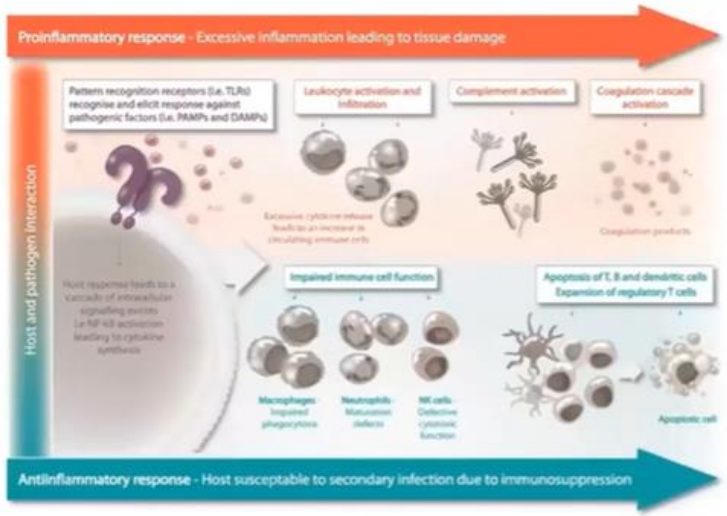
Virus removal: Is it possible ?

Ioannis Griveas, MD, PhD

athens-NEPHROLOGY



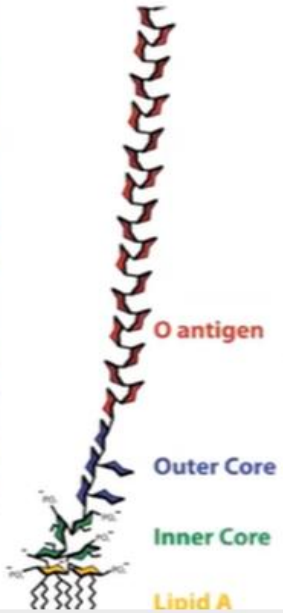
"Inflammation is a NECESSARY EVIL"

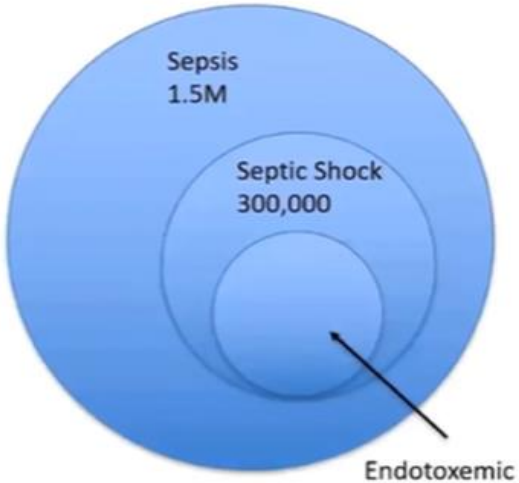
Nedeva C, Menassa J, Puthalakath H. Front Cell Dev Biol. 2019

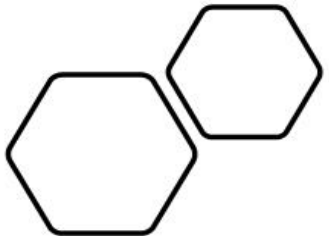
Event	Year(s)	Major Findings
Discovery of microorganisms	1676	Robert Hooke and Antoni van Leeuwenhoek independently discover living microorganisms by careful microscopy using lenses to identify microbes.
Proving the germ theory of disease	1860s	Louis Pasteur (1822–1864) and Robert Koch (1843–1910) demonstrate that microorganisms in infected tissues directly cause tissue injury. Organisms can be transmitted between animals and humans.
Ignas Semmelweis	1850s	Semmelweis (1818–1865) proves in 1847 that microbial pathogens can be transmitted by the hands of doctors and cause potentially lethal puerperal fever; hand hygiene prevents this from happening.
Discovery of Endotoxin	1892	Robert Koch and his colleague Richard Pfeiffer first prove that about 70% of the cell wall of Gram-negative bacteria is protease resistant and lipid sensitive material. They demonstrate that purified endotoxin injected intravenously is lethal to laboratory animals, forming Koch's Postulates.
Gram's stain aids to detect and define bacteria	1884	Hans Christian Gram (1853–1938) first develops a method to rapidly classify and identify bacteria as either Gram-positive or Gram-negative by differential staining and microscopy.
Polymyxin B bound hemofilters remove endotoxin	1994	Tohru Tani and Hisataka Shoji, et al. develop the cationic filters which will bind to circulating endotoxin and remove endotoxin from the circulation and can rescue patients from endotoxemia.

Shoji H, Opal SM. . Int J Mol Sci. 2021

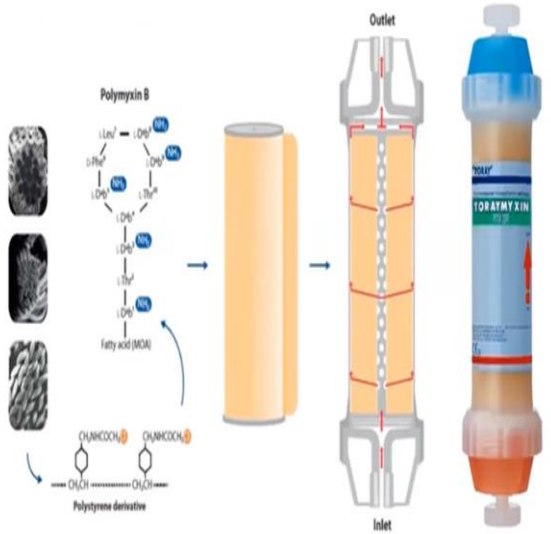
Endotoxin and Endotoxemia





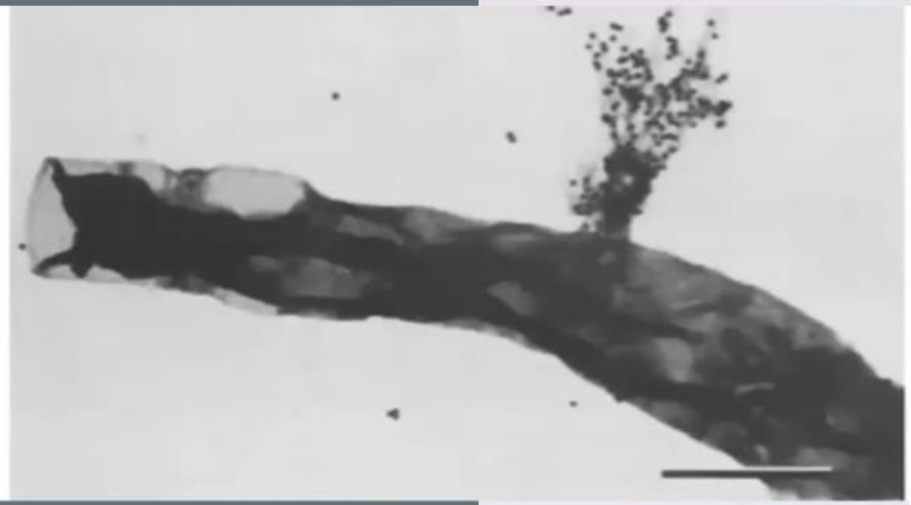


In the mid-1970s, polymyxin B was discovered to be protective against endotoxin-induced hemodynamic shock b
time, was demonstrated to be extremely toxic for the kidney and central nervous system, which precludes its systemic use

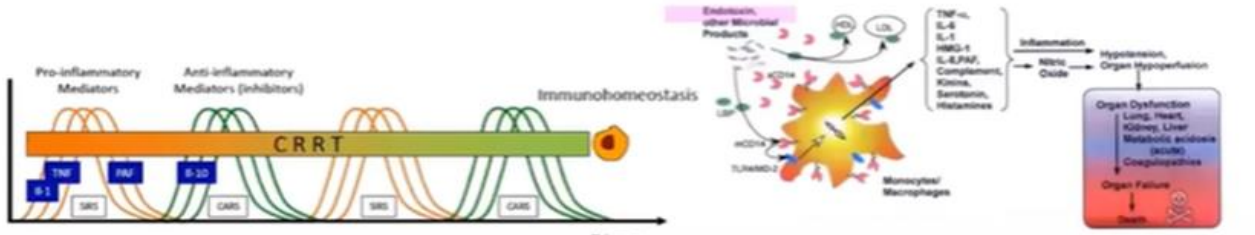


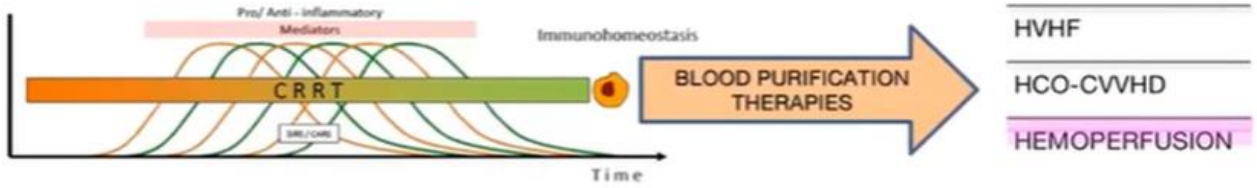
PMX is composed of polymyxin B (PL-B) covalently bonded to polystyrene-derivative fibers.

Since 1994, polymyxin B has been bound and immobilized to polystyrene fibers



Antibiotic-induced liberation of the bacterial endotoxin LPS may have immediate adverse effects promoting septic shock in patients





Editorials

November 30, 1964

"ENDOTOXIN SHOCK"

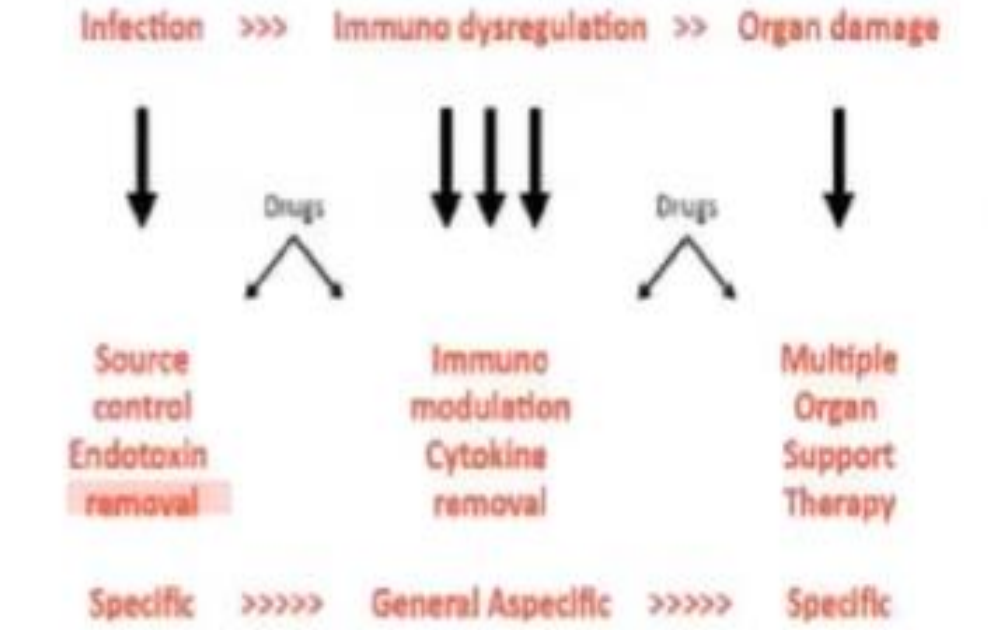
JAMA. 1964;190(9):847-848.
doi:10.1001/jama.1964.03070220053016

Abstract

Endotoxin shock," so called because it is assumed to be caused by the release of toxin from gram-negative bacteria, presents the clinician with a therapeutic dilemma. Despite a variety of available procedures, no technique exists for removal or inactivation of the causative agent once it enters the circulation. Consequently the only successful treatment is symptomatic. In a recent evaluation of current management, Weil et al[1] indicate that none of the available therapeutic methods has been successful when used alone; however, used in judicious combi-

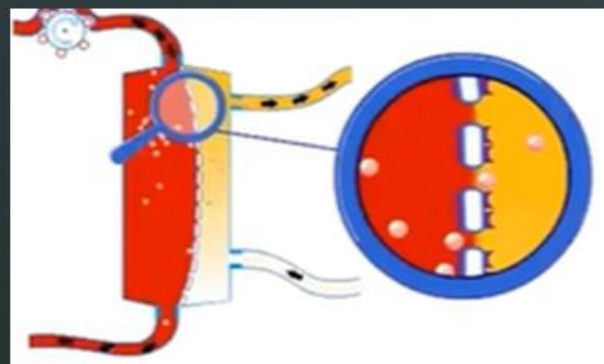
2020

SEPTIC PATIENT and THERAPEUTIC TARGETS



De Rosa S. et al. Purif. 2019

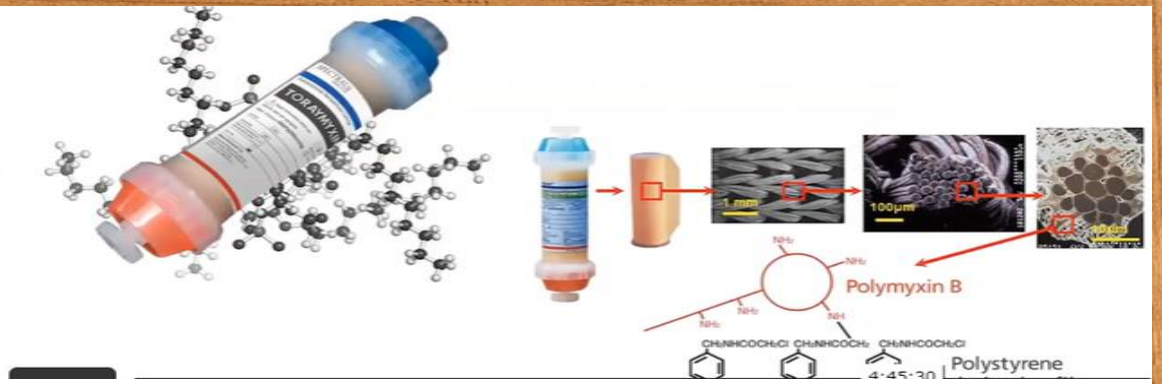
4:59:39



ADSORPTION: beyond filtration

..... is an extracorporeal process in which molecules dissolved in plasma or blood (in particular peptides and proteins) bind to the membrane structure or to other adsorbing substances such as resins or gels.....

- The characteristics that influence molecule-membrane interaction are typical for each molecule (i.e., dimension, charge, etc.) and for each particular membrane (i.e., porosity, hydrophobicity, etc.)
- **Adsorption cartridges should be evaluated in terms of their device adsorption capability (DAC) and their selectivity**
- DAC represents the total quantity of a specific molecule that the device is able to adsorb
- Selectivity is a safety parameter, as it defines what the device does not adsorb



2002

Multiple organ support therapy (MOST)

The concurrent application mechanical interventions with the aim to correct physiological alterations induced by a diseases

2017

Extracorporeal organ support (ECOS)

A wide range of extracorporeal therapies that aim to manipulate both solutes and solvent of the bloodstream in order to support organ functions.

2020

Sequential Extracorporeal Therapy in Septic Shock (SETS)

The concurrent application of interventions that aim to correct pathological alterations and restore organ cross-talk

5:08:19

ADQI XXX Adsorption-Based Therapies

ADQI

FONDAZIONE IRRIV

THE UNIVERSITY OF MELBOURNE

UNIVERSITÀ DEGLI STUDI DI PADOVA

Acute Disease Quality Initiative

ADQI XXX
Consensus Conference
on
Adsorption-based Extracorporeal Therapies

SCHOOL OF MEDICINE
UNIVERSITY OF SURREY

A process towards developing consensus and recommendations for adsorption-based extracorporeal therapies

www.ADQI.net

June 9th - 12th 2023

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UNIVERSITY OF SURREY

The specific objectives for this conference are:

- *To develop a series of consensus statements on Adsorption-based Extracorporeal Therapies. Activities include:*
  - Pre-conference literature search (nomenclature will be provided)
  - Identification of key questions and controversies
  - Assessment of current practice and analysis of mechanisms, available technology and potential applications
  - Assessment of available evidence and discussion
  - Definition of techniques, nomenclature, indications and rationale for the use of adsorption therapies
  - Design a research agenda at several levels: conceptual, programmatic & individual study designs
  - Draft summary statements for each topic to be used for Post-conference state-of-the-art manuscript preparation

Group 1 **Rationale and physicochemical principles**
Chair: *R. Mehta*
Members: *V. Cantaluppi, W. Clark, H. Gomez, A. Lorenzin, E. See, G. Villa, R. Basu*

Group 2 **Techniques and modalities of adsorption-based therapies**
Chair: *L. Forni*
Members: *G. Ankawi, I. Baldwin, M. Joannidis, T. Reis, Z. Ricci, T. Rimmelé, A. Schneider, A. Whaley-Connell*

Group 3 **Indications, prescription and monitoring**
Chair: *A. Zarbock*
Members: *S. De Rosa, F. Husain-Syed, K. Kashani, P. Murray, J. Prowle, S. Goldstein, V. Premužić*

Group 4 **End-points: biochemical (molecules), biological (processes), physiological (parameters), clinical (outcomes).**
Chair: *M. Ostermann*
Members: *S. Bagshaw, D. Fuhrman, R. Murugan, N. Pannu, D. Soranno, M. Rosner*

Group 1
Rationale & Physicochemical Principles

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- Hemoadsorption is an extracorporeal treatment
- Aim is to increase extracorporeal removal of :
  - Solutes
  - Cells
  - Pathogens
- Which, due to their physical-chemical features (e.g., dimension, protein binding or lipophilicity), are not amenable to diffusive or convective clearance

Rationale

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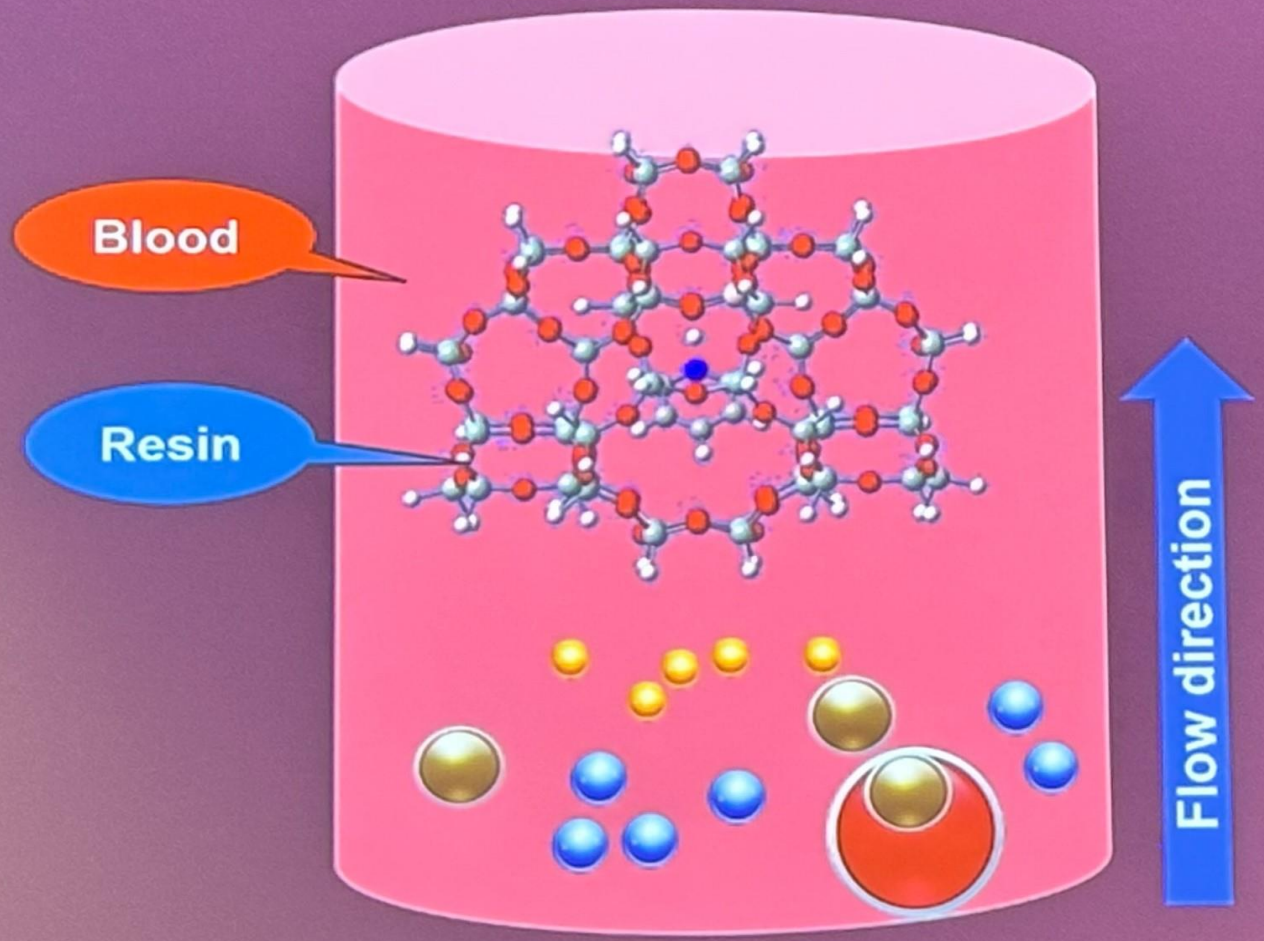
ADQI XXX Adsorption-Based Therapies



Hemoperfusion is a method that uses adsorbent to adsorb toxins, drugs and metabolites and clear them from blood.

