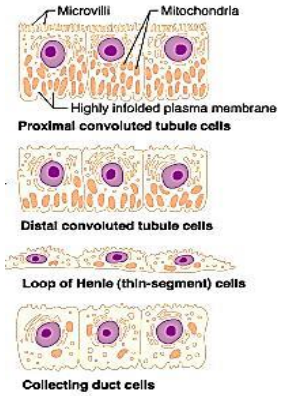
Specific >>>>>> General Aspecific >>>>>> Specific

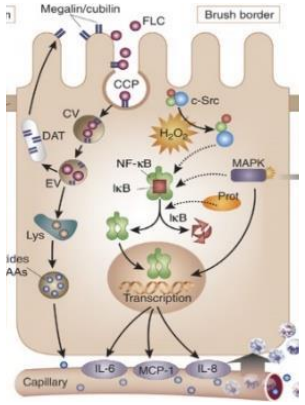
INTEGRATED APPROACH TO SEPSIS

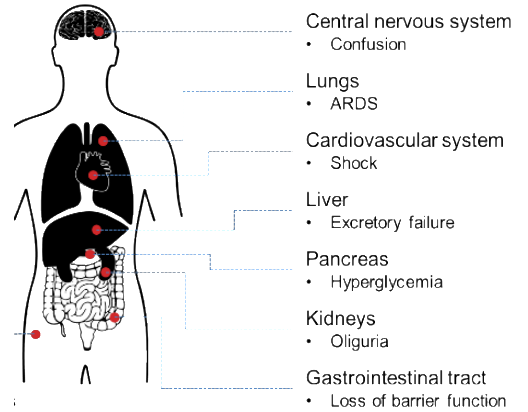
Infection >>> Immuno response >>> Organ Damage





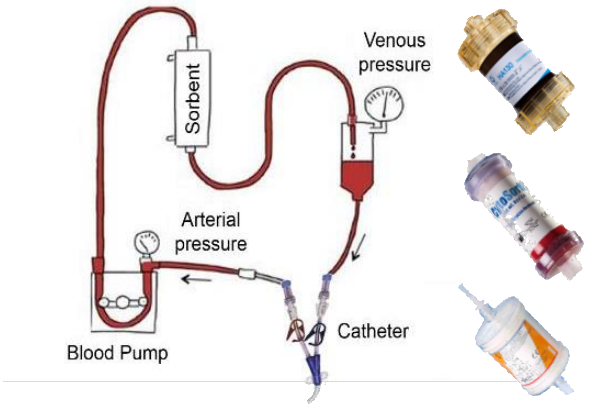


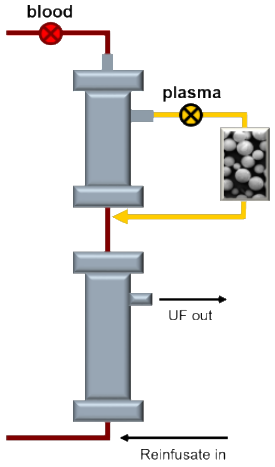


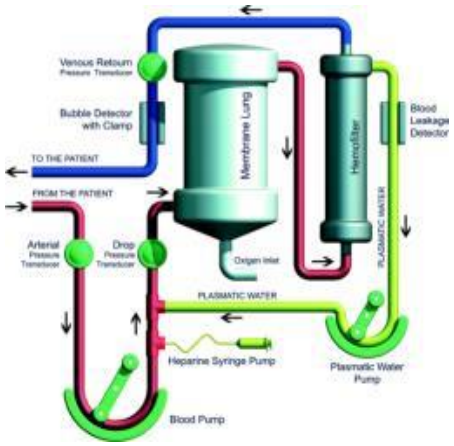


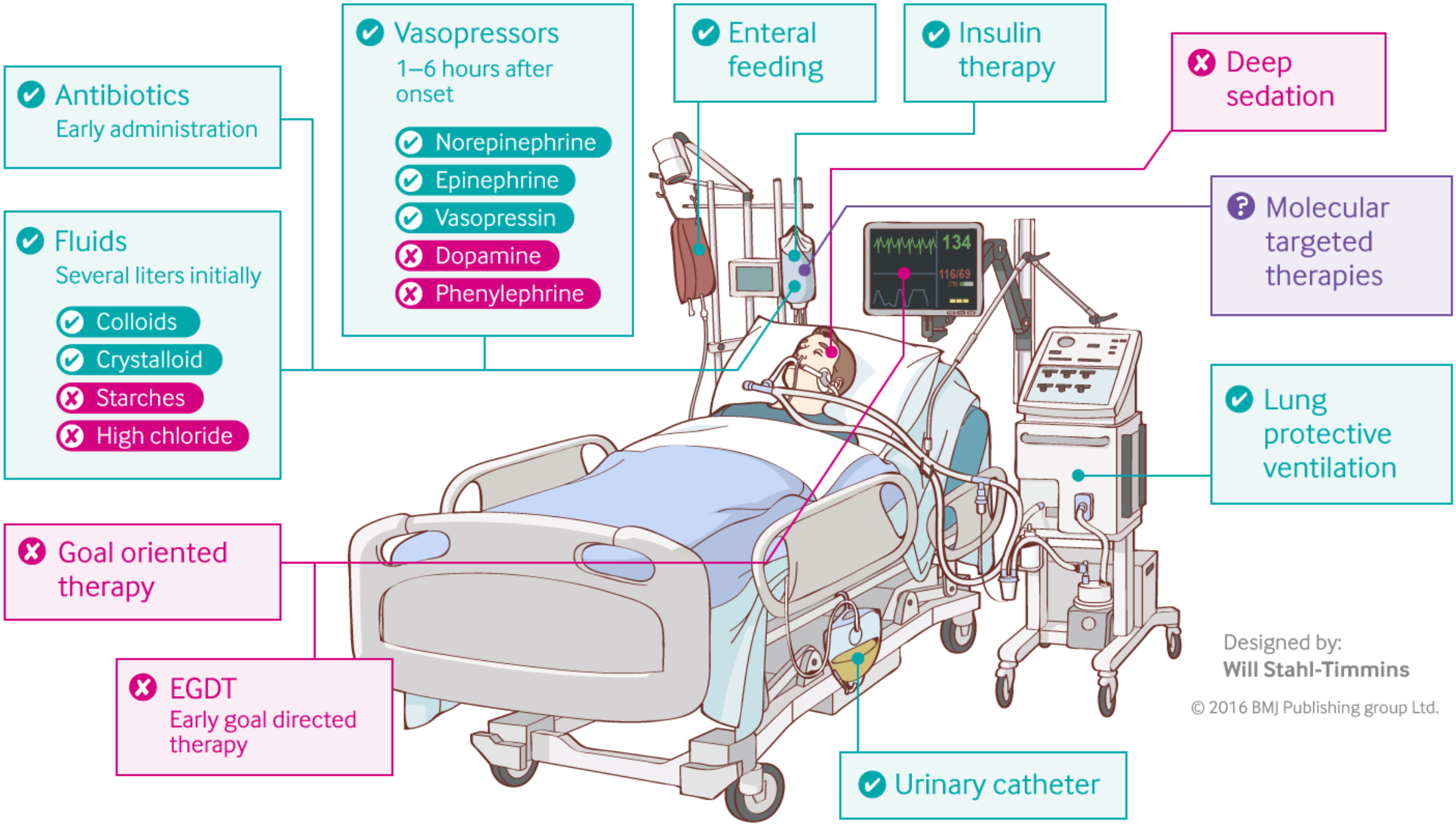
LPS/Virus >>> Cytokines/Chemokines >>> Org. Failure