RBC

Small molecules

Target

Target

Rationale

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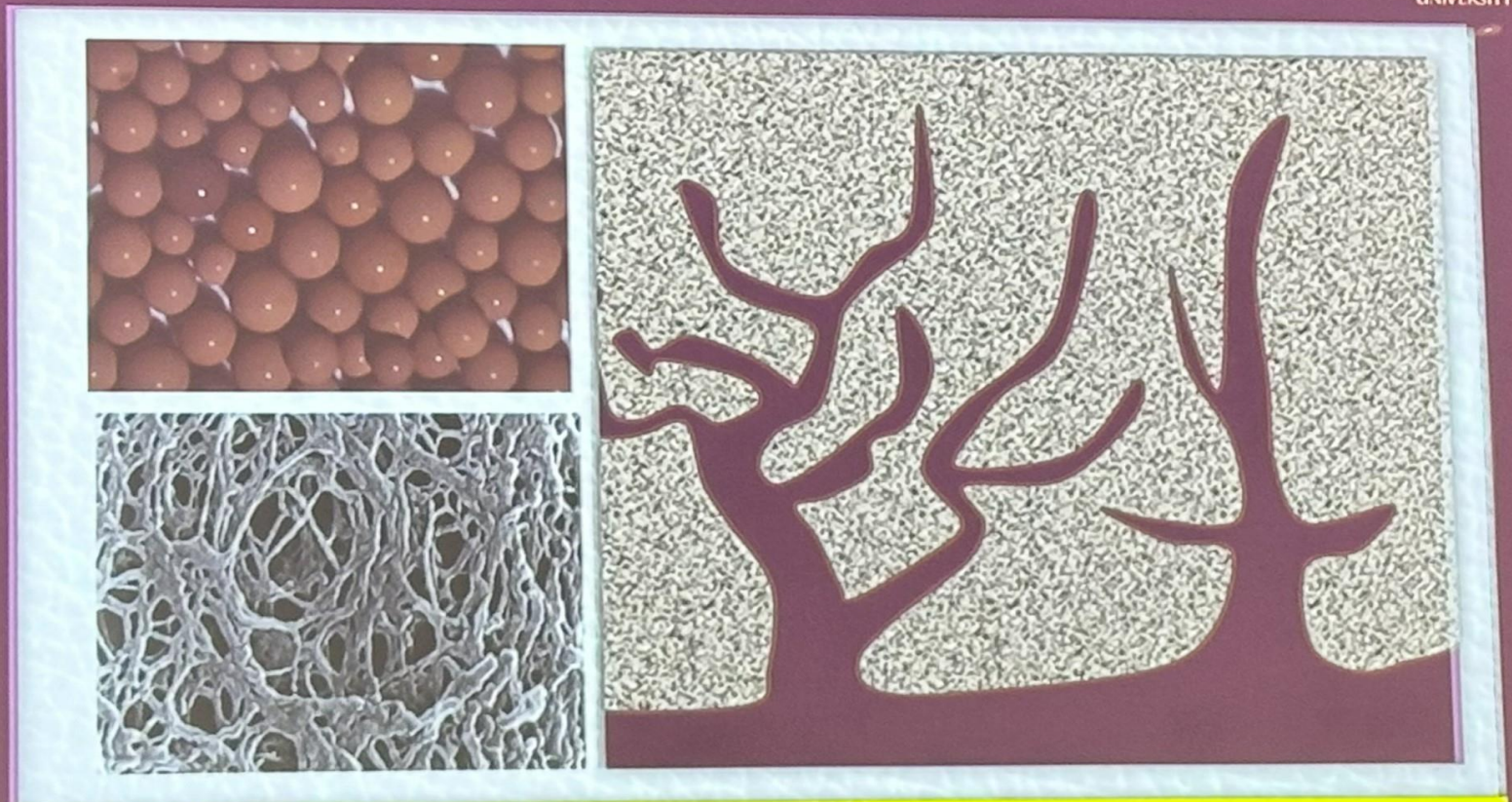
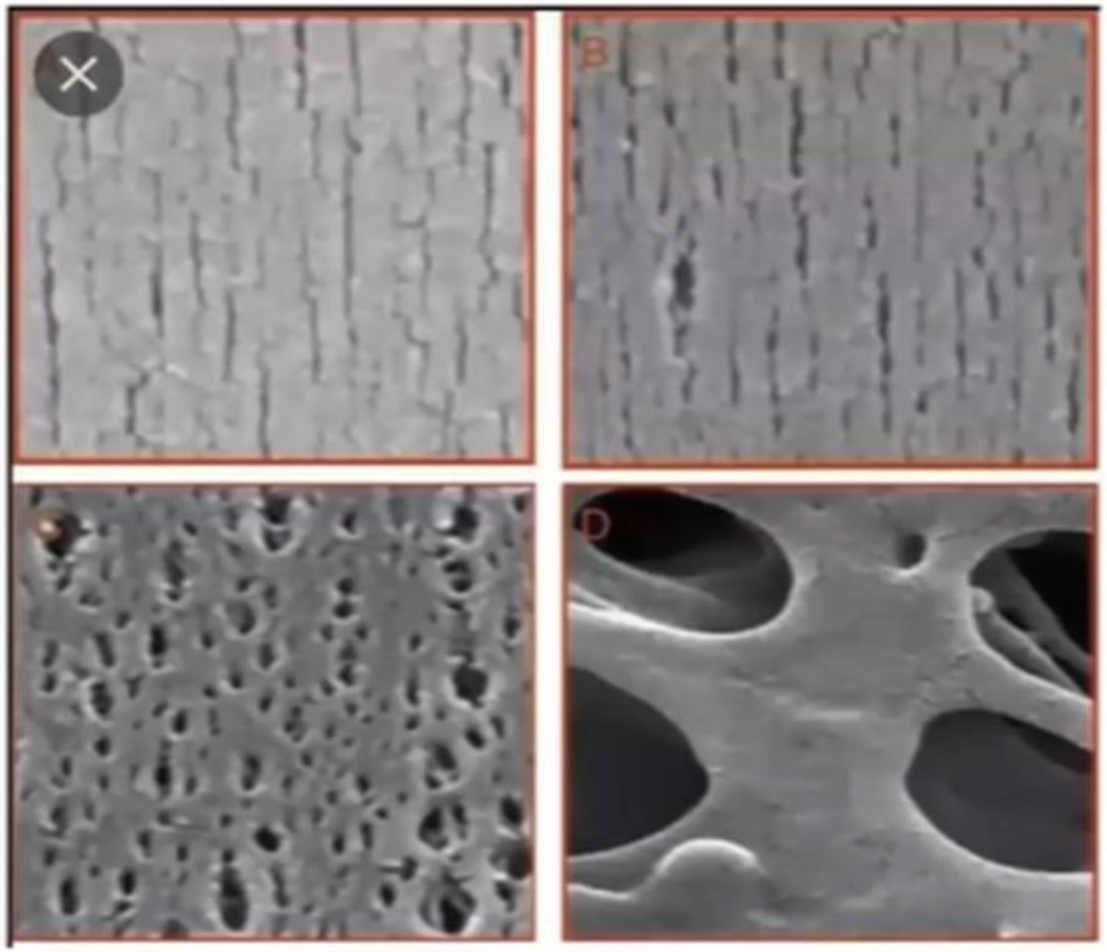
ADQI XXX Adsorption-Based Therapies



Effectively adsorb middle-large molecules and protein bound substances



ELECTRON MICROSCOPE IMAGE OF THE INTERNAL SURFACE OF MEMBRANES

A – High flux (HF)

B – Medium Cut-off (MCO)

C – High Cut-off (HCO)

D – Plasma Filter

60,000X magnification

Nefrologia 2018;38-4-7

Rationale

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- Some hemoadsorption can occur in the setting of conventional dialytic therapies employing membranes with avid binding properties

- Using agglomerates (e.g., beads) with very large surface area to volume ratios offers the ability to target more specific molecules or molecular classes and the opportunity to remove greater amounts of such solutes

Physicochemical Principles

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- Chemical adsorption (chemisorption) is a relatively specific, energy-intensive process forming of chemical bonds between the solute and sorbent

- Physical adsorption is a non-specific process typically mediated by hydrophobic interactions between solute and sorbent

Physicochemical Principles

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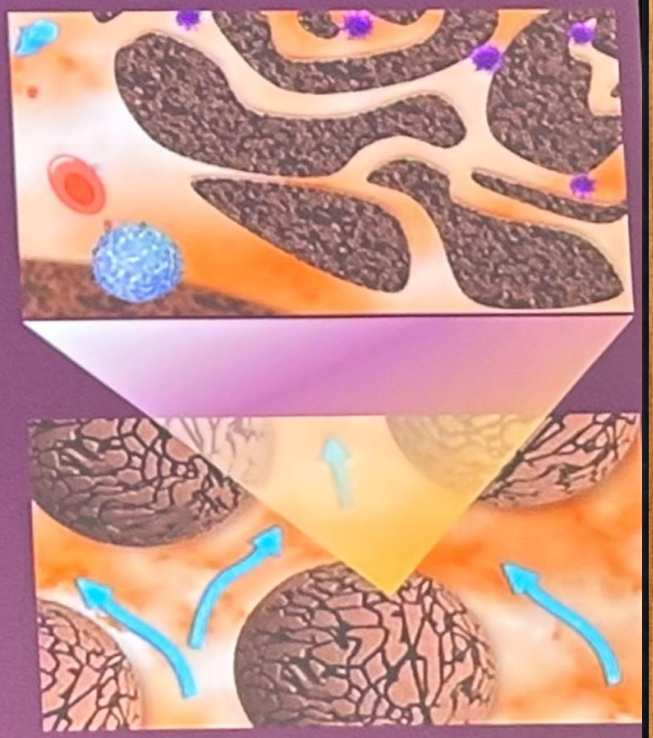
ADQI XXX Adsorption-Based Therapies

One or more of these mechanisms may be active, and the features of the adsorptive surface and the device configuration (bead size, packing density, etc.) determine the efficiency of adsorption



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Physicochemical Principles

- Adsorption is based on certain basic principles:
  1) Solute reaches the vicinity of the specific binding through mass transfer which is impacted by flow rate and solution characteristics
  2) "Active" binding area is within the pore structure (pore size is a critical determinant of access to the sorbent
  3) When a solute reaches a potential binding site, the likelihood of adsorption influenced by factors related to the solute, solvent, and sorbent

Quantifying Haemadsorption

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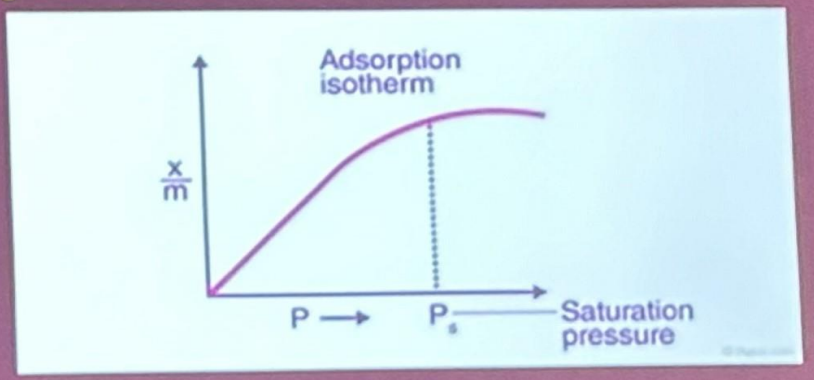
Adsorptive capacity can be measured in terms of efficiency

1) *in vitro* quantified using isotherm equations, elution of the adsorbates and mass transfer zone



2) *in vitro* and *in vivo* using the removal ratio over time

Rationale & Physicochemical Principles

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- Selectivity of adsorption is influenced by the properties of the adsorptive membrane/device, device configuration, the characteristics of the adsorbates and the conditions
- In different clinical conditions and type of diseases, selectivity of adsorption may vary according to both device and patient features
- The passage of blood/plasma through a sorbent may lead to a selective (i.e., endotoxin with polymyxin-B) or broad-spectrum (i.e. cytokines) removal of mediators

Group 2: Techniques & Modalities

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Modality = the adsorptive methods by which blood or plasma are exposed to a sorbent or a membrane

- Eg, removal of endotoxin through a specific endotoxin adsorbing filter differs from that where viruses are removed through a heparin bonded filter

Technique = mechanism by which the treatment acts via an extracorporeal circuit.

Modalities : Examples

ADQI XXX Adsorption-Based Therapies

Material	Commercial Name (Manufacturer)	Target of Removal via Adsorption
FILTERS		
AN69-PEI-heparin	oXiris (Baxter)	Middle molecules, endotoxin
AN69-ST	ST series/sepXiris (Baxter)	Middle molecules
PMMA	Hemofeel (Toray)	Middle molecules
CARTRIDGES		
Heparin covalently bound to polyethylene	Seraph 100 (ExThera)	Bacteria, fungi, viruses
Porous polymer beads – polystyrene divinylbenzene	BS80, BS330, HA60, HA130, HA230, HA330, HA330-II and HA380 (Jafron); CytoSorb and DrugSorb (CytoSorbents); MediaSorb (Medtronic); MG150, MG250 and MG350 (Biosun); MHC-I (Wego); Plasorba BR-350(L) (Asahi); Yangquan	Protein-bound compounds, middle molecules, iodinated contrast, drugs, poisons, bilirubin, bile acids, platelet $P2Y_{12}$ inhibitors, factor Xa inhibitors, organophosphates, paraquat, myoglobin
PMX covalently bound to polypropylene-polystyrene fiber	Toraymyxin (Toray)	Endotoxin
Cationic peptide with affinity to lipid A moiety on polyethylene matrix	Alteco (Alteco Medical)	Endotoxin
Synthetic ligand of the lipid A domain covalently immobilized to a polystyrene matrix	Efferon LPS (Efferon)	Endotoxin
Activated charcoal	Adsorba 150 C, 300 C (Baxter); Hemosorba CHS-350 (Asahi)	Hydrophilic and lipophilic drugs
Phenylalanine immobilized polyvinylalcohol gel	Immunosorba PH-350(L) (Asahi)	Antibodies
Tryptophan immobilized polyvinylalcohol gel	Immunosorba TR-350(L) (Asahi)	Antibodies, complement factor C3 and C4, fibrinogen
Protein A immobilized in sepharose matrix	Immunosorba (Fresenius)	Antibodies
Peptide GAM immobilized in sepharose matrix	GLOBAFFIN (Fresenius)	IgG antibodies

AN, acrylonitrile; PEI, polyethylenimine; PMMA, poly (methyl methacrylate); PMX, polymyxin B.

Conclusions

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ADQI XXX Adsorption-Based Therapies

There is a strong rationale for and much evidence about modern haemoadsorption

Haemoadsorption has clinically acceptable:

- Biocompatibility and safety
- Technical feasibility
- Experimental evidence of target molecule removal

Extracorporeal blood purification techniques available in 2024

HEMOADSORPTION (Sorbents)

PMX-B (Toray/Estor)
Cytosorb (Cytosorbents)
LPS adsorber (Alteco)
HA330, HA380 (Jafron)
MG350 (Biosun)

CRRT filters (kidney support + blood purification)

high adsorptive hemofiltration (oXiris, Baxter – PMMA, Toray)

high cut-off membranes (Emic2, Fresenius Medical Care)

MISCELLANEOUS, OTHER TECHNIQUES

High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

Coupled Plasma Filtration Adsorption

NEW BLOOD PURIFICATION THERAPIES

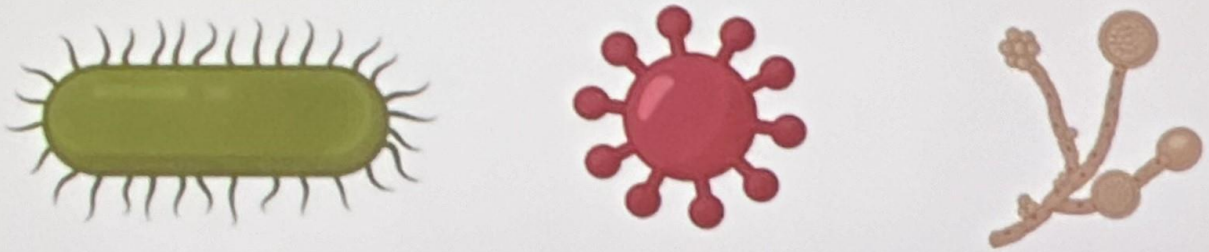
(capable of leukocyte or bacteria or virus removal)

Seraph® (Exthera Medical)

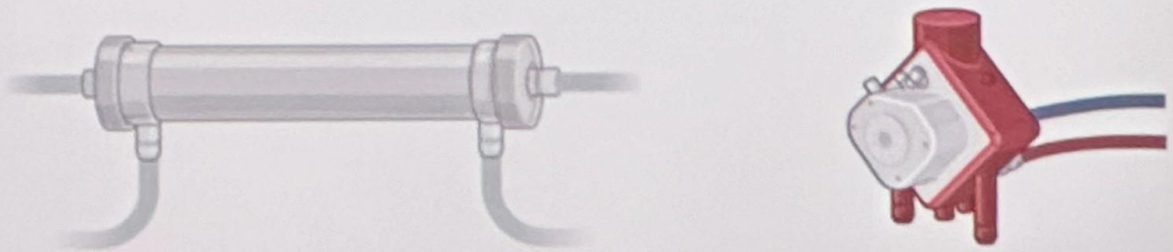
FcMBL protein (Opsonix)
Hemopurifier® (Aethlon Medical)
other selective cytapheresis technology...

Seraph® 100 Microbind® Affinity Blood Filter

Broad Pathogen Binding Capacity

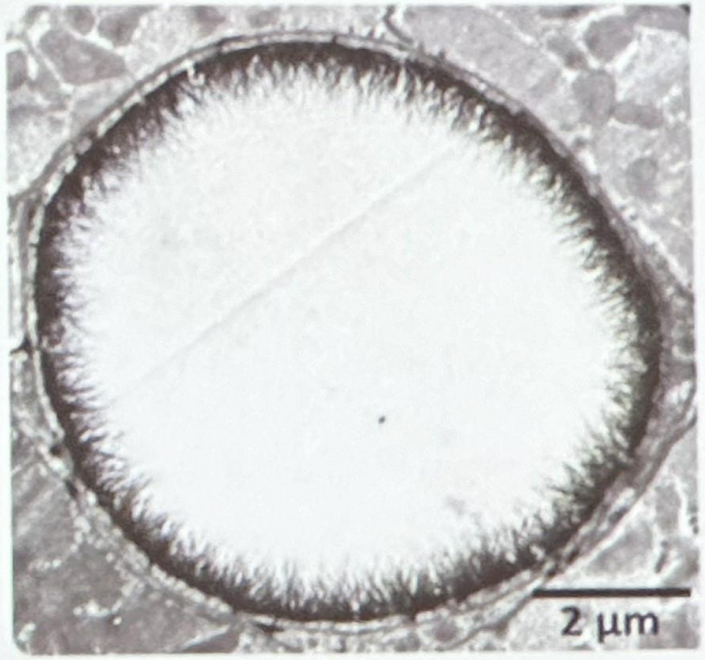


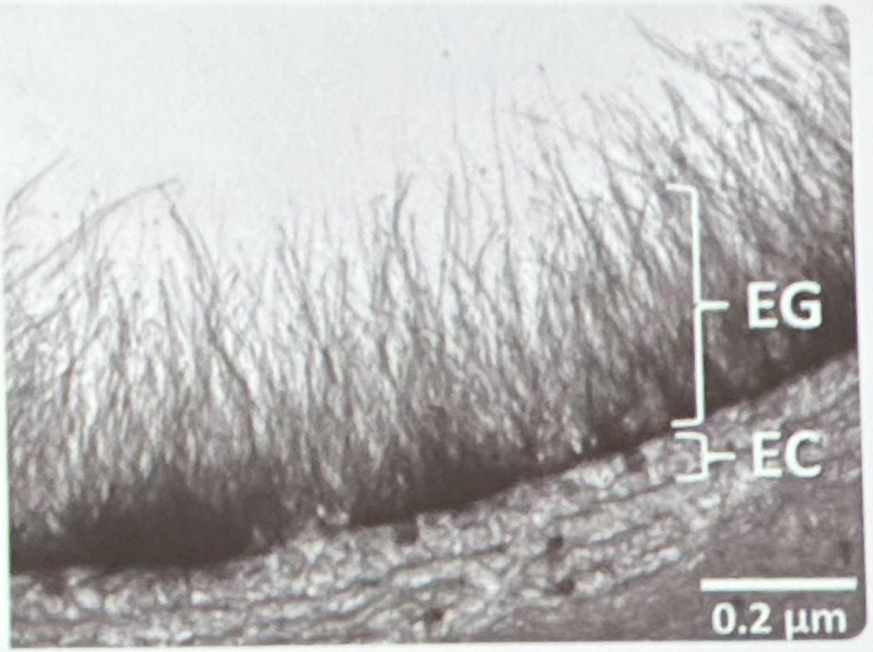
Compatible with IHD, CRRT, and ECMO



1. FDA Emergency Use Authorization: EUA200165 Instructions For Use (IFU) CP021 Rev A
2. Kielstein et al, Hemofiltration with Seraph 100® Microbind Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill..., Critical Care 25.1(2021):1-48.
3. Schmidt & Eden et al, In vitro elimination of anti-infective drugs by the Seraph 100 Microbind affinity blood filter, CKJ, 2020, vol 13, no. 3, 421-424
4. Chitty et al, A Multicenter Evaluation of Blood Purification with Seraph 100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19: A Preliminary Report, (2021)
5. Seffer et al, Heparin 2.0: A New Approach to the Infection Crisis, Bld Purification (2020), Jul 2, 1-7

Mechanism of Action: The Endothelial Glycocalyx





- A matrix lining the vascular endothelium, regulates vascular permeability
- Pathogens bind to *heparan sulfate* proteoglycans which facilitates initial pathogen attachment and promotes infection

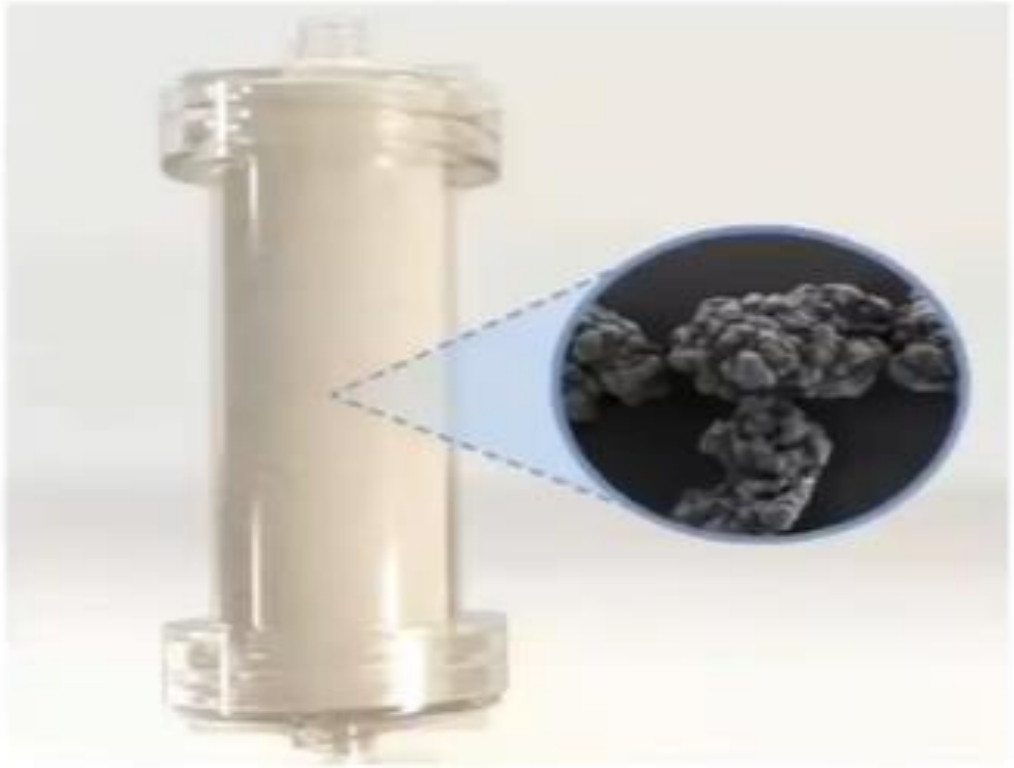
Biddle C. Like a slippery fish, a little slime is a good thing: the glycocalyx revealed. AANA J. 2013 Dec;81(6):473-80. PMID: 24597010
Bartlett et Al , Heparan Sulfate Proteoglycans in Infection, in: Pavao M. (eds) Glycans in Diseases and Therapeutics. Biology of Extracellular Matrix. Springer, 2011

Seraph 100 Removes Pathogens

- Polyethylene Beads with end point-attached Heparin

- Bacteria, viruses, fungi, and toxins bind to the immobilized heparin in a similar way to the interaction with heparan sulfate on the cell surface

Seraph 100

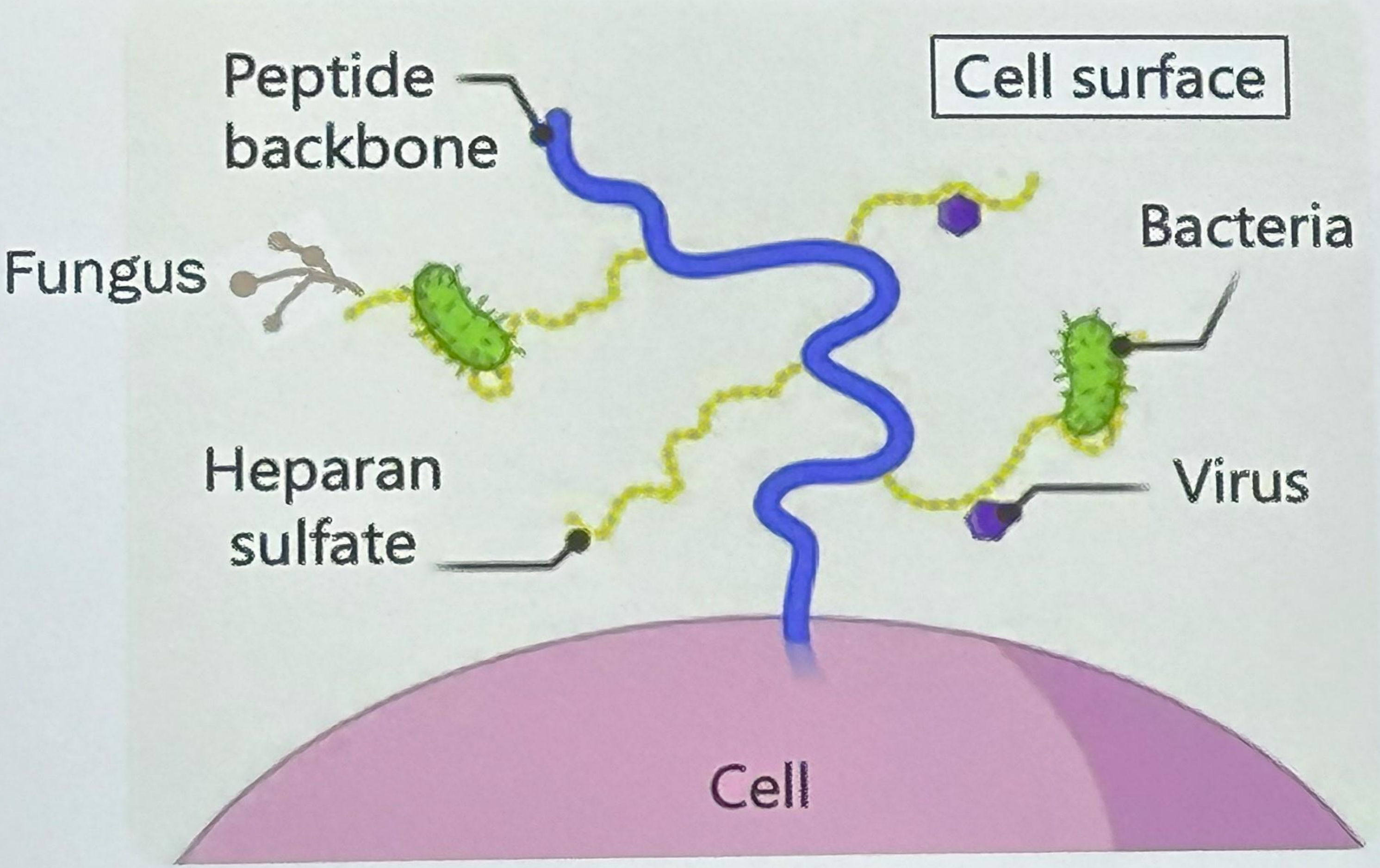


Heparin Surface Area of 40 m^2

Approval Status
CE Mark
FDA – Emergency Use Authorized (EUA)
For the Treatment of COVID19

Seraph® 100 is measuring 22 × 7 cm. After priming with a volume of 160 mL, the entire assembly weighs about 400 g.
Electron microscopic image (magnification 144×) from the heparin-coated beads – the active ingredient of the Seraph® 100.

Mechanism of Action: The Endothelial Glycocalyx



Adapted from Seffer et al. Heparin 2.0: A New Approach to the Infection Crisis. Bio Publications ([illegible]); [illegible]

Heparin: Is It More Than An Anticoagulant?

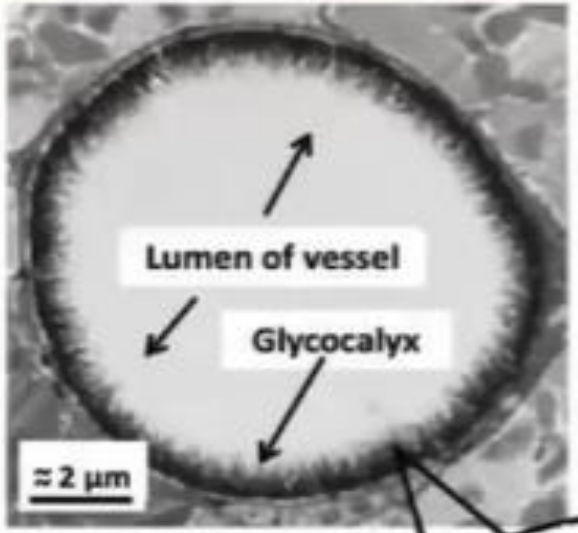
Heparin : More Than An Anticoagulant?

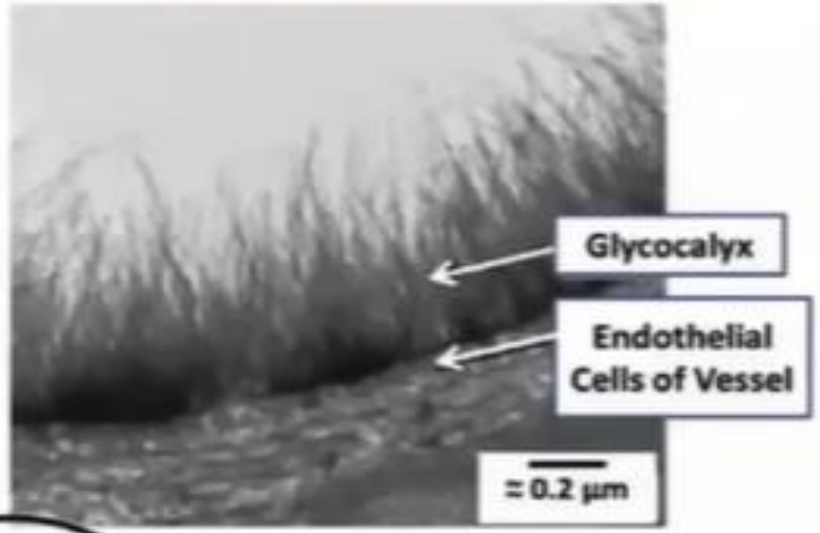
- Several HS proteoglycans (HSPGs) can serve as virus receptors
- Heparin-binding activity is also found in bacteria
- The structure of HS may also affect tissue tropism of HPV and other HS-binding pathogens

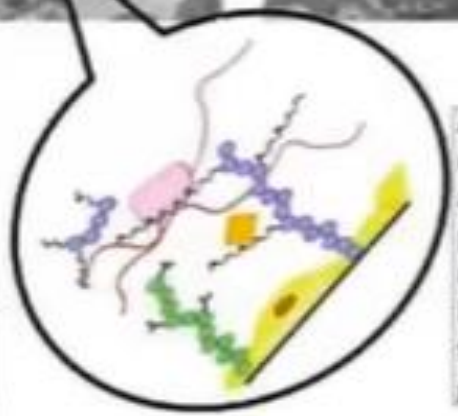
- Soluble Heparin and Surface Heparin are fundamentally different

- Heparin as a surface presents an intriguing molecule for designing new approaches for the development therapeutic agents against various infections

Soluble Heparin versus Heparin as a Surface





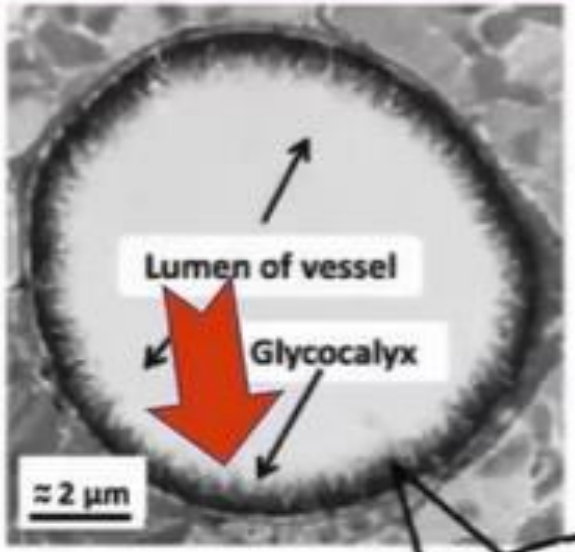


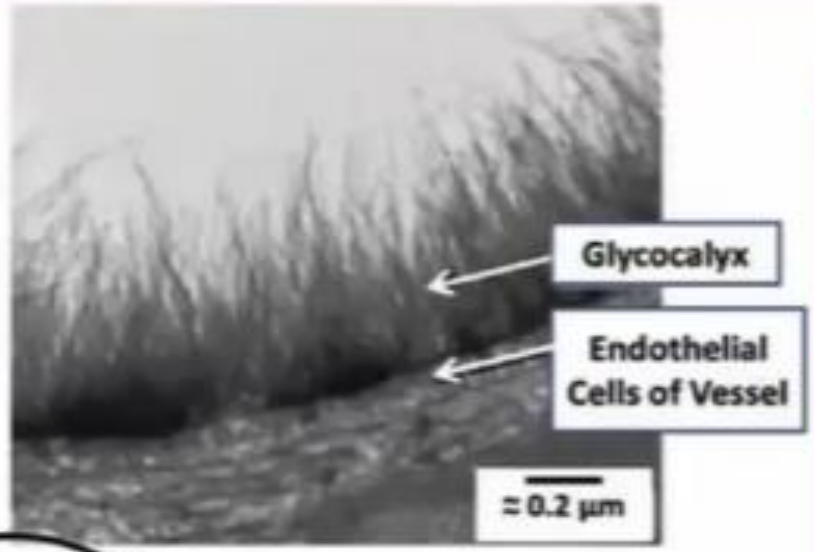
Slippery, gel-like network of negatively charged molecules residing on the luminal side of the vascular endothelium

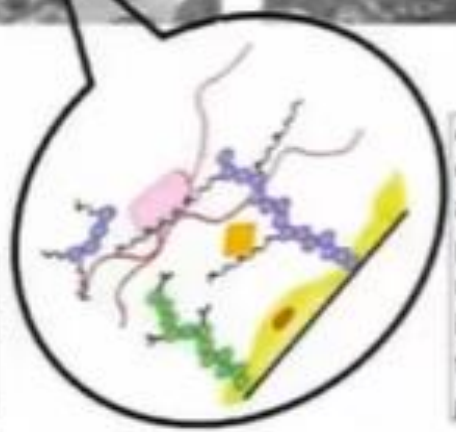
A carbohydrate-rich layer connected to the endothelium via backbone proteoglycans and glycoproteins. A complex network of plasma- and epithelium-derived soluble molecules is continuously incorporated into the glycocalyx. A dynamic equilibrium forms between blood constituents and the glycocalyx—it is not a static structure.

Biddle, Chuck. *AANA journal* 81.6 (2013)

Soluble Heparin versus Heparin as a Surface





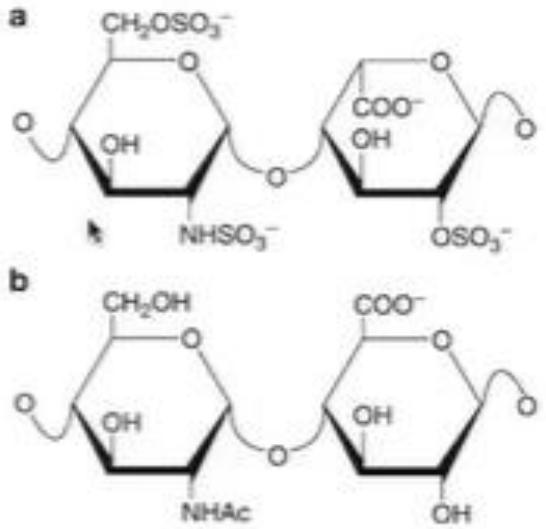


Slippery, gel-like network of negatively charged molecules residing on the luminal side of the vascular endothelium

A carbohydrate-rich layer connected to the endothelium via backbone proteoglycans and glycoproteins. A complex network of plasma- and epithelium-derived soluble molecules is continuously incorporated into the glycocalyx. A dynamic equilibrium forms between blood constituents and the glycocalyx—it is not a static structure.

Biddle, Chuck. *AANA journal* 81.6 (2013)

Heparin Sulfate

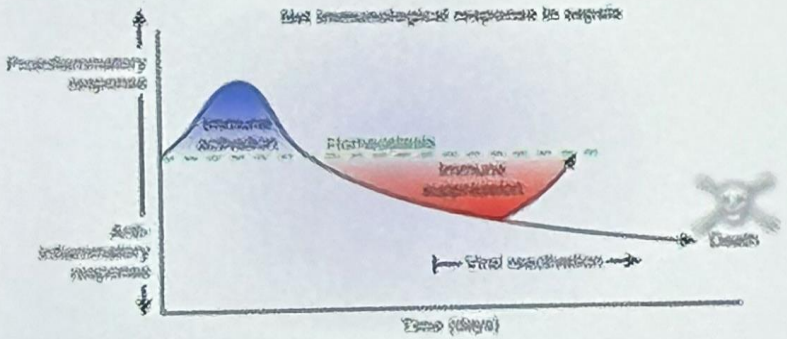


Heparan Sulfate

Seraph 100 is Endothelial Glycocalyx Replacement Therapy

- Source control – removes pathogen
- Coagulopathy – remove micro-thrombosis/attenuate DIC
- ROS effects – remove oxygen free radicals

The extracorporeal blood purification concept in sepsis



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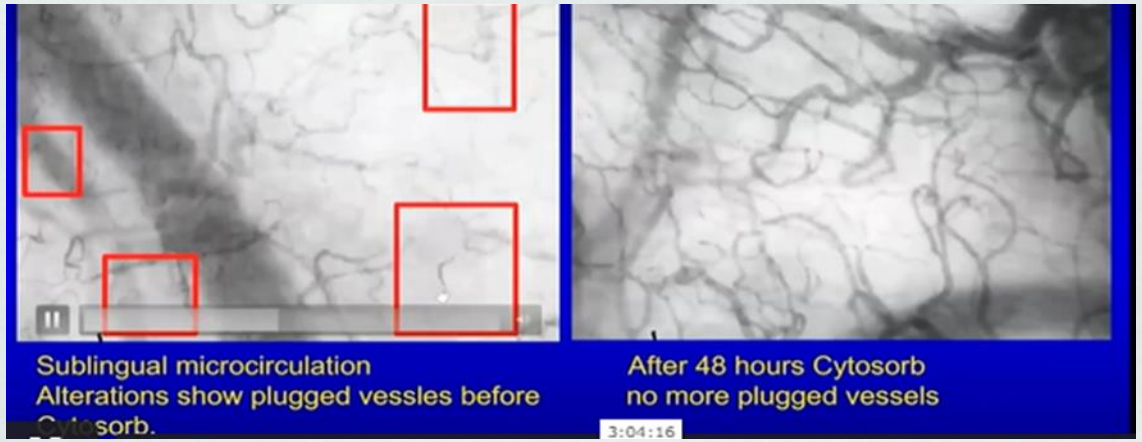
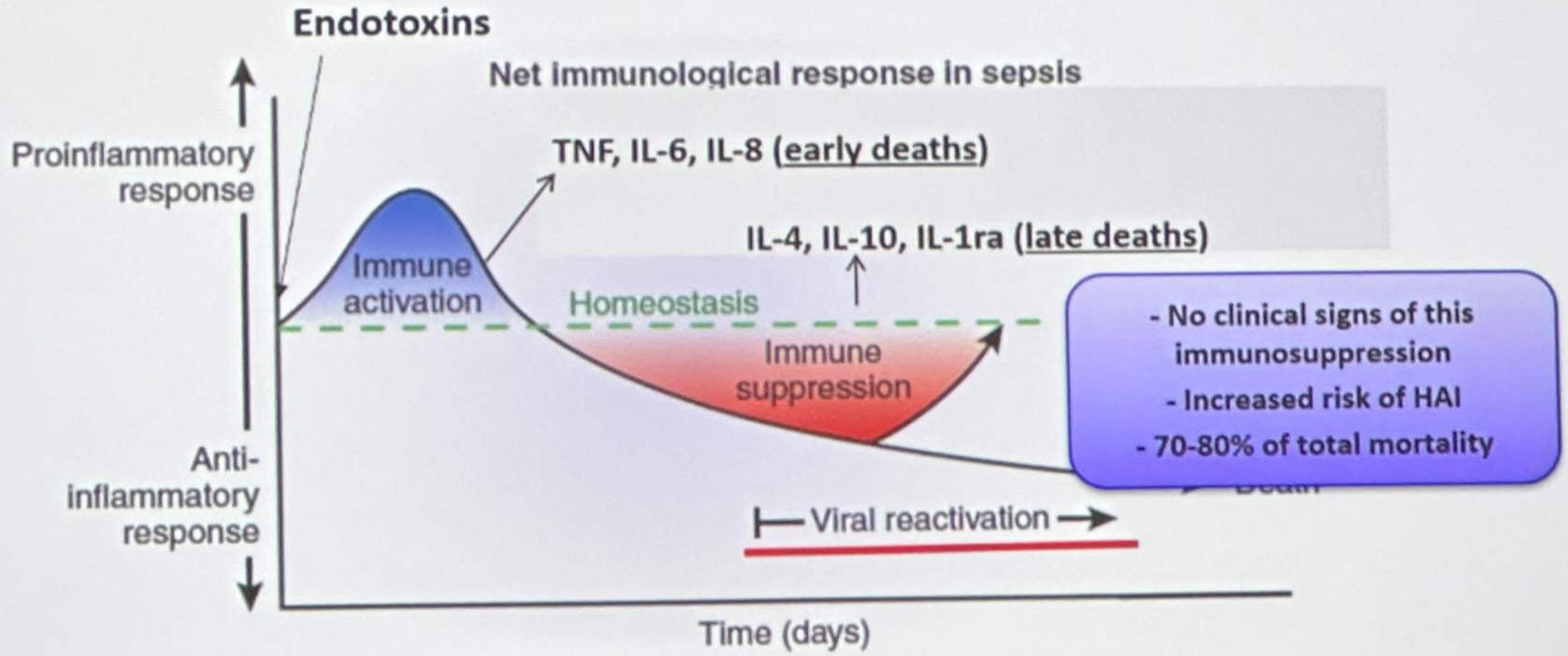
Improved
patient outcomes ?



Septic shock: Hyperinflammation followed by severe immunosuppression



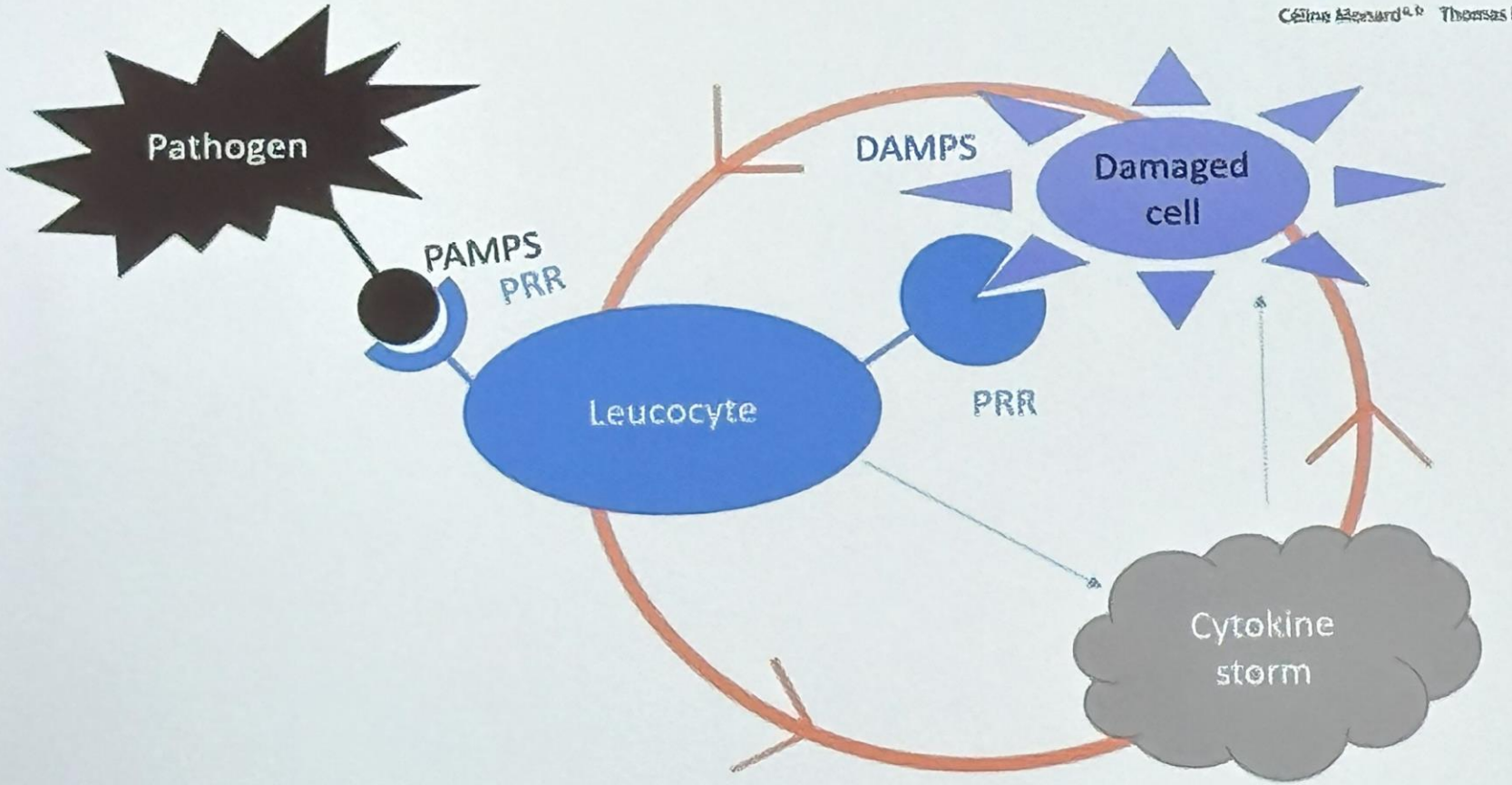
Hotchkiss et al. *Nat Med* 2009

« Classic » targets for Blood Purification Therapies

Blood Purification

Extracorporeal Blood Purification Therapies for Sepsis

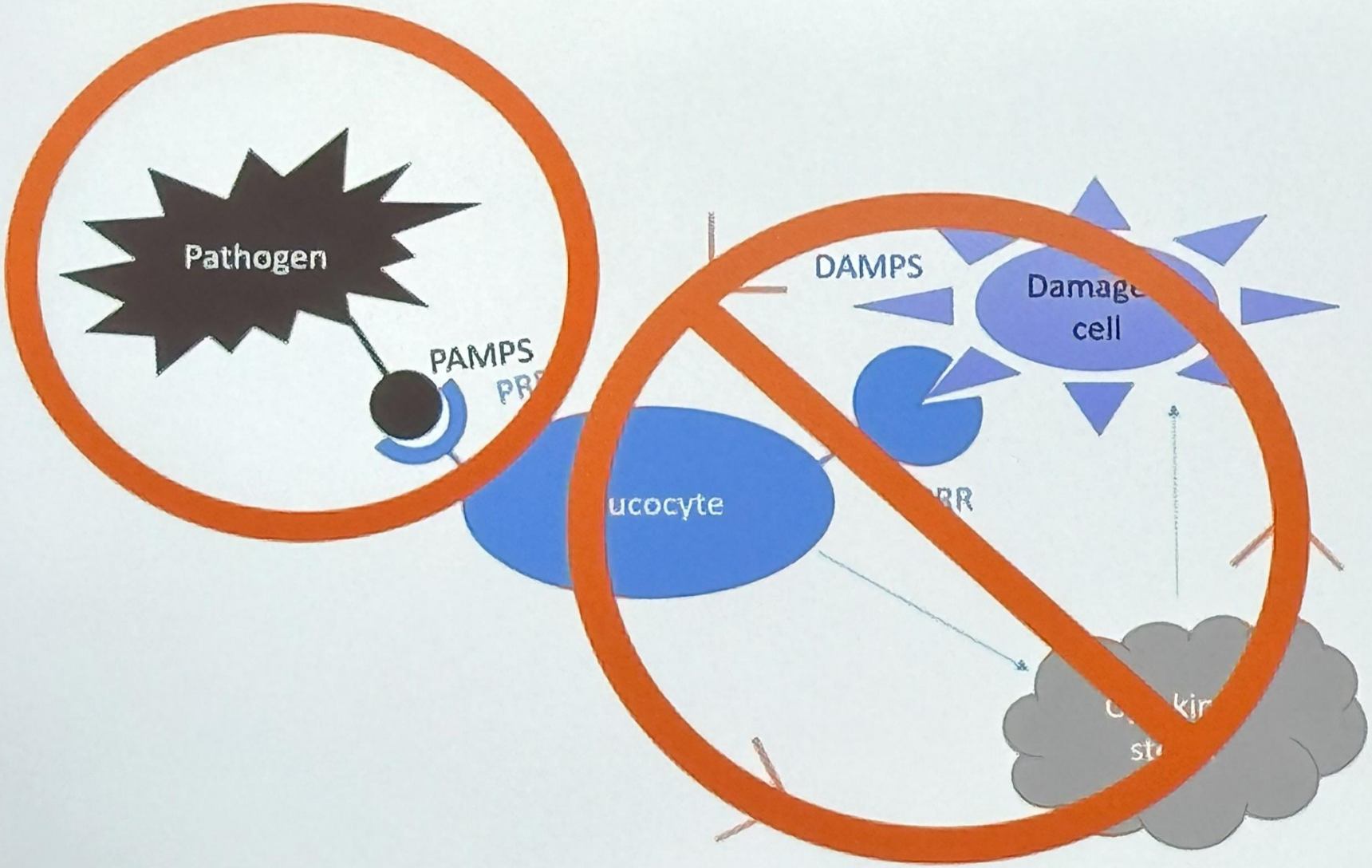
Céline Monard[a,b] Thomas Rimmelé[a,b] Claudio Ronco[c–e]



PRR = Pattern Recognition Receptor

Monard et al. Blood Purif 2019

Acting directly at the pathogen level?



« Classic » targets for Blood Purification Therapies

Blood Purification
Blood Purif 2019;47(suppl 3):1–14
DOI: 10.1159/000499520
Published online: April 11, 2019

Extracorporeal Blood Purification Therapies for Sepsis

Céline Monard[a, b] Thomas Rimmelé[a, b] Claudio Ronco[c–e]

Pathogen

PAMPS

PRR

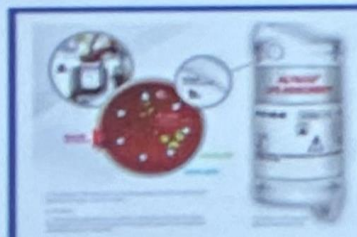
Leucocyte

DAMPS

Damaged cell

PRR

Alteco® LPS Adsorber



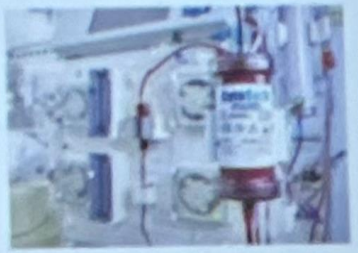
Polymyxin B hemoadsorption

Oxiris® highly adsorptive membrane

Cytokine storm

HA 380 ® Hemoadsorption

Cytosorb® hemoadsorption



Device	Company	Composition	Mechanism	Substance eliminated
Toraymyxin 20R	Toray Industries, Japan	Polymyxin B covalently bound to polypropylene-polystyrene fibers fabric	Adsorption	Endotoxin
LPS adsorber	Alteco Medical, Sweden	Synthetic polypeptide bound to porous polyethylene discs	Adsorption	Endotoxin
oXiris	Gambro-Hospal, France	AN69-based membrane, surface treated with a polyethyleneimine (PEI) and grafted with heparin	Adsorption Convection	Endotoxin Cytokines
MATISSE	Fresenius SE, Germany	Human serum albumin immobilised on polymethacrylate beads	Adsorption	Endotoxin
CPFA	Bellco, Italy	Polyethersulfone Plasma filter with adsorption on an unselective hydrophobicresin cartridge, and a synthetic high-permeability polyethersulfone hemofilter for continuous hemofiltration	Adsorption Plasma filtration	Cytokines
Cytosorb	Cytosorbents, USA	Polystyrenedivinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone coating.	Adsorption Convection	Cytokines

Esteban F. et al. Mediators of ... ion 2013

5:00:50

Blood Purification

Research Article

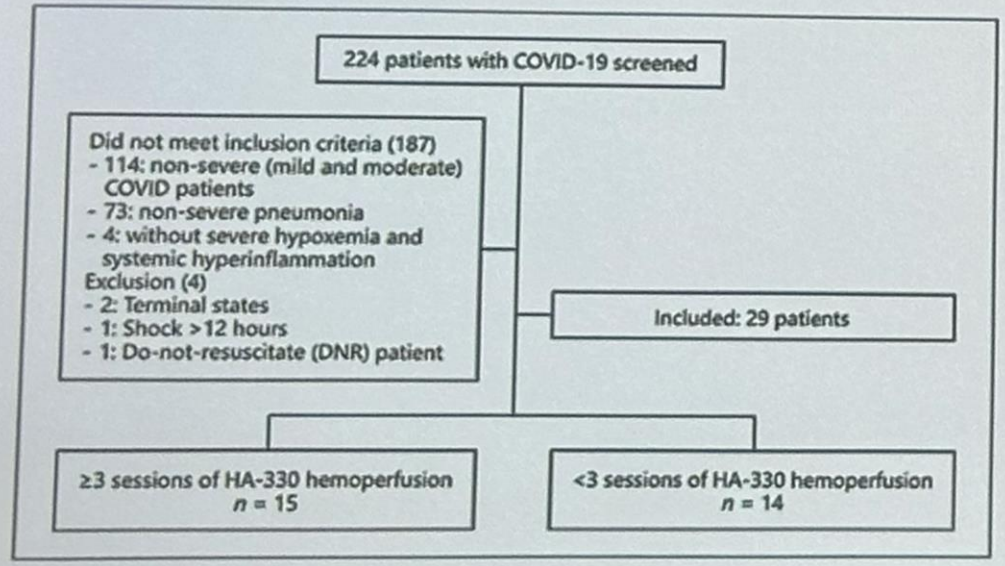
Blood Purif 2022;51:879–888
DOI: 10.1159/000521713

Received: September 28, 2021
Accepted: December 27, 2021
Published online: February 9, 2022

The Efficacy of Early Additional Hemoperfusion Therapy for Severe COVID-19 Patients: A Prospective Cohort Study

Karjbundid Surasit[a] Nattachai Srisawat[b, c, d, e]

[a]Nakornping Hospital, Chiang Mai, Thailand; [b]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [c]Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [d]Critical Care Nephrology Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [e]Academy of Science, Royal Society of Thailand, Bangkok, Thailand



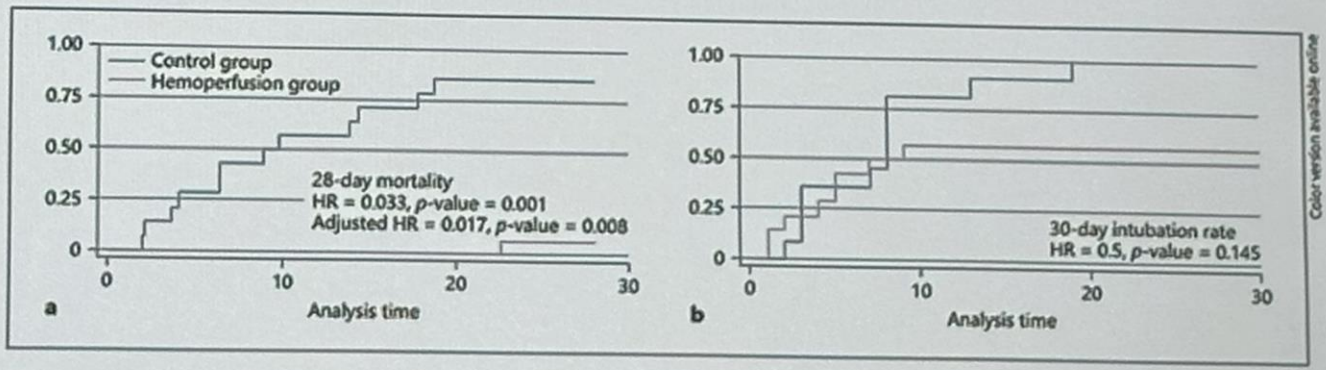
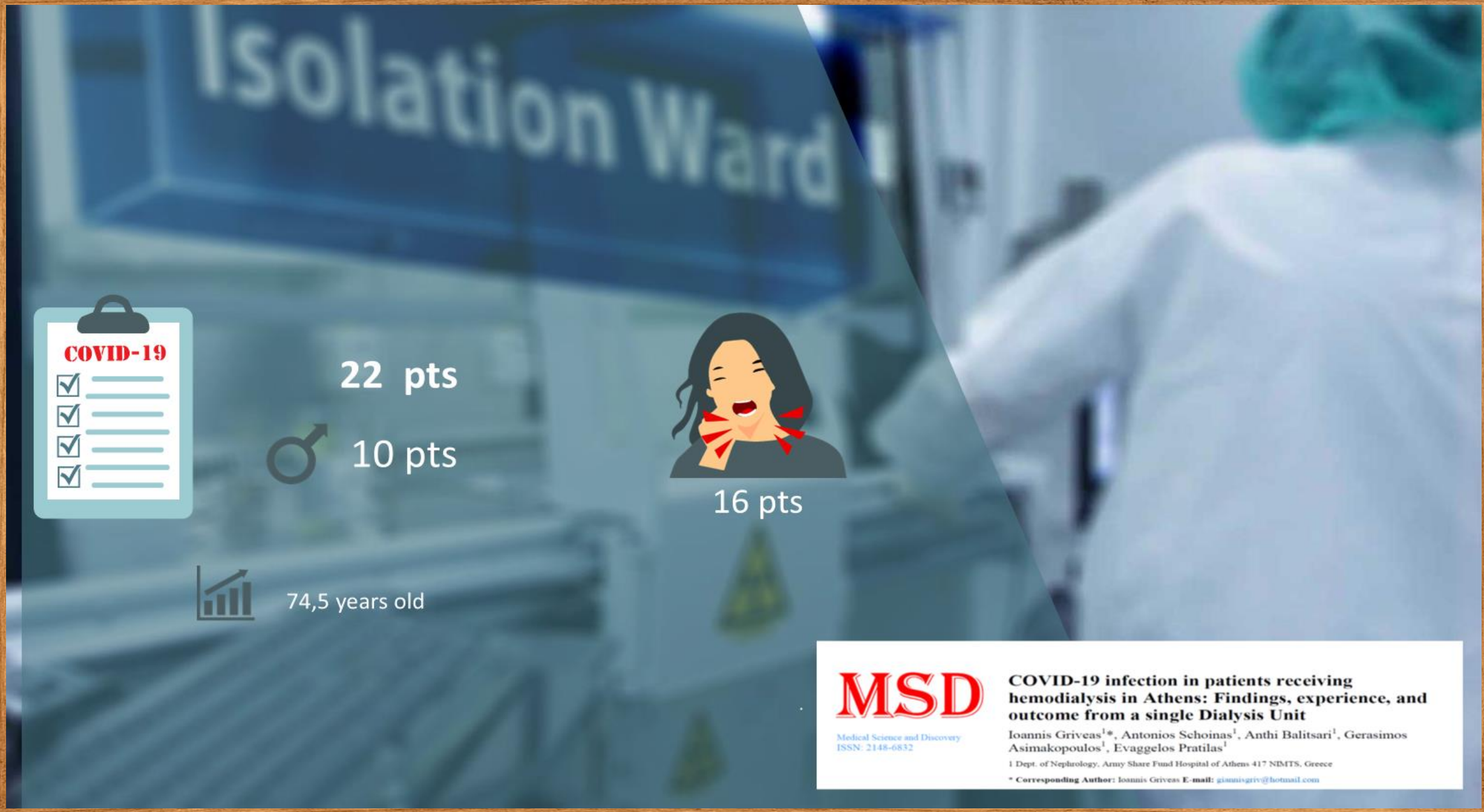


Fig. 3. The Kaplan-Meier curve for cumulative 28-day survival (**a**) and 30-day intubation rate (**b**) of patients in hemoperfusion group versus control group.

COVID-19
PANDEMIC
CORONAVIRUS



22 pts

♂ 10 pts

16 pts

74,5 years old

MSD

Medical Science and Discovery
ISSN: 2148-6832

COVID-19 infection in patients receiving hemodialysis in Athens: Findings, experience, and outcome from a single Dialysis Unit

Ioannis Griveas[1]*, Antonios Schoinas[1], Anthi Balitsari[1], Gerasimos Asimakopoulos[1], Evaggelos Pratilas[1]

1 Dept. of Nephrology, Army Share Fund Hospital of Athens 417 NIMTS, Greece

*** Corresponding Author:** Ioannis Griveas **E-mail:** giannisgriv@hotmail.com

COVID-19

MSD

Medical Science and Discovery
ISSN: 2148-6832

COVID-19 infection in patients receiving hemodialysis in Athens: Findings, experience, and outcome from a single Dialysis Unit

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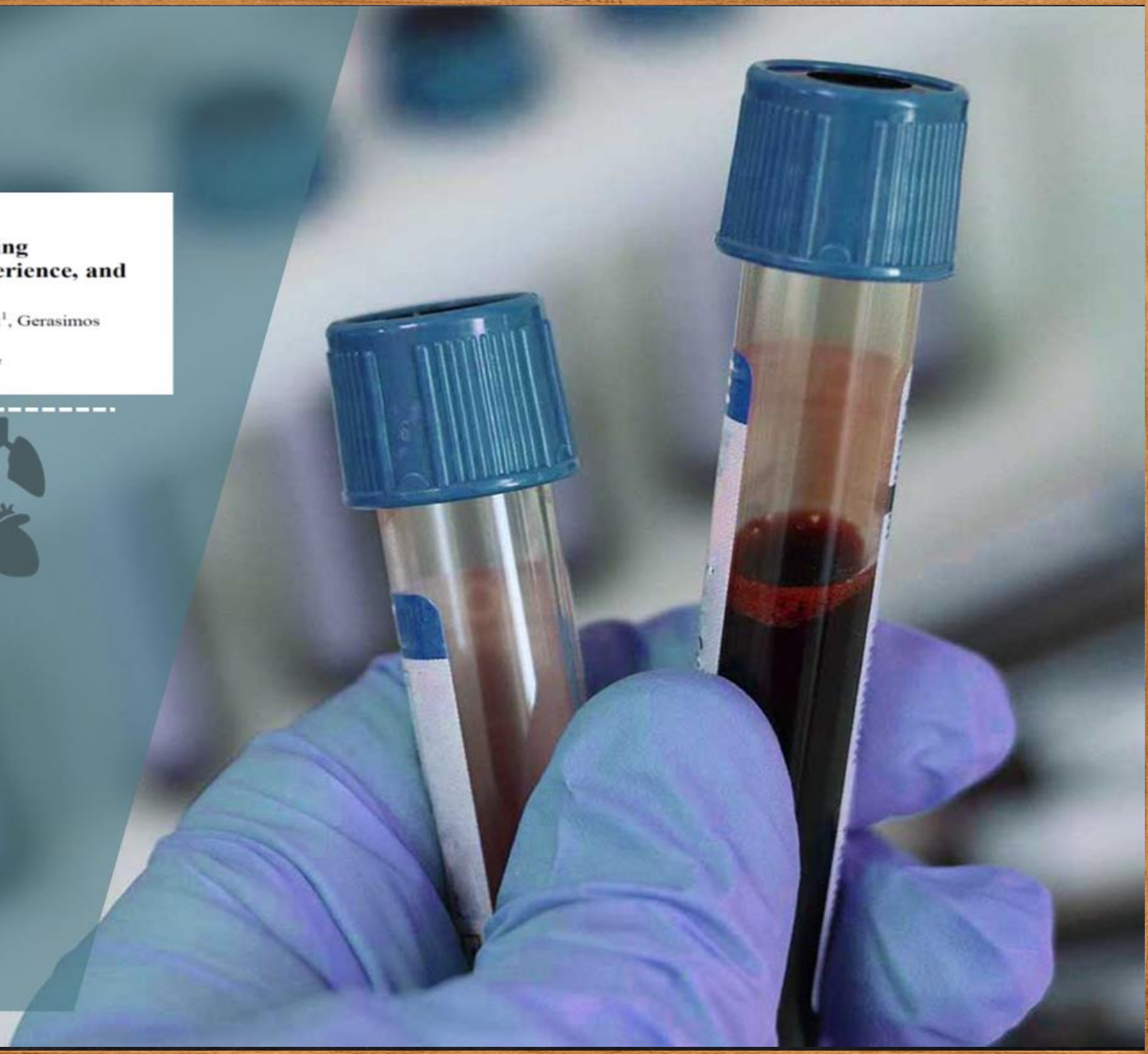
1 Dept. of Nephrology, Army Share Fund Hospital of Athens 417 NIMTS, Greece

* **Corresponding Author:** Ioannis Griveas **E-mail:** giannisgriv@hotmail.com

- **12 pts/ 79 years**
- **8**
- 4 pts
- 2 pts
- **3 pts ICU**
- 14,5 days (1-38)
- 6 pts



Nephrology Dialysis Transplantation

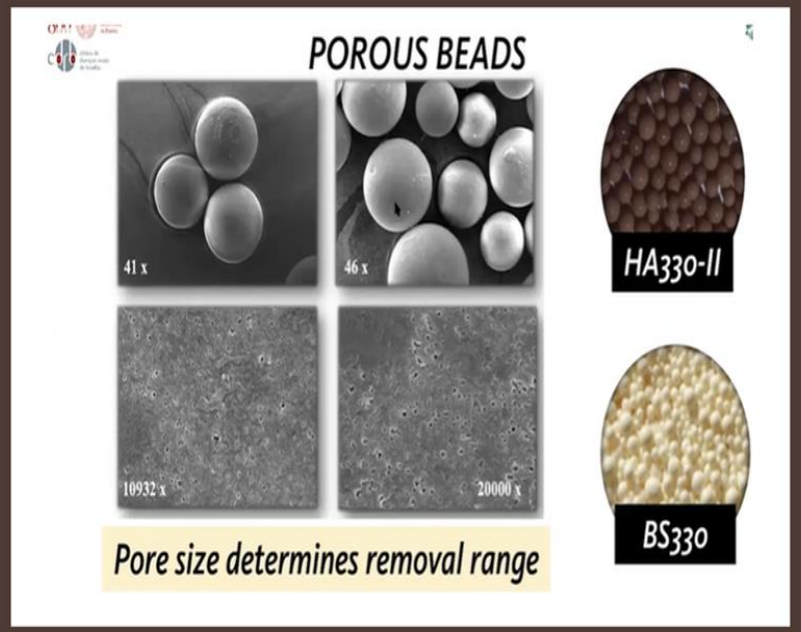
MO857

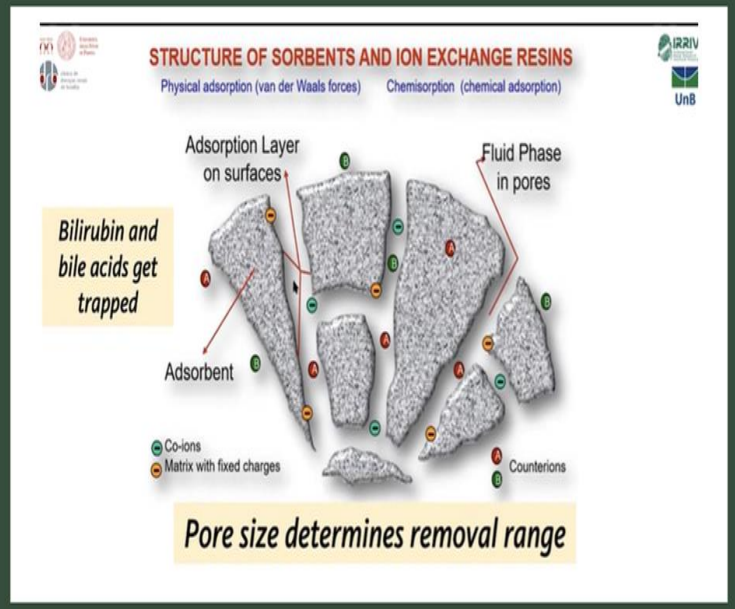
HEMOPERFUSION IN HEMODIALYSIS PATIENTS WITH COVID-19 INFECTION: IMPACT ON CLINICAL COURSE

Ioannis Griveas[1], Antonis Schinas[1], Anthoula Balitsari[1], Gerasimos Asimakopoulos[1], Evangelos Pratilas[1]

[1]*Army Share Fund Hospital 417 (NIMTS), Nephrology, Athens, Greece*

Did you know?





ORIGINAL ARTICLE | ASIAN JOURNAL OF MEDICAL SCIENCES

Soluble urokinase plasminogen activator receptor and its complicated role in hemodialysis (HD) patients with Covid-19 infection

Ioannis Griveas[1], Antonios Schoinas[2], Anthi Balitsari[3], Gerasimos Asimakopoulos[4], Evaggelos Pratilas[5]

[1]Medical Director and Consultant Nephrologist, [2,3]Consultant Nephrologist, [4,5]Resident in Nephrology, Nephrology Department, Army Share Fund Hospital of Athens, Greece, 417 NIMTS

Submission: 18-04-2021 Revision: 29-05-2021 Publication: 01-07-2021

Management of Sepsis (Shock)

Source Control

Debridement
Abscess Drainage

- Removes Pathogens from the Bloodstream

Host Response

Inflammation
Coagulopathy

- Removes DAMPS and PAMPS
- Impacts coagulopathy

Decreases pro-inflammatory cytokines

Hemodynamic Stability

Fluids
Vasopressors

- Case reports show improved hemodynamics

*** Does not remove anti-virals (remdesivir) or antibiotics

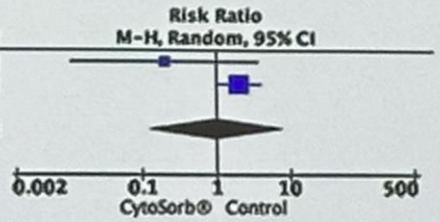
Jiovany Jhan Carlos Saldaña-Gastulo[1], María del Rosario Llamas-Barbarán[2], Lelis G. Coronel-Chucos[1], Yamilée Hurtado-Roca[1]

Cytokine hemoadsorption with CytoSorb® in patients with sepsis: a systematic review and meta-analysis

A. Randomized control trial

Study or Subgroup	CytoSorb® Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hawchar 2019	0	10	2	10	31.0%	0.20 [0.01, 3.70]
Schädler 2017	17	47	9	50	69.0%	2.01 [0.99, 4.06]
Total (95% CI)		57		60	100.0%	0.98 [0.12, 8.25]
Total events	17		11			

Heterogeneity: $Tau^2 = 1.58$; $Chi^2 = 2.35$, $df = 1$ ($P = 0.13$); $I^2 = 57\%$
Test for overall effect: $Z = 0.02$ ($P = 0.99$)



B. Non Randomized Studies of Interventions

Study or Subgroup	CytoSorb® Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Akil 2020	0	13	4	7	2.1%	0.06 [0.00, 1.03]
Brouwer 2019	35	67	35	49	35.4%	0.73 [0.55, 0.98]
Rugg 2020	15	42	26	42	27.7%	0.58 [0.36, 0.92]
Schittek 2020	31	43	22	33	34.8%	1.08 [0.80, 1.47]
Total (95% CI)		165		131	100.0%	0.74 [0.49, 1.13]
Total events	81		87			

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.01$, $df = 3$ ($P = 0.02$); $I^2 = 70\%$
Test for overall effect: $Z = 1.38$ ($P = 0.17$)

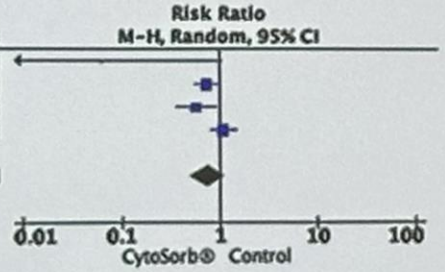


Figure 3 - Forest plot effect of CytoSorb® on mortality at 28 - 30 days. (A) Randomized controlled trial; (B) Nonrandomized studies of interventions.

studies found or the lack of data.

Conclusion: Our study found very low certainty evidence, due to imprecision, risk of bias, and heterogeneity, thereby showing no benefit of CytoSorb® use in terms of mortality at 28 - 30 days. We cannot recommend the use of CytoSorb® in septic or septic shock patients outside clinical trials. Further high-quality randomized trials with a common intervention arm are needed to evaluate the influence of CytoSorb® in this population.

Saldana-Gastulo et al. *Crit Care Sci* 2023

SARA GIRONI CARNEVALE

Scientists are drowning in COVID-19 papers. Can new tools keep them afloat?

By **Jeffrey Brainard** | May. 13, 2020 , 12:15 PM

First US COVID-19 Patients Treated with Seraph

Case Report

Critical Care Explorations

Treatment for Severe Coronavirus Disease 2019 With the Seraph-100 Microbind Affinity Blood Filter

Stephen W. Olson, MD[1-3]; James D. Oliver, MD, PhD[1-3]; Jacob Collen, MD[2]; Jessica Bunin, MD[2]; Todd D. Gleeson, MD[2,3]; Brian E. Foster, DO[2,3]; Mark P. Simmons, PhD[3]; Hua W. Chen, PhD[3]; Jennifer B. Ficke, MD[4]; Tara E. Brown, MD[4]; Mark T. Nau, MD[4]; Brennan R. Cebula, MD[5]; Jan Kielstein, MD[5]; Kevin K. Chung, MD[1]

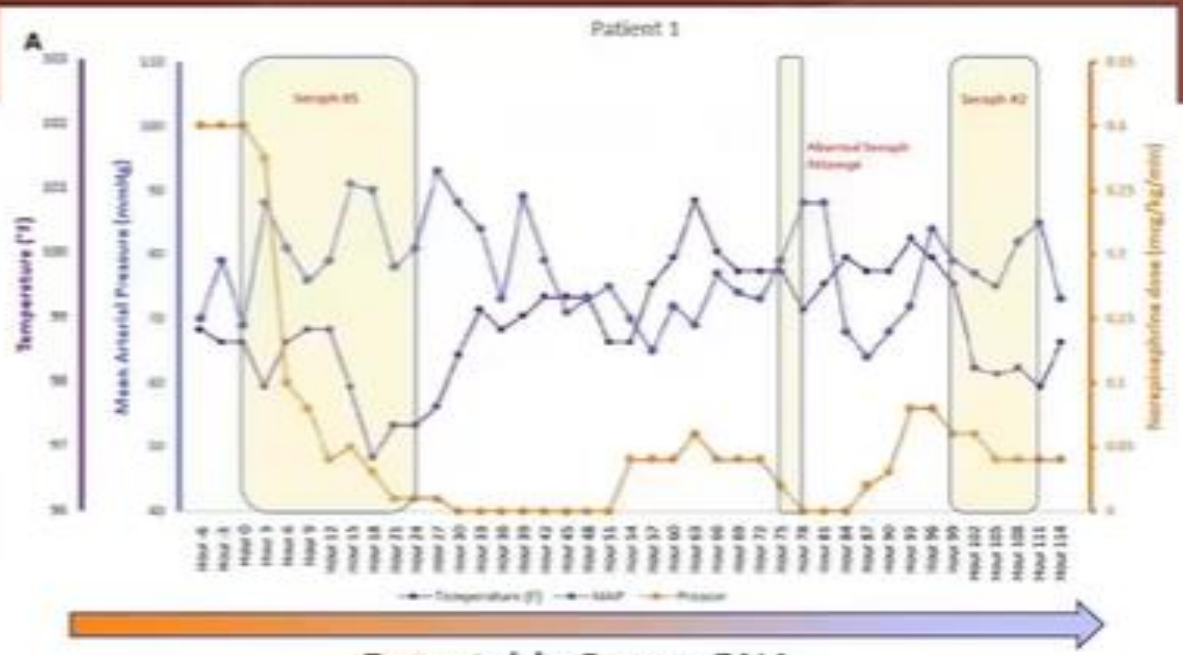


TABLE 1. In Vitro Binding Study of Severe Acute Respiratory Syndrome Coronavirus 2 to Seraph Media

	Before		After	
	Copies/Reaction (10^6)	Copies/mL (10^6)	Copies/Reaction (10^6)	Copies/mL (10^6)
Filter 1	15.770	985.625	10.98	686.250
Filter 2	14.550	909.375	12.40	775.000
		912.500	11.93	745.625

20:55

COVID is Viral Pneumonia – Role of Viremia

- Why does treating viremia improve lung disease?

Viral Load is High in Severe COVID19

Bermejo-Martin et al. Crit Care (2020) 24:691
https://doi.org/10.1186/s13054-020-03398-0

Critical Care

RESEARCH Open Access

Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19

Jesús F. Bermejo-Martin[1,2,3†], Milagros González-Rivera[4,5†], Raquel Almansa[1,2,3†], Dariela Micheloud[6†], Ana P. Tedim[1,2], Marta Domínguez-Gil[7†], Salvador Resino[8†], Marta Martín-Fernández[1,2], Pablo Ryan Murua[9], Felipe Pérez-García[10], Luis Tamayo[1,11], Raúl Lopez-Izquierdo[12], Elena Bustamante[13], César Aldecoa[1,14,15], José Manuel Gómez[16], Jesús Rico-Feijoo[1,15], Antonio Orduña[17], Raúl Méndez[18], Isabel Fernández Natal[19], Gregoria Megías[20], Montserrat González-Estecha[4,5], Demetrio Carriedo[21], Cristina Doncel[1,2,3], Noelia Jorge[1,2,3], Alicia Ortega[1,2,3], Amanda de la Fuente[1,2,3], Félix del Campo[22], José Antonio Fernández-Ratero[23], Wysali Trapiello[24], Paula González-Jiménez[18], Guadalupe Ruiz[24], Alyson A. Kelvin[25,26], Ali Toloue Ostadgavahi[25,26], Ruth Oneizat[7], Luz María Ruiz[7], Iria Miguéns[6], Esther Gargallo[6], Ioana Muñoz[6], Sara Pelegrin[15], Silvia Martín[1,15], Pablo García Olivares[16], Jamil Antonio Cedeño[16],

Sicker Patients Have Higher Viral Loads

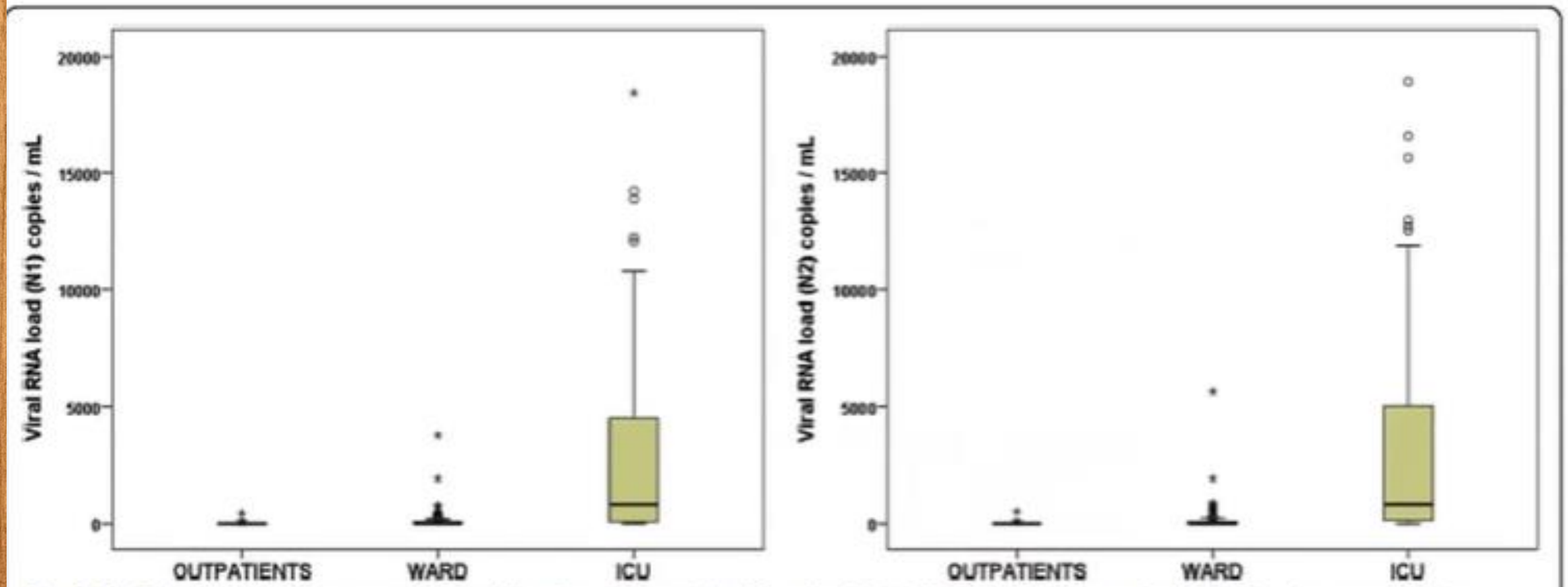
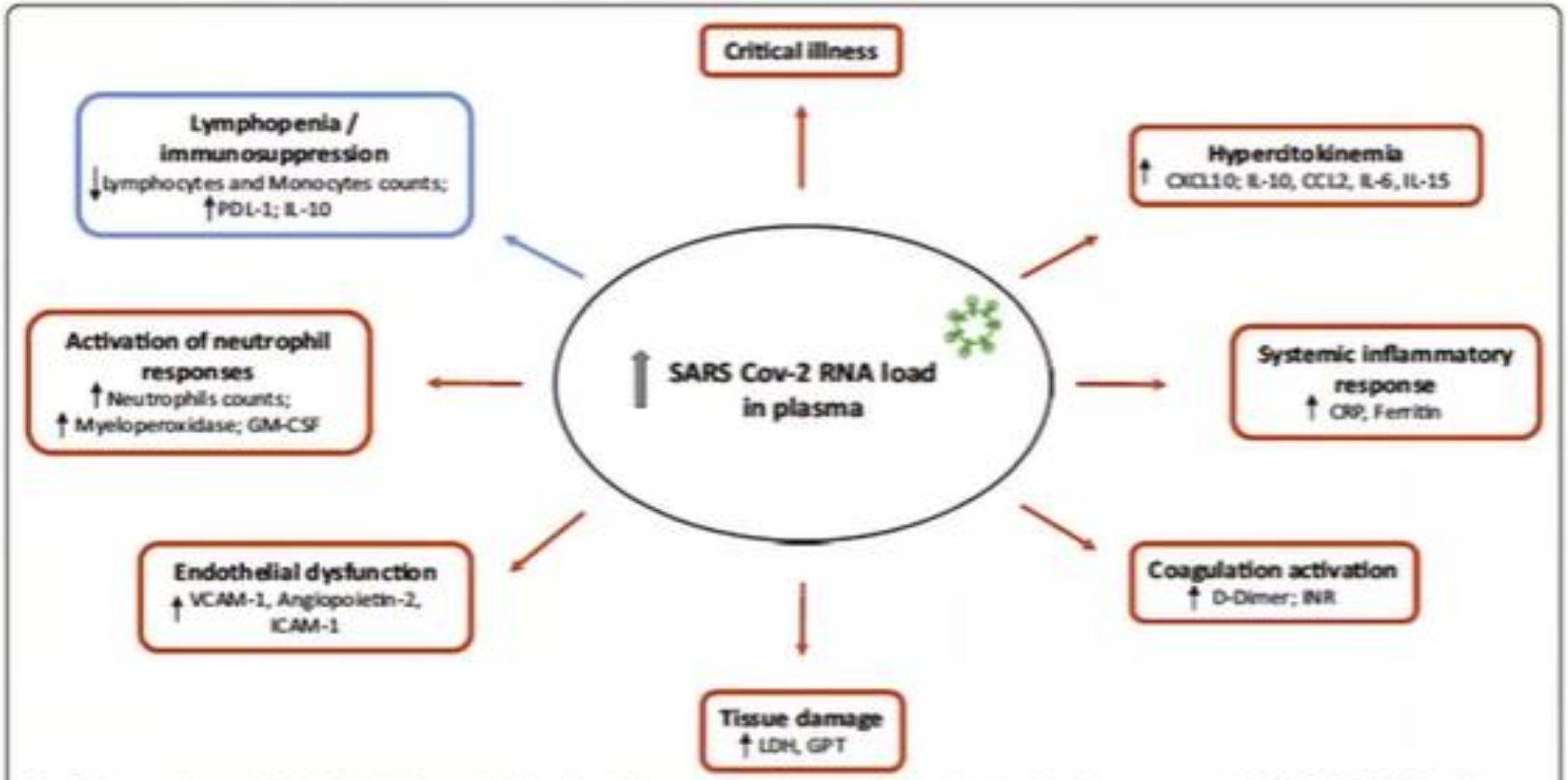


Fig. 1 Viral RNA load in plasma, targeting the N1 region (left) and the N2 region (right), in the three groups of patients. Results are provided as copies of cDNA pe[illegible]esma

Negative Effects of SARS-CoV-2 Viremia



ative model depicting the correlations found between the indicators of host dysregulated responses and SARS-CoV-2 RNA load in

Treatment Thesis of EC Viral Removal

- High levels of SARS-CoV-2 viremia are common in critically ill patients with COVID-19
- Uncommon in patients who less sick
- Viremia appears to be an important modulator of multi-system organs failure

Thus, if viremia is the key activator of multi-system organ dysfunction, the effective removal of SARS-CoV-2 should improve outcomes

Devices To Remove SARS-CoV-2

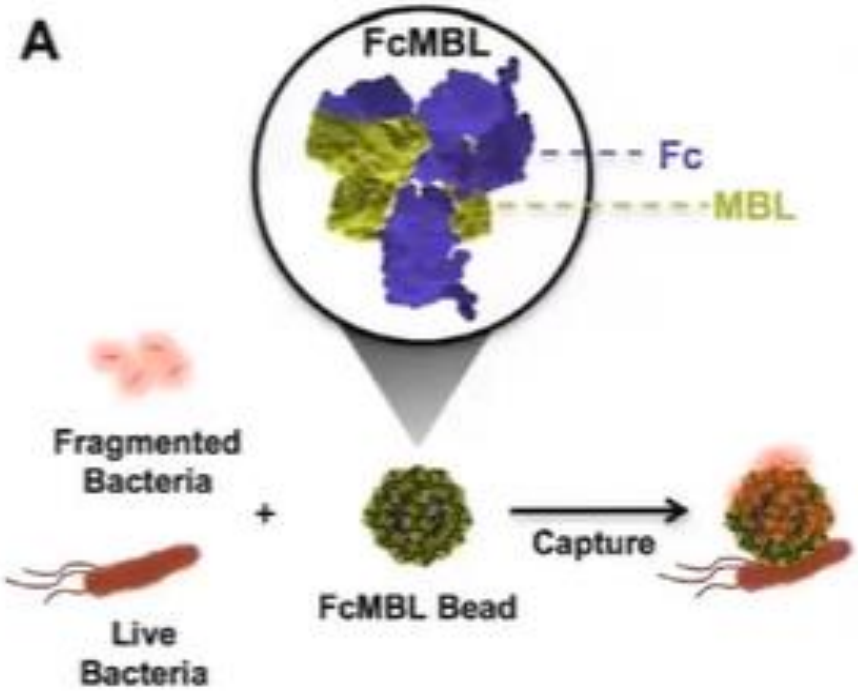
- Aethelon Hemopurifier
- BOA
- Seraph 100

Aethlon Hemopurifier

- Lectin affinity
- Uses immobilized Galanthus nivalis agglutin (GNA)
- Hemopurifier has been shown to bind HIV, Hep C, and Ebola
- May remove SARS CoV 2
- Not yet approved

BOA Biomedical

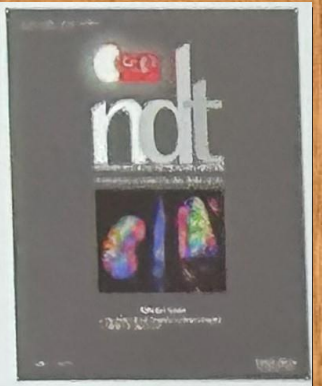
- Fc Mannose-binding lectin
- Entering Phase 1
- No patient level data on SARS CoV 2



Interim analysis of the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry

Schmidt J, Borchina D, Kielstein J, et al for the COSA Investigators

Hannover Medical School, Hannover, Germany
Academic Teaching Hospital Braunschweig, Braunschweig, Germany
KfH Klinikum Siloah, Hannover Germany



Nephrol Dial Transplant. (2022)

Treatment within 60 hrs

ICU to Seraph:
≤ 60 hours

Mortality:
34.5%
(predicted 51.7%)

vs.

p=0.04

Treatment after 60 hrs

ICU to Seraph:
> 60 hours

Mortality:
62.5%

PURIFY-RCT: Blood Purification for the Treatment of Critically Ill Patients with Pathogen Associated Shock

PI: Ian Stewart

Department of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland

ClinicalTrials.gov
NCT05011656

Inclusion Criteria:

- Age ≥ 18 years
- Pathogen Associated Shock
  - On vasopressors
  - Positive blood cultures

Exclusion Criteria:

- Not anticipated to survive >24 hours
- Known allergy to heparin
- Cannot tolerate placement of HD catheter
- Inability to tolerate extracorporeal therapy
- Hypotension of etiologies other than sepsis

PURIFY-RCT multicenter interventional trial design: https://www.clinicaltrials.gov/ct2/show/NCT05011656

Seraph® 100 EU Target Patient Population: Pathogens that can be targeted

Seraph 100 Adsorbs Across a Broad Therapeutic Spectrum

Pathogen *Drug-Resistant Bacteria	Reduction in 4 hr. @300 mL/min	Adsorbate	Calculated Max. Reduction in 4 hr. @300 mL/min
MRSA *S. aureus* *K. pneumoniae* **K. pneumoniae* (CRE)* **K. pneumoniae* (MDR)* *E. coli* **E. coli* (CRE)* *S. pneumoniae* *E. faecalis* **E. faecalis* (VRE)* *E. faecium* *A. baumannii* S. epidermidis *Methicillin-Resistant *S. epidermitis** *S. pyogenes* *S. marcescens* *P. aeruginosa*	>99.7%	HSV-1 and HSV-2 (blood) Ebola (infected NHP serum) Zika (blood) Adenovirus (blood) CMV (blood) ***SARS-CoV-2 (COVID-19)*** *C. albicans* *S. aureus* a-hemolysin (PBS) *B. anthracis* Protective Antigens (PBS) Heparin-Binding Protein Histone H4	>99.7%

Seffer et al, Heparin 2.0: A New Approach to the Infection Crisis, Bld Purification (2020); Jul 2, 1-7
Koch, B., et al. "Protecting the Endothelium with Hemoperfusion During Sepsis." Infection (2019)., 47;(Suppl 1):S1-S67
Exthera Medical Corp.: Data on file
Olson et al, Treatment for Severe Coronavirus Disease 2019 With the Seraph-100 Microbind Affinity Blood Filter, Critical Care Explorations, (2020), 2(8),1-6

Seraph® 100 PURIFY OBS Preliminary COVID-19 Outcome Data (US): April 26, 2021

A Multicenter Evaluation of Blood Purification with Seraph-100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19: A Preliminary Analysis

Stephen A. Chitty, MD; Sarah Mobbs, PharmD, BCPS; Brian S. Rifkin, MD; Steven W. Stogner, MD; Andrew M. Wilhelm, DO; Michael S. Lewis, MD; Jaime Betancourt, MD; Jeffrey DellaVolpe, MD; Fadi Abouzahr, MD; Harold M. Szerlip, MD; Robert M. Garcia, DO; Ian Rivera, MD; James D. Odum, MD, PhD; Stephen W. Olson, MD; Subrata Debnath, MBBS, MPH, PhD; Sean P. Barnett, MD; Amay Parikh, MD; Robert J. Walter, MD; Nhat T. Nguyen, MD; Brendan Sullivan, MD; Karl C. McCrea, PhD; Lan J. Stewart, MD; Kathleen P. Pratt, PhD; Kumar Sharma, MD; Kevin K. Chung, MD for the PURIFY Investigators

Design: Prospective observational patient registry[3]

- Primary Endpoint: Time spent on medications used to increase blood pressure
- Secondary Endpoints: Time on mechanical ventilation, ICU LOS, Hospital LOS, Time spend on dialysis, Mortality
- 99 patients included in preliminary preprint publication
- **Mortality was much lower in the Seraph 100 treated group compared to the historical controls: 37.7% vs. 67.4% respectively (p=0.003)**
- Multivariable logistic regression analysis yielded an odds ratio of 0.27 (95% confidence interval 0.09- 0.79, p=0.016): **Nearly 4X improvement in survivability odds when severely ill COVID-19 patients are treated with Seraph 100**
- **Significant reduction of 10.5 median ICU LOS compared to matched controls (p = 0.052)**
- These results support the 2021 launch of a US multicenter randomized controlled feasibility trial of the Seraph 100 for septic shock due to any pathogen

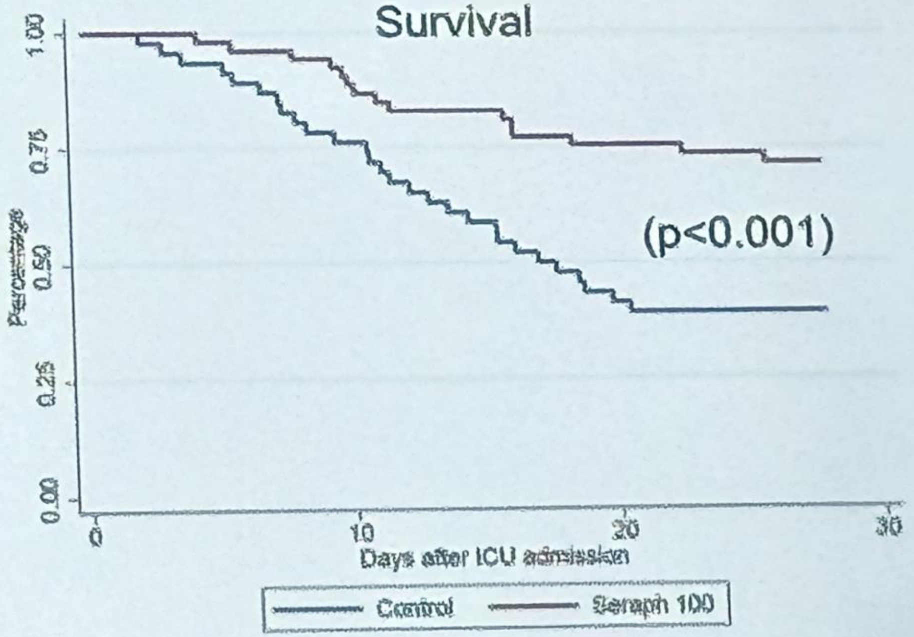


Table 3. Outcomes stratified by study cohort

	Treatment	Control	P value
Mortality (%)	37.7	67.4	0.003
ICU free days, Median (IQR)ᵃ	10.5 (0-19.5)	0 (0-12.5)	0.052
RRT dependent at discharge (%)ᵇ	0	9.4	0.541
Hospital length of stay (day), Median (IQR)ᵇ	17 (10-35.5)	15 (5-32)	0.170

RRT= renal replacement therapy
ᵃData available for 88 subjects
ᵇAmong survivors, data missing for one study subject

9. Chitty et al. A Multicenter Evaluation of Blood Purification with Seraph 100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19. A Preliminary Report. (2021)

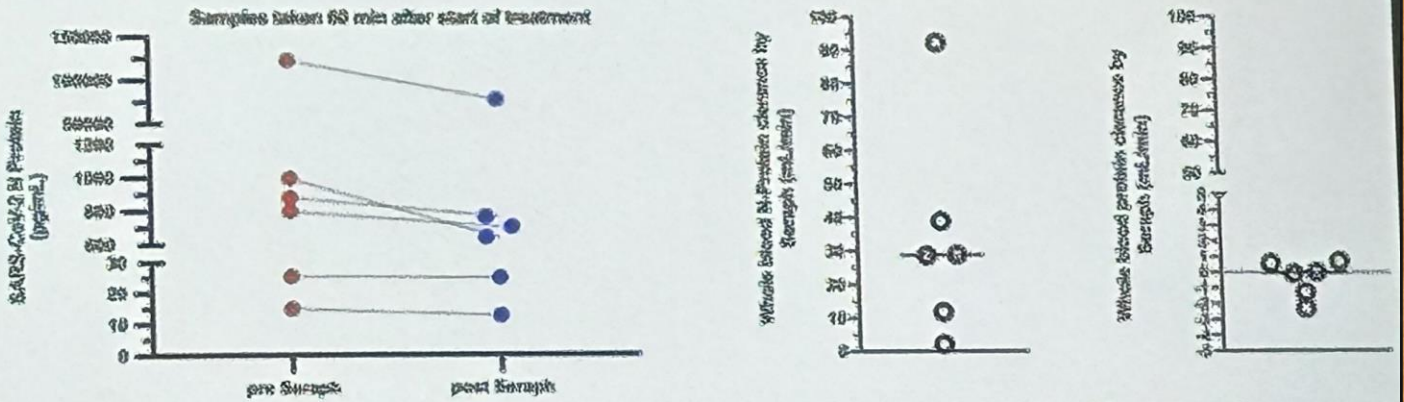
Seraph 100 Rapidly Reduces Viremia

Critical Care

Hemofiltration with the Seraph® 100 Microbind® Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill COVID-19 patients

Jan J. Kielstein ✉, Dan-Nicolae Boschina, Thomas Hüfner, Satyam Arora, Dawn Mattson & Andrew J. Ball

Critical Care 25, Article number 190 (2021) | Cite this article

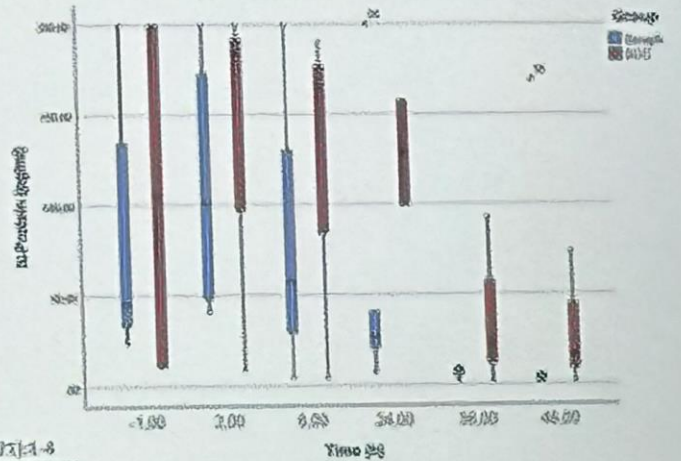


Concentration of the nucleocapsid protein pre (upstream) and post (downstream) of the Seraph® at 60 min of treatment (upper part of the figure) and the resulting device clearance for the N-protein as well as the total plasma protein (lower part of the figure)[15]

Preliminary Results on SARS-CoV-2 Clearance from the Blood

SARS-CoV-2 RCT study in Europe[16]

Sample analysis from the first 8 enrolled patients shows trending data indicating more rapid viral clearance in Seraph treated patients compared to standard of care control patients. This is after only a single 4-hour Seraph 100 treatment.



15. Kielstein et al. Hemofiltration with Seraph 100® Microbind Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill.... Critical Care 25.1(2021):1-8
16. Safety & Effectiveness Evaluation of Seraph 100 in Treatment of Pts With COVID-19 (CP012) – Protein Data on file: https://clinicaltrials.gov/ct2/show/NCT04547257

What we do NOT want to remove!

Reduction Ratio
0-5 min

Table 1. Summary of the in vitro anti-infective drug elimination profile of the Seraph® 100

Drug	C_0	Cl_0	$Cl_{5'}$	Cl_{30}	Cl_{60}	RR_{0-5}	RR_{5-60}	RR_{0-60}
Aciclovir	58.6 ± 8.3	−2.12	1.07	10.73	−2.3	20	0	22
Amphotericin B	12 ± 2.1	8.45	8.5	−5.52	−20.69	19	8	26
Ceftazidime	276 ± 22.8	−2.07	−7.23	29.09	−4.12	14	2	11
Cefazolin	828.8 ± 86.7	0.52	−2.09	17.78	−2.35	20	0	15
Clindamycin	9.9 ± 3.3	3.53	5.51	17.77	3.19	−1	−2	20
Daptomycin	68.5 ± 3.5	17.32	−22	0	−2.17	−4	19	15
Fluconazole	28.5 ± 4.9	−5.35	−20.41	−40	60.05	19	−25	−1
Fosfomycin	953.9 ± 427.8	−14.1	−4.9	2	−8	14	−3	10
Gentamycin	6.4 ± 0.1	24.6	−30.61	−9.09	−14.15	54	12	59
Levofloxacin	89.6 ± 17.9	−1.51	−2.08	9.11	−13.21	9	3	9
Linezolid	109.4 ± 10.9	−1.51	−2.08	10.12	−13.21	11	3	14
Meropenem	125.6 ± 17.9	−3.48	11.36	12.39	−6.05	13	−2	15
Moxifloxacin	67.4 ± 7.1	0.8	2.48	9.65	−11.78	9	3	11
Piperacillin	1364.3 ± 193	18.87	16.44	9.93	−50.08	11	5	16
Rifampicin	109.4 ± 4.4	−0.97	−5	9.86	0.99	7	1	7
Tazobactam	142.3 ± 16.7	11.33	7.89	44.92	−36.6	12	5	17
Tobramycin	18.8 ± 6.5	48.7	−4.19	−25.07	−4.56	62	7	62
Vancomycin	179.8 ± 23.8	0.46	−1.63	13.48	−1.05	20	2	23

C_0 = plasma drug concentration at the beginning of the experiment (mg/l). $Cl_{\dots}$ = mean drug plasma Cl of the seraph adsorber at different investigated measure time points in milliliters per minute. RR (%) of the investigated drug during the first 5 min and during the rest of the experiment.

In vitro study

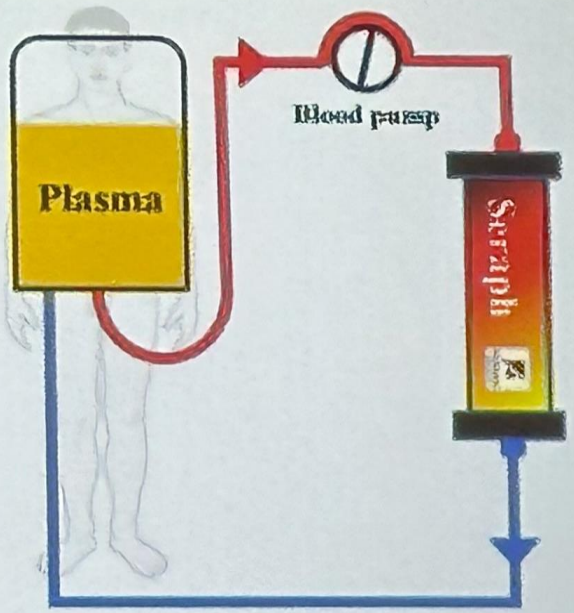


FIGURE 1 Schematic overview of the experimental setup. Plasma was circled through the Seraph cartridge by a roller pump. Plasma samples were obtained before and after passing through the Seraph device.

- Therapeutic Drug Monitoring
- Administer Aminoglycosides after the Seraph session

Schmidt et al. Clin Kidney Journal 2020

ICU Case 1: Endocarditis

- Male, 67yo
- Hypertension
- ESRD, peritoneal dialysis
- Fever and asthenia for 1 week

- **ICU admission**
- HR 130
- MAP 60mmHg
- Procalcitonin : 95ng/ml

- Antibiotics
  - Vancomycin
  - Ceftazidime
- Norepinephrine
- CRRT
- **Seraph 100 HA**

Positive blood culture 12h post ICU admission (MRSA)

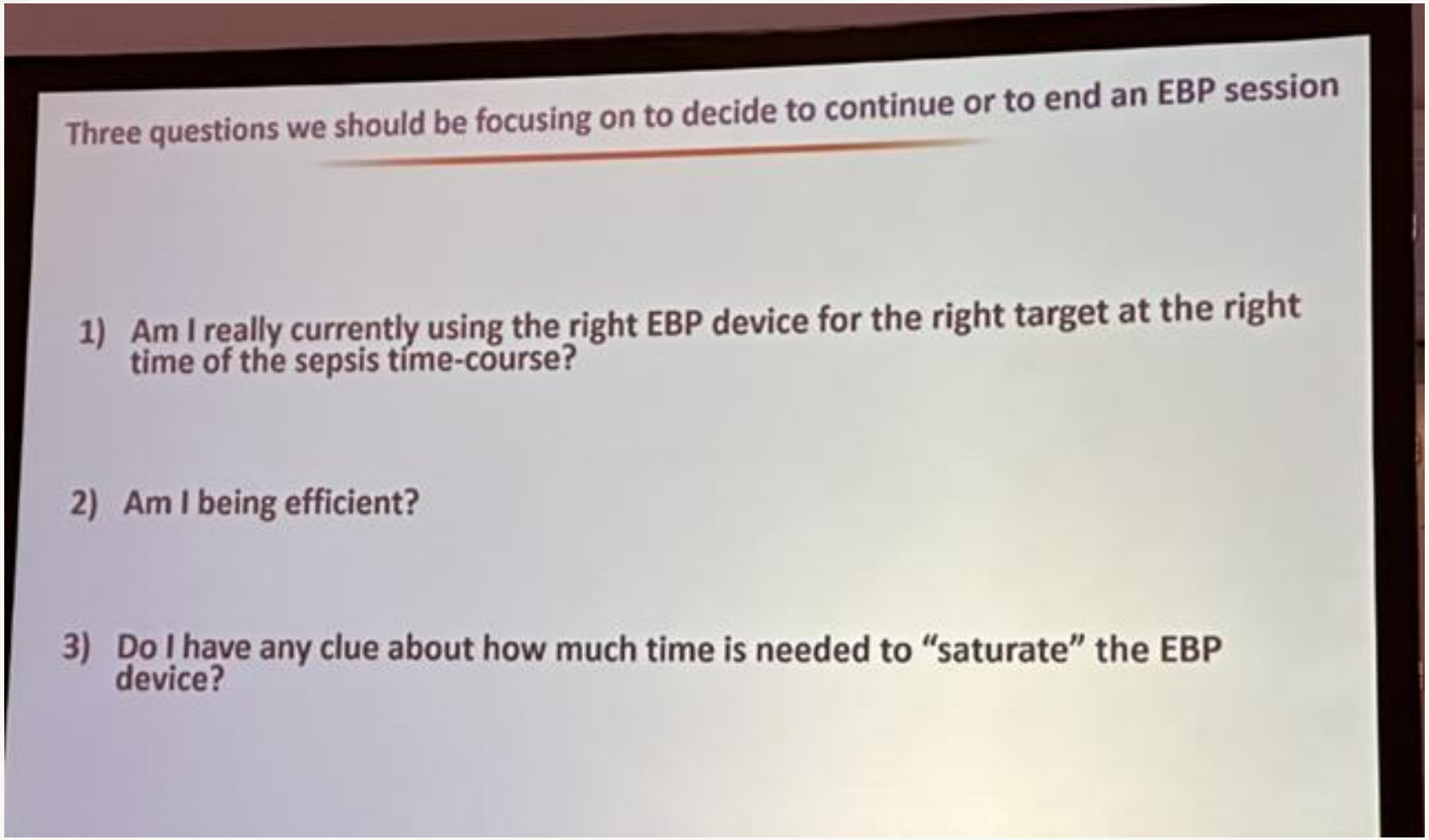
- Nephrology on day 5
- Cardiologic follow-up
- Home on day 18

Η ΑΙΜΟΠΡΟΣΡΟΦΗΣΗ ΩΣ ΜΕΡΟΣ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΝΤΙΜΕΤΩΠΙΣΗΣ ΛΟΙΜΩΔΟΥΣ ΕΝΔΟΚΑΡΔΙΤΙΔΑΣ ΣΕ ΑΣΘΕΝΗ ΜΕ ΧΡΟΝΙΑ ΝΕΦΡΙΚΗ ΝΟΣΟ ΤΕΛΙΚΟΥ ΣΤΑΔΙΟΥ ΥΠΟ ΑΙΜΟΚΑΘΑΡΣΗ (ΧΝΑ-ΤΝ)

Ι. Γριβέας, Ε. Πρατήλας, Α. Μπαλιτσάρη

Νεφρολογική Κλινική, 417 Νοσηλευτικό Ίδρυμα Μετοχικό Ταμείο Στρατού (ΝΙΜΤΣ)

Ελληνική Εταιρεία Αιμαφαίρεσης


Three questions we should be focusing on to decide to continue or to end an EBP session
1) Am I really currently using the right EBP device for the right target at the right time of the sepsis time-course?
2) Am I being efficient?
3) Do I have any clue about how much time is needed to "saturate" the EBP device?

CONCLUSION

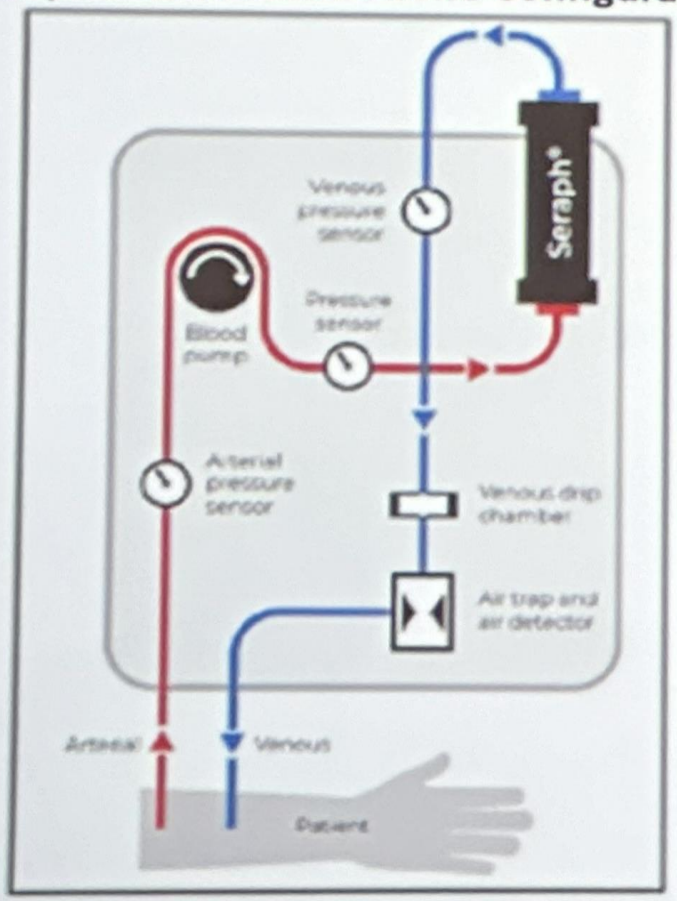
- In 2023, still many unanswered questions in the field of EBP for sepsis
  - How do these therapies exactly interfere with sepsis pathophysiology?
  - Which patients exactly?
  - Which Timing (initiation and termination)?
  - What to ultimately remove?

- Look at how the patient is responding (1- clinically 2- biologically 3- targeted molecule) to the EBP session when it comes to decide to continue (2^{nd} session?) or to stop

- We do need more information about the saturation capacity of the EBP devices

Hemoadsorption with Seraph: different possible configurations

Seraph 100 in Stand-Alone Configuration



- To be chosen when no indication of RRT
- Available on a specific hemoadsorption machine OR with several CRRT machines having a hemoadsorption mode

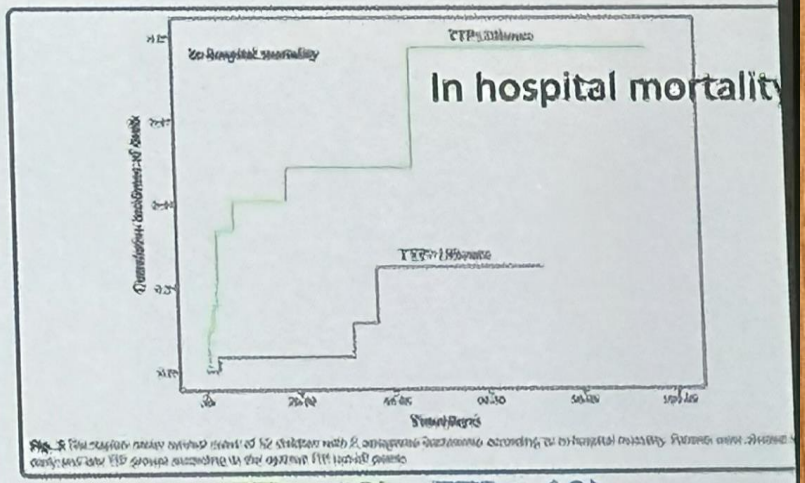
Rapidly Decreasing the Bacterial Blood Load is of major importance for patient prognosis

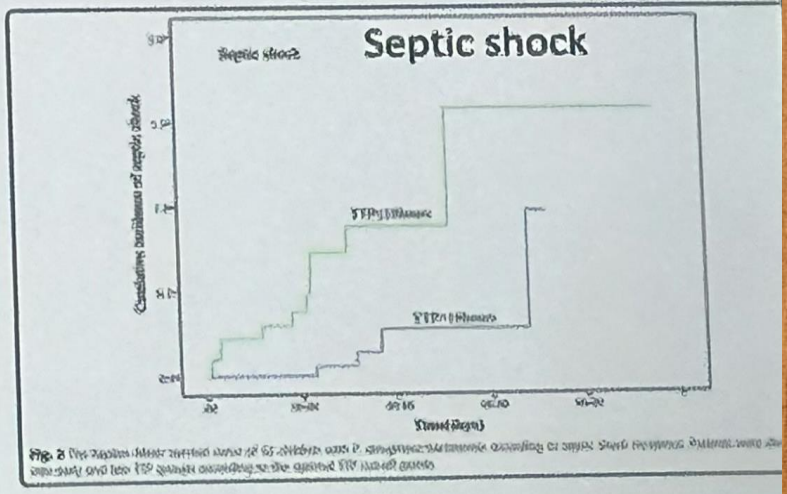
TABLE 1. Comparison of variables between deceased and surviving patients with *Staphylococcus aureus* bacteraemia persisting for >48 h

	Survivors, n = 52 (%)	Deceased, n = 35 (%)	Univariate p-value	Multivariate p-value	OR (95% CI)
Age (years)	63.4 ± 16.1 (range, 25–87)	67.3 ± 16.3 (range, 31–92)	0.19	0.68	1.01 (0.98–1.04)
Male gender	27 (52)	22 (63)	0.31		
Hospital acquisition	14 (27)	14 (40)	0.25		
MRSA	28 (54)	25 (57)	0.76		
Underlying disease					
Diabetes mellitus	32 (62)	20 (57)	0.68		
ESRD	24 (46)	13 (37)	0.41		
Malignancy	7 (14)	5 (14)	0.91		
Liver cirrhosis	3 (6)	4 (11)	0.39		
Pitt bacteraemia score	2.1 ± 2.1	3.6 ± 2.8	0.01	0.065	1.37 (1.13–1.77)
Focus of infection					
Catheter	17 (33)	10 (29)	0.68		
IE	8 (15)	8 (23)	0.38		
Bone and soft tissue	13 (25)	3 (9)	0.13		
Pneumonia/empyema	2 (4)	6 (17)	0.05	0.17	3.84 (0.57–25.76)
Vascular other than IE	7 (13)	1 (3)	0.15	0.9	
Primary bacteraemia	2 (4)	4 (11)	0.19		
Intra-abdominal infection	3 (6)	3 (9)	0.67		
Other*	3 (6)	1 (3)	0.63		
Intervention					
Catheter removal	17 (33)	9 (26)	0.45		
Catheter removal within 48 h	3 (6)	2 (6)	0.49		
Surgical intervention	10 (19)	5 (14)	0.54	0.75	0.61 (0.13–3.0)
Adequate empirical therapy	35 (67)	18 (51)	0.14		
First TTP of <12 h	32 (62)	23 (66)	0.70		
Second TTP of <12 h	2 (4)	0 (0)	0.52		
Second TTP/first TTP ratio of >1.3	37 (71)	17 (49)	0.04	0.004	0.20 (0.07–0.59)

ESRD, end-stage renal disease; IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; TTP, time to positivity.
*Excluded urinary track infection, purulent pericarditis, endophthalmitis, and epidural abscess.

Hsu et al. Clin Microbiol 2014





Xu et al. BMC Inf Dis 2020

When to think of Seraph?

- Suspicion of bacteremia
  - Endocarditis
  - CRBSI
  - Septic shock
  - Specific indications (vascular sepsis, fistula infection, ...) ?
- Do not wait for positive blood cultures
- Monitor the efficacy of the treatment
- Control the treatment dose
- Repeat if necessary ?

Of course Never Differ
Antimicrobials
and **Source Control**

Negative Blood Culture
Increase TTP
Hemodynamic improvement

Blood Flow rate
Treatment duration
Treatment stability
Patient weight

In vitro (in blood) (Drug-Resistant) Bacteria Binding Evaluate @ March 2, 2017	Seraph Single Pass Pathogen Reduction (% Removed)	Calculated Maximum Reduction in 4 hr. @300 mL/min (w. Source Control)
MRSA	92	>99.9 %
S. aureus	66	>99.9 %
K. pneumoniae	37	99.7%
K. pneumoniae (CRE)	99	>99.9 %
K. pneumoniae (Multi-Drug Resistant)	36	99.7%
E. coli	99	>99.9 %
E. coli (CRE)	99	>99.9 %
S. pneumoniae	53	>99.9 %
E. faecalis	99	>99.9 %
E. faecalis (VRE)	91	>99.9 %
E. faecium	56	>99.9 %
A. baumannii	79	>99.9 %
S. epidermidis	58	>99.9 %
Methicillin-Resistant S. epidermidis	66	>99.9 %
S. pyogenes	76	>99.9 %
Serratia marcescens	73	>99.9 %
P. aeruginosa	83	>99.9 %

Viruses, Fungus, Toxin & HBP Binding:

In Vitro	Seraph Single Pass Pathogen Reduction (% Removed)	Calculated Maximum Reduction in 4 hr. @300 mL/min
HSV-1 and HSV-2 (blood)	99.9	>99.9 %
Ebola (Infected NHP serum)	(39-99)	>99.9 %
Zika (blood)	87	>99.9 %
Adenovirus (blood)	62	>99.9 %
CMV (blood)	79	>99.9 %
C. albicans	36	99.7 %
Endotoxin* (blood)	98	>99.9 %
S. aureus a-hemolysin (PBS)	below detection	>99.9 %
B. anthracis Protective Antigen (PBS)	below detection	>99.9 %
Heparin-Binding Protein	99.99	>99.9 %

*Seraph 200 result

Summary of Seraph's Pathogen Binding Capacity from Blood

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UNIVERSITY OF SURREY

Pathogen Removal by Hemadsorption

Based on typical bacteria (fungi) concentrations in blood of infected patients and the quantitative capture of pathogens using Seraph media, this chart presents the excess capacity that a Seraph device may have.

Elimination of Staphylococcus aureus from the bloodstream using a novel biomimetic sorbent haemoperfusion device

Malin-Theres Seffer,1,2 Gabriele Eden,1 Susanne Engelmann,2 Jan T Kielstein 1

1. Nephrology | Rheumatology | Blood Purification, Academic Teaching Hospital Braunschweig, Braunschweig, Lower Saxony, Germany [2]Microbial Proteomics, Helmholtz Centre for Infection Research, Braunschweig, Lower Saxony, Germany

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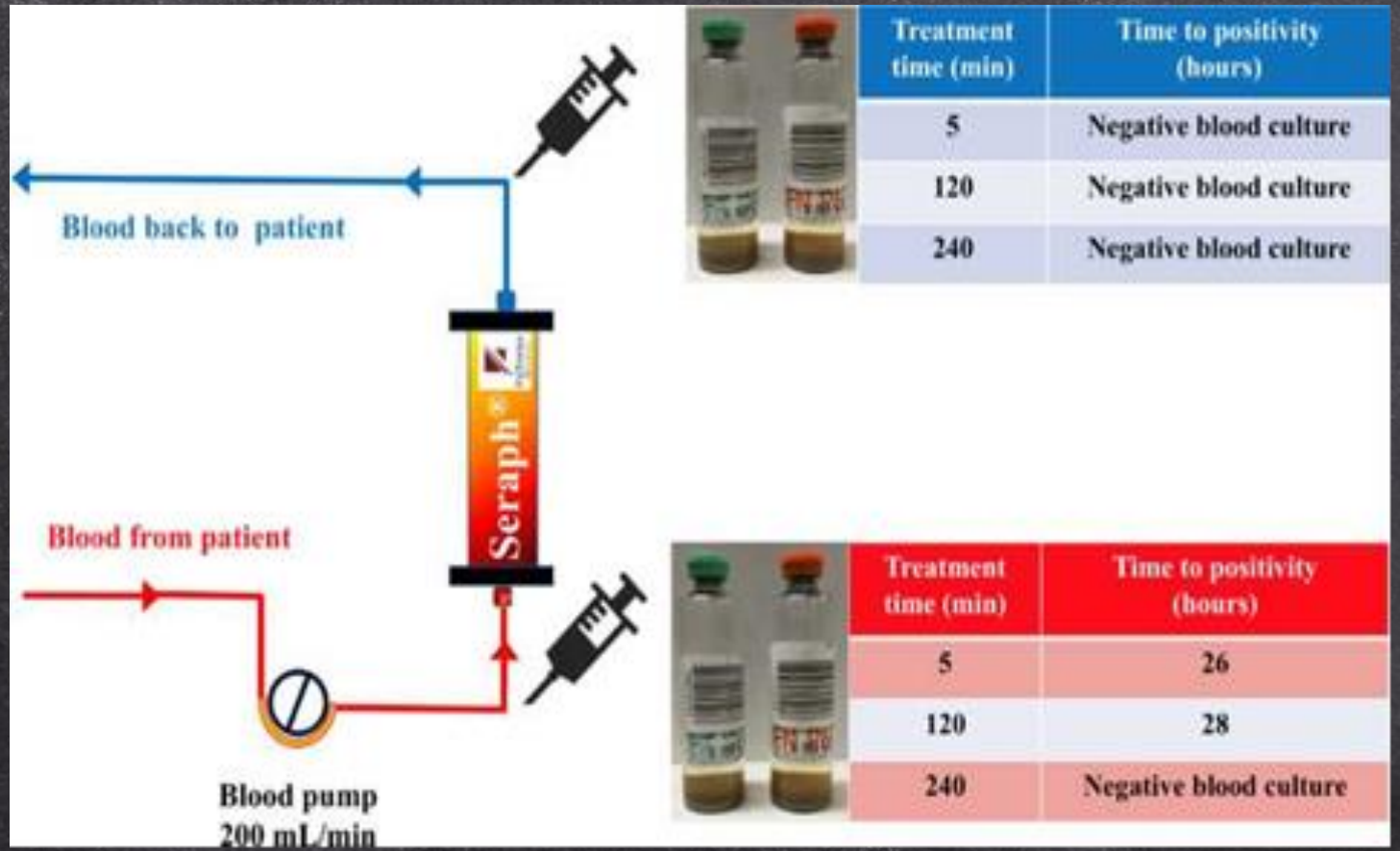
Accepted 24 June 2020



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

SERAPH® 100 – ONGOING CLINCIAL STUDIES & PUBLISHED DATA

Seraph 100 does not clear most anti-infective drugs[2]

ckj OXFORD era EDTA

Clinical Kidney Journal, 2020, vol. 13, no. 3, 421–424

Advance Access Publication Date: 21 May 2020
Original Article

ORIGINAL ARTICLE

In vitro elimination of anti-infective drugs by the Seraph® 100 Microbind® affinity blood filter

Julius J. Schmidt [1,*], Gabriele Eden[2,*], Malin-Theres Seffer[2], Manuela Winkler[2] and Jan T. Kielstein [2]

[1]Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany and [2]Medical Clinic V, Nephrology | Rheumatology | Blood Purification, Academic Teaching Hospital Braunschweig, Braunschweig, Germany

*These authors contributed equally to this study and are both considered first authors.
Correspondence to: Julius J. Schmidt; Email: schmidt.julius@mh-hannover.de

"Our work indicates that the Seraph 100 does not affect plasma levels of the investigated anti-infective drugs to a clinically important degree. Therefore we predict no interference… thus avoiding the need for a dose adaption or an additional dose after treatment with the Seraph 100.[2]

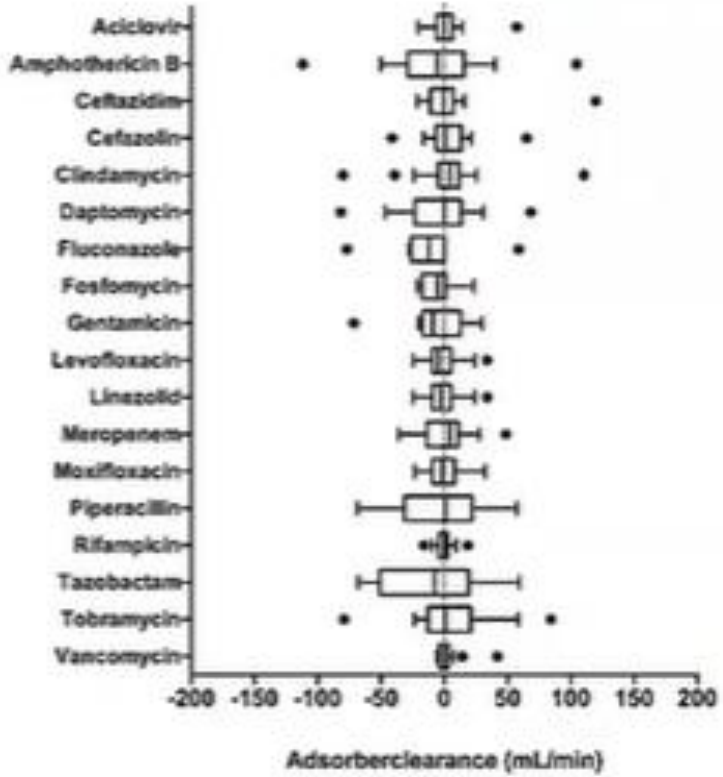


FIGURE 2: Tukey boxplot of the Seraph® 100 plasma CL of the investigated anti-infective drugs during the procedure in millilitres per minute.

Are Other Blood Components Removed?

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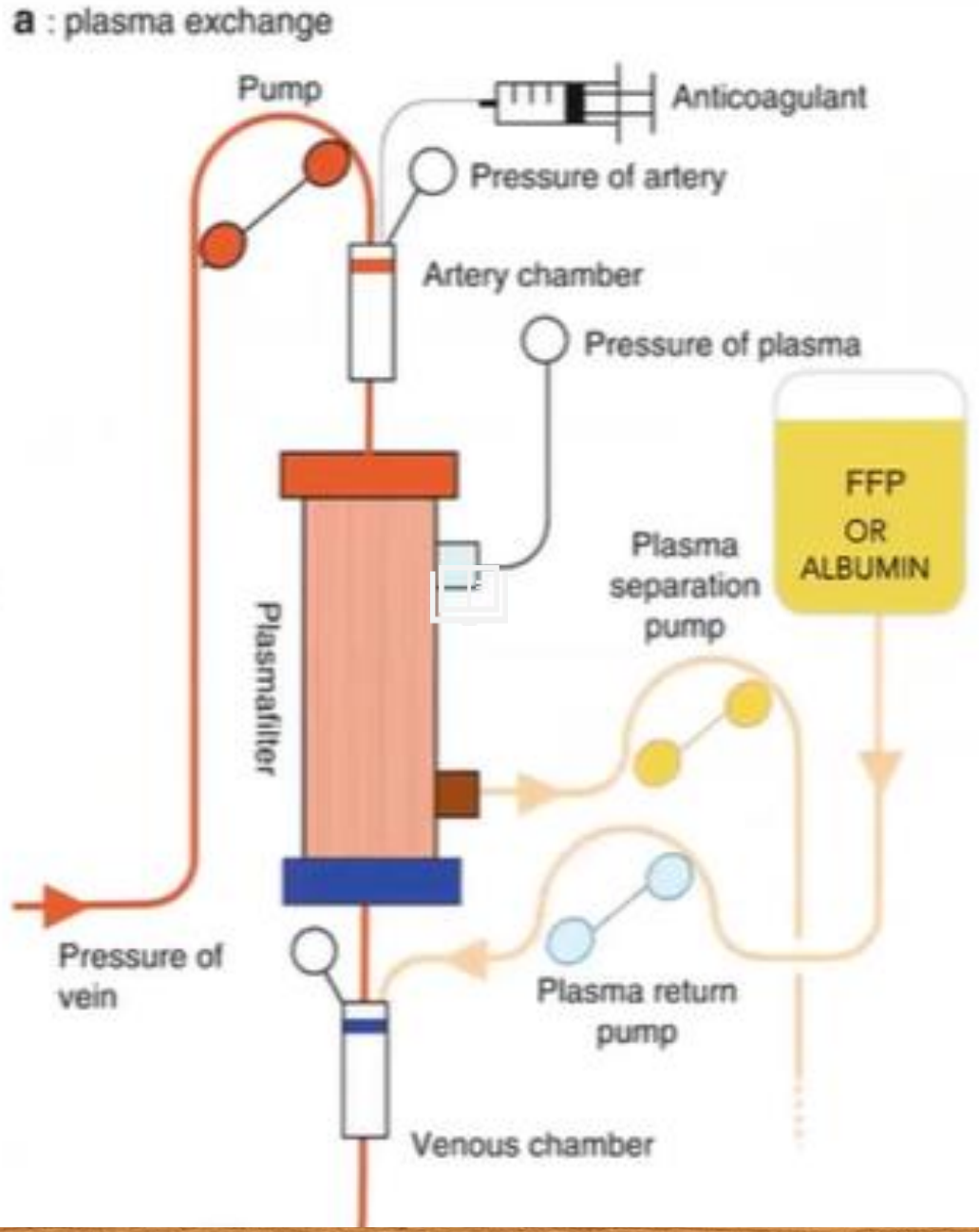
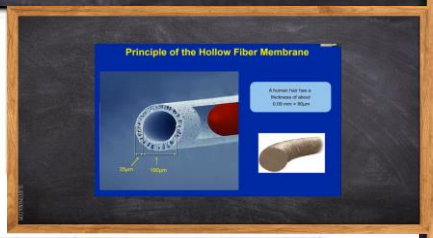
- **Blood Proteins**

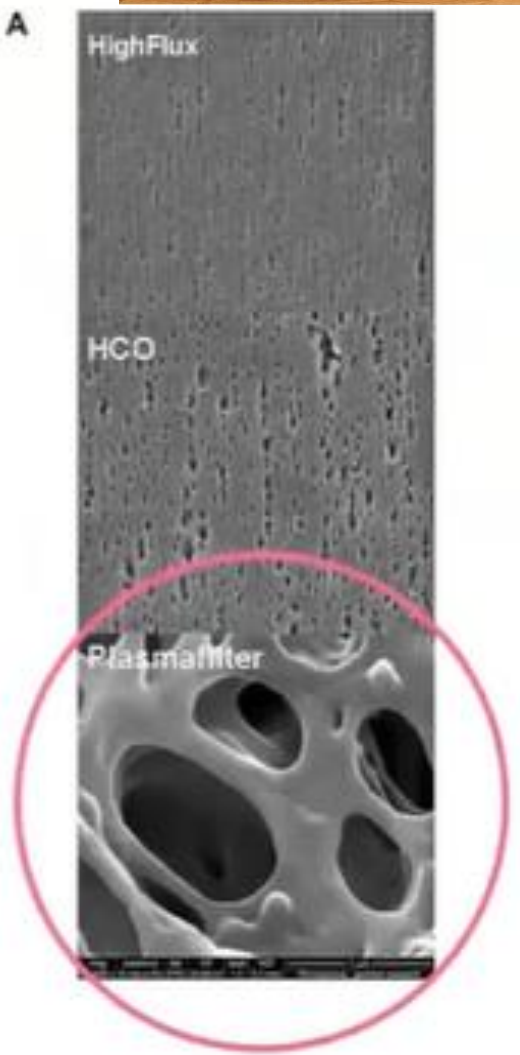
Albumin	No
Protein C	No
ATIII	Small amounts, but bound ATIII is still able to act on thrombin and provides blood compatibility
IgG, IgA, IgM, IgE	No

- **Drugs**
  - Some antibiotics *may* bind
  - Drug removal is normal in hemodialysis and nephrologists routinely adjust dosing to compensate

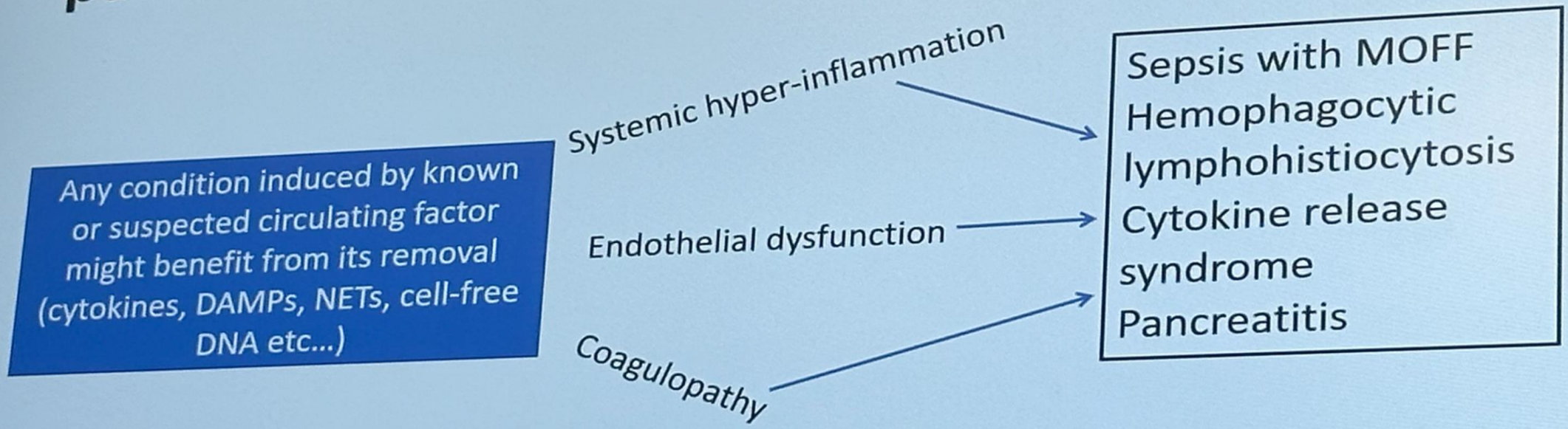
THERAPEUTIC PLASMA EXCHANGE



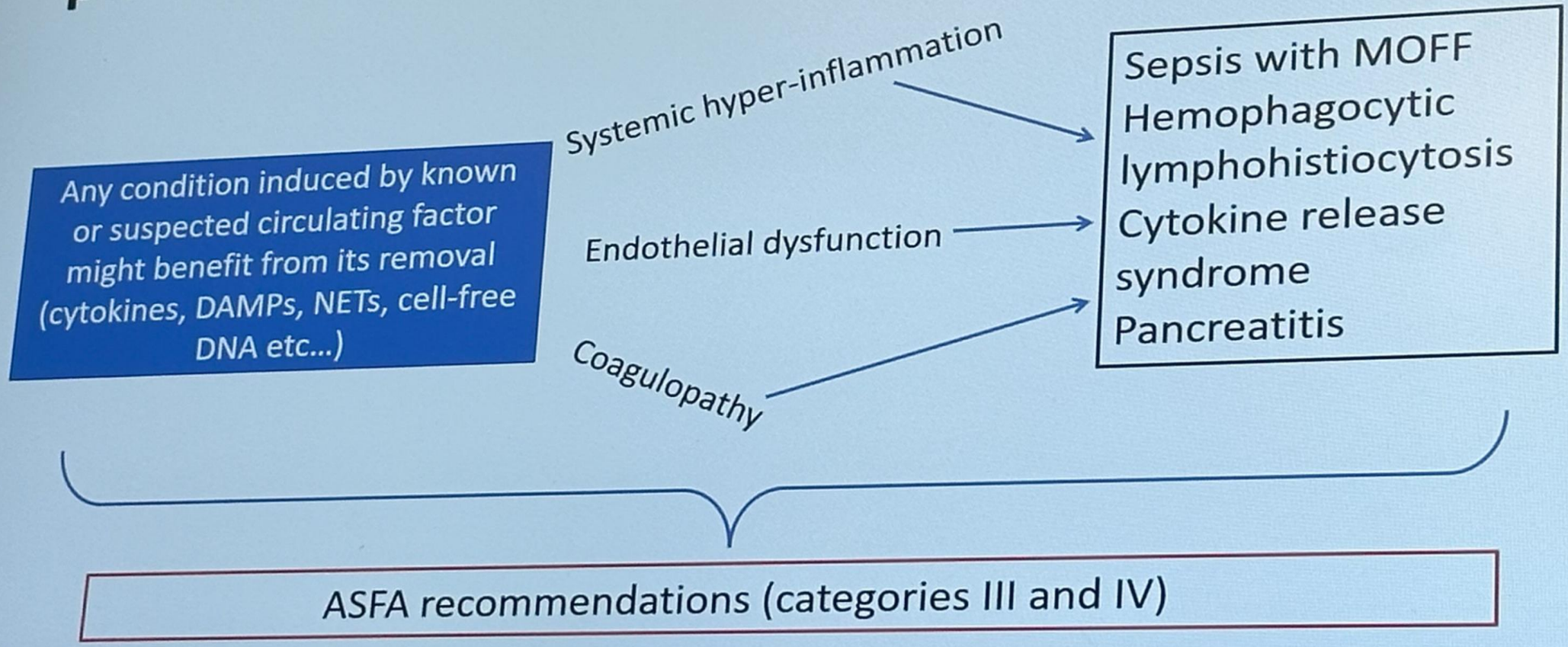




What are „new“ TPE indications for critically ill patients?



What are „new“ TPE indications for critically ill patients?



TPE in septic conditions

- The theoretical rationale for TPE goes beyond the simple elimination of circulating injurious molecules.
- The exchange of septic with healthy plasma might also replace consumed protective factors that are of importance to maintain microcirculatory flow (e.g., ADAMTS13) and counterbalance vascular leak (e.g., Angiopoietin-1).
- The American Society For Apheresis (ASFA) grades "sepsis with multi-organ dysfunction" as potential 2B, category III indication for TPE (= optimum role not established, decision should be individualized).

We should be careful of the increasing gap between technological progres and medical knowledge!

Medical knowledge

Increasing gap!

EBP device

Technological progress

Past

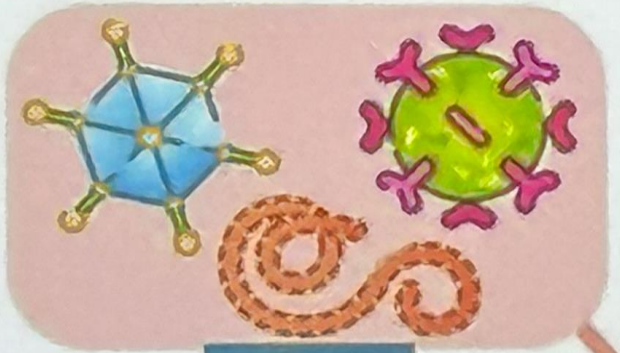
Future

FOUR IMPORTANT UNANSWERED QUESTIONS :

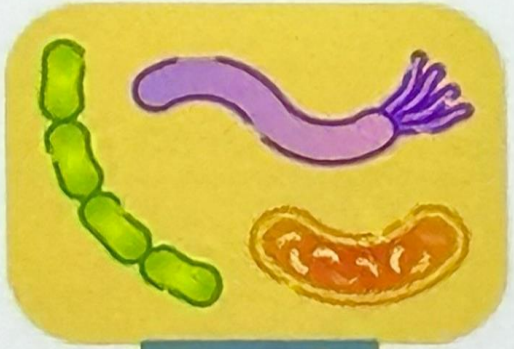
a- How do these therapies exactly interfere with sepsis pathophysiology?
b- Which patients exactly?
c- Which timing?
d- What to ultimately remove?

Cancer and COVID19

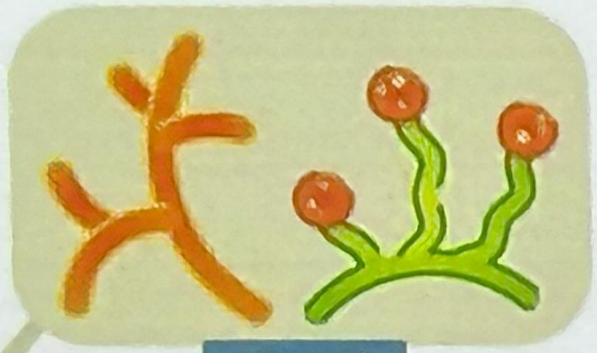
Pathogen Removal by Hemadsorption



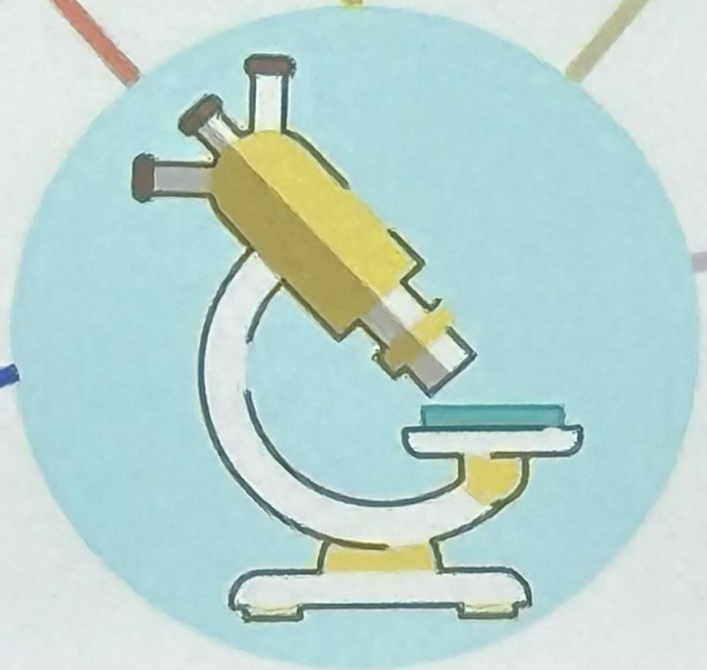
Virus



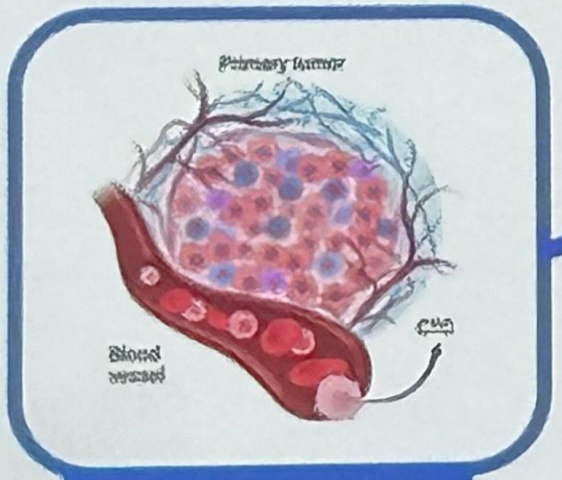
Bacteria



Fungi

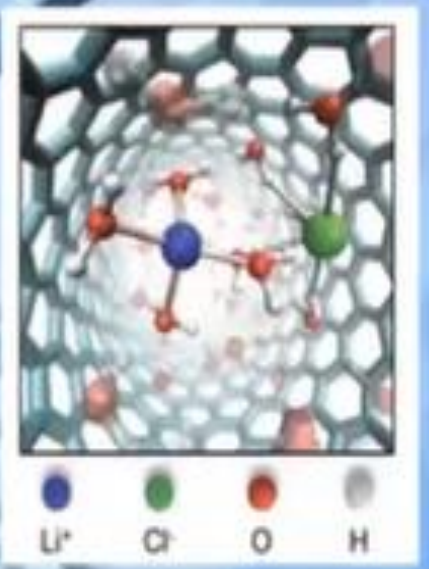


Protists

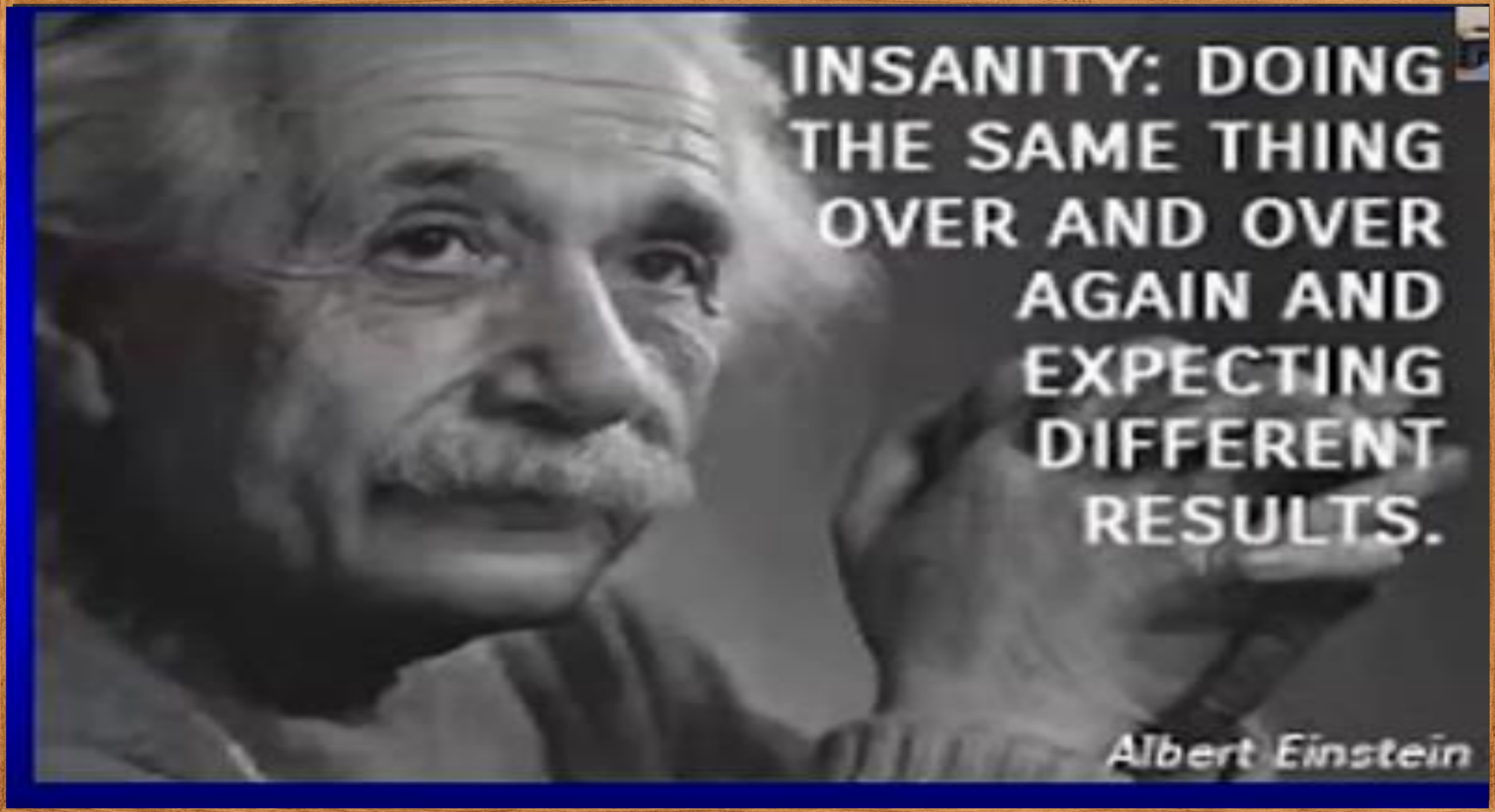


Cancer Cells

NEW CARBON NANOTUBES CAN DRAMATICALLY ENHANCE TRANSPORT: CNT CAN UNLOCK DIALYSIS PROCESSES WITH UNPRECEDENTED EFFICIENCY



Steven F. Buchsbaum et al. **Fast Permeation of Small Ions in Carbon Nanotubes**. *Advanced Science* (2020). DOI: 10.1002/advs.202001802


INSANITY: DOING THE SAME THING OVER AND OVER AGAIN AND EXPECTING DIFFERENT RESULTS.
Albert Einstein


José Moura-Neto
" It's kind of fun to
do the impossible "
Walt Disney

Thank you!

Do you have any questions?

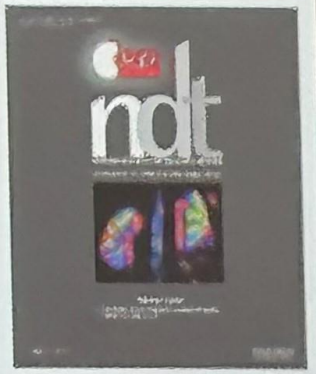
giannisgriv@hotmail.com

www.athens-nephrology.gr

Interim analysis of the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry

Schmidt J, Borchina D, Kielstein J, et al for the COSA Investigators

Hannover Medical School, Hannover, Germany
Academic Teaching Hospital Braunschweig, Braunschweig, Germany
KRH Klinikum Siloah, Hannover Germany



Nephrol Dial Transplant. (2022)

12 ICUs

6 countries

82 patients

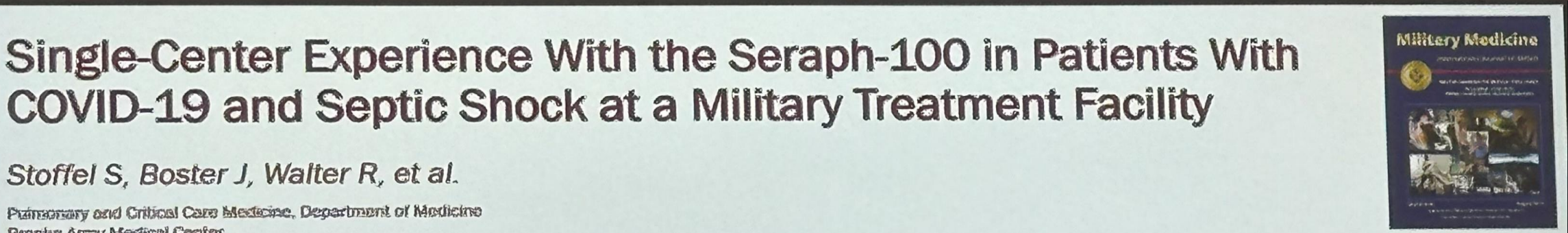
Primary Outcome: 30-day survival

Secondary Outcome: Adverse events, clotting rates, time to ICU discharge

Single-Center Experience With the Seraph-100 in Patients With COVID-19 and Septic Shock at a Military Treatment Facility

Stoffel S, Boster J, Walter R, et al.

Pulmonary and Critical Care Medicine, Department of Medicine
Brooke Army Medical Center
JBSA Fort Sam Houston, Texas

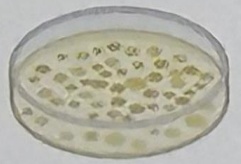


Military Medicine (2023)

28 patients treated with Seraph

9 with septic shock

5 on VV ECMO



Baseline SOFA score: 13

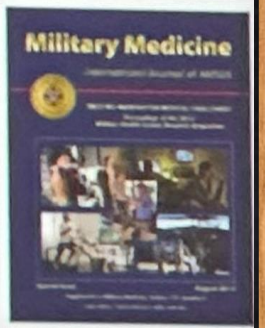
Organisms:

- **MRSA**
- **MSSA**
- **K. *pneumoniae***
- **E. *faecalis***
- **P. *aeruginosa***
- **Candida**
- **Saccharomyces**

Single-Center Experience With the Seraph-100 in Patients With COVID-19 and Septic Shock at a Military Treatment Facility

Stoffel S, Boster J, Walter R, et al.

Pulmonary and Critical Care Medicine, Department of Medicine
Brooke Army Medical Center
JBSA Fort Sam Houston, Texas



Military Medicine (2023

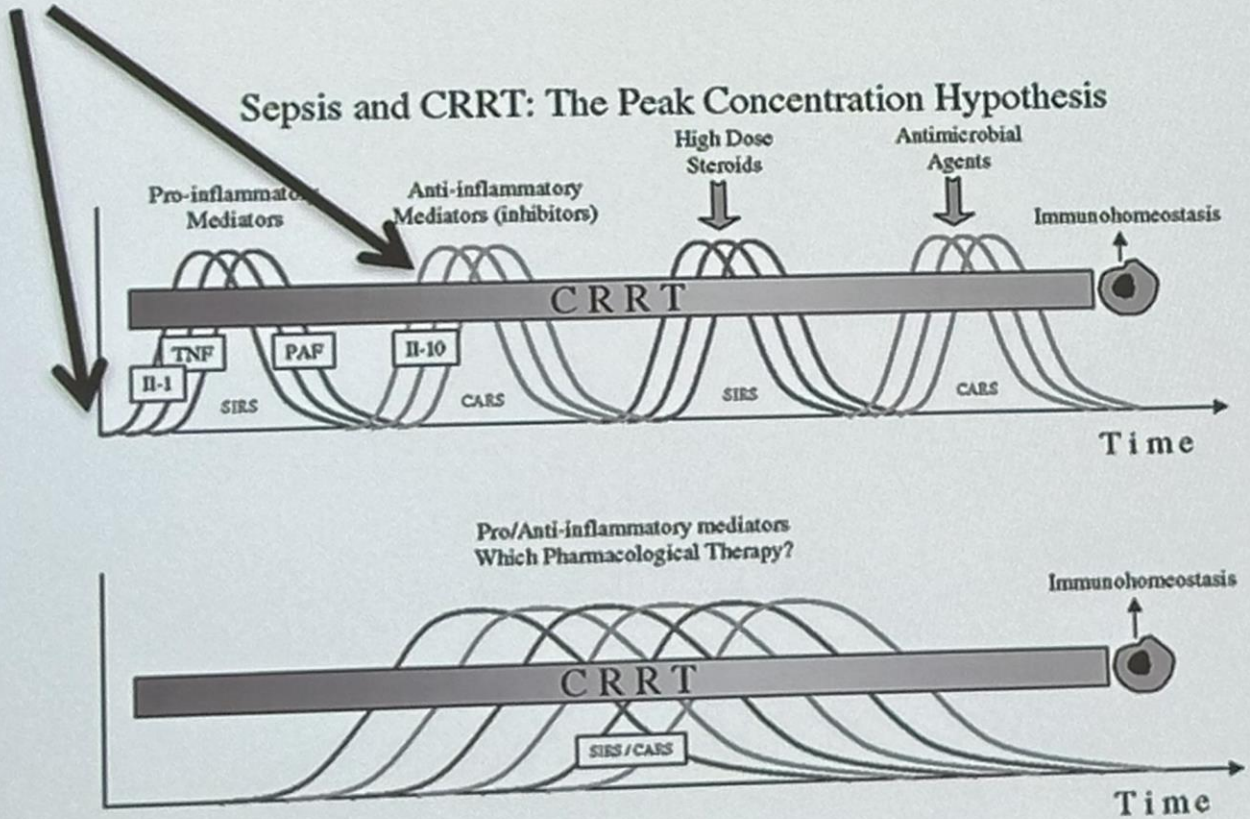
Outcome	Pre-Seraph (mean ± SE)	24-hours Post-Seraph (mean ± SE)	P-value
Mean arterial pressure (mmHg)	64.2 ± 2.36	76.2 ± 2.68	<.0001
Heart rate, mean (beats per minute)	128 ± 6.6	100.3 ± 6.07	<.0001
FiO_2 delivery (%)	74.4 ± 10.58	60.3 ± 10.35	<.001
Lactate (mmol/L)	6.14 ± 1.25	2.8 ± 1.14	.001
pH	7.29 ± 0.03	7.39 ± 0.04	.020
Norepinephrine (mcg/min), $n = 11$	36.3 ± 4.74	8.3 ± 3.92	<.001
Vasopressin (units/min), $n = 11$	0.04 ± 0.004	0.02 ± 0.003	<.001
Angiotensin II (ng/kg/min), $n = 7$	34.5 ± 6.4	3.3 ± 5.26	<.001
Dobutamine (mcg/kg/min), $n = 2$	2.3 ± 1.00	0.2 ± 0.75	.006
Epinephrine (mcg/min), $n = 9$	12.8 ± 5.75	9.9 ± 5.5	.377

Predicted mortality:
>95.2%

Observed Mortality:
55.6%

CRRT OXIRIS set: 3 goals for one filter

Endotoxins removal + cytokines removal + kidney support



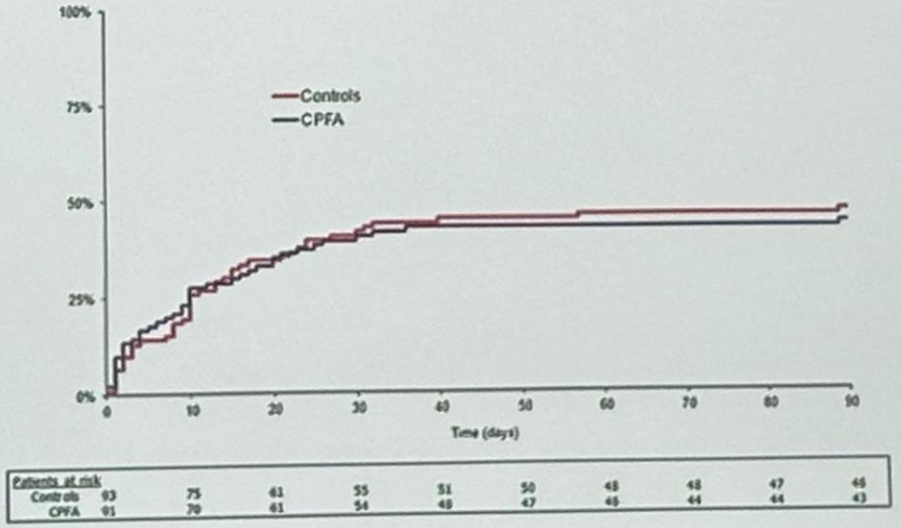
Ronco et al. *Artificial Organs* 2

BMJ Open

Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

Sergio Livigni,[1] Guido Bertolini,[2] Carlotta Rossi,[2] Fiorenza Ferrari,[1] Michele Giardino,[2] Marco Pozzato,[3] Giuseppe Remuzzi,[2] GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units

Figure 3 Survival curves.



Livigni et al. *BMJ open* 2014

Seraph® 100 Prelimanary Outcome Data COVID-19: COSA COVID-19 Patient Registry (EU)

Interim-analysis of the COSA (COVID-19 patients treated with the Seraph® 100 Microbind® Affinity filter) registry

Julius J Schmidt, Dan Nicolae Borchina, Mariet van´t Klooster, Khalida Bulhan-Soki, Reuben Okioma, Larissa Herbst, Diego Sandoval Rodríguez, Vedran Premužić, Stefan Büttner, Birgit Bader, Wojciech Serednicki, Ewa Zasada, Michael Schmitz, Ralf A Quabach, Maria Hrincheva, Thomas Fühner, Jan T Kielstein ✉

Nephrology Dialysis Transplantation, gfab347, https://doi.org/10.1093/ndt/gfab347
Published: 07 December 2021

Design: Prospective multicenter observational study[20]

- Primary Endpoint: Overall 30-day survival after Seraph 100 therapy session
- Secondary Endpoints: Adverse events, clotting rates, time to ICU discharge
- 82 Patients documented to-date (Median SOFA Score: 9)
- **Significant survival improvement for Seraph treatment(s) initiated <60 hrs (2.5 days) after ICU admission** (1.73 [1.5-3.2] vs. 4.58 [2.05-11.4] days p=0.0023)
  → 34.5% vs. 62.5% ICU mortality (p=0.04)
- 66.7% Patients treated on mechanical ventilation
- 43.1% Hemoperfusion (HP) modality/stand-alone treatment
- Seraph 100 treatments well tolerated, low rate of clotting, no serious adverse events

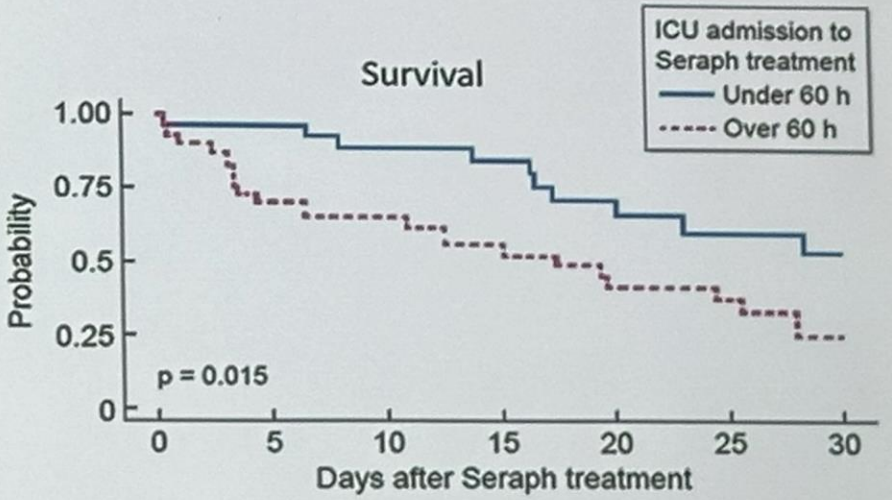