PMX-B
Seraph 100
Hemopurifier





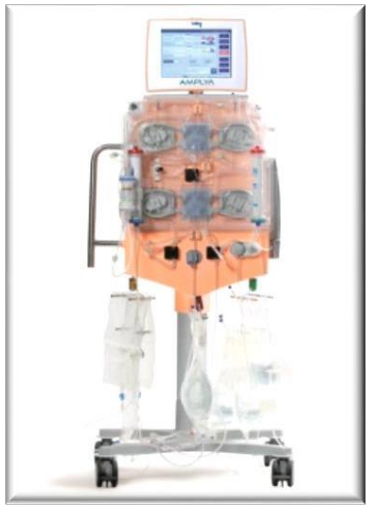



Antibiotics
Early administration
Fluids
Several liters initially
Colloids
Crystalloid
Starches
High chloride
Vasopressors
1–6 hours after onset
Norepinephrine
Epinephrine
Vasopressin
Dopamine
Phenylephrine
Enteral feeding
Insulin therapy
Deep sedation
Molecular targeted therapies
Lung protective ventilation
Goal oriented therapy
EGDT
Early goal directed therapy
Urinary catheter
134
116/69
Designed by:
Will Stahl-Timmins
© 2016 BMJ Publishing group Ltd.

we have to support the kidney, we have to support the liver, we have to support the lungs, the heart,…BUT before that >>> we have to create a condition in which no further damage occurs in out pt.

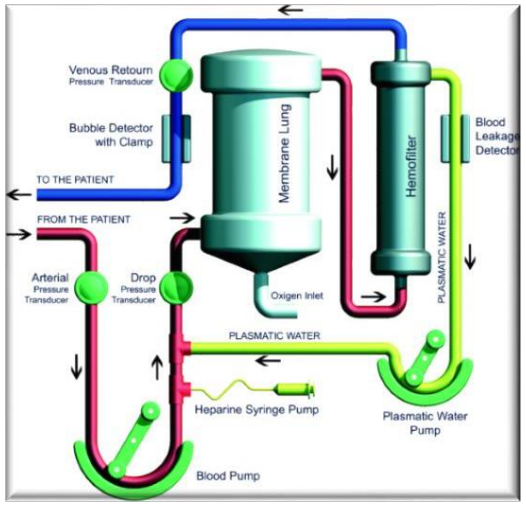
Multiple Organ Support in Critical Illness and Sepsis

AKI & Sepsis

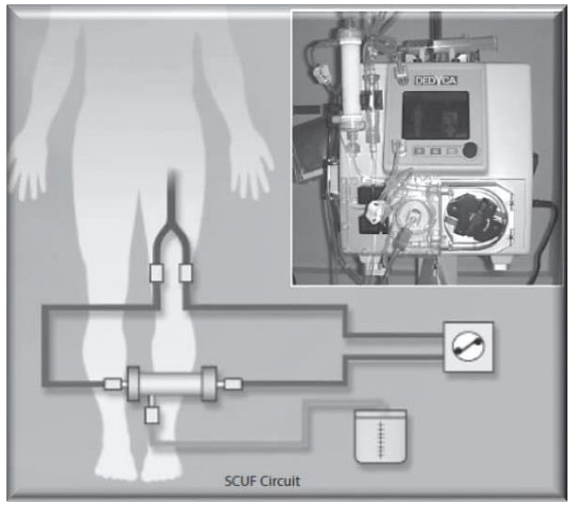


Liver Support

Lung Support $ECCO_2R$



Heart Failure



Sequential Approach

- Pharmacologic Approach
- Timely Pathogen/Endotoxin removal
- Immunomodulation
- Adequate organ support

Personalized Therapy
Precision Therapy

MERCI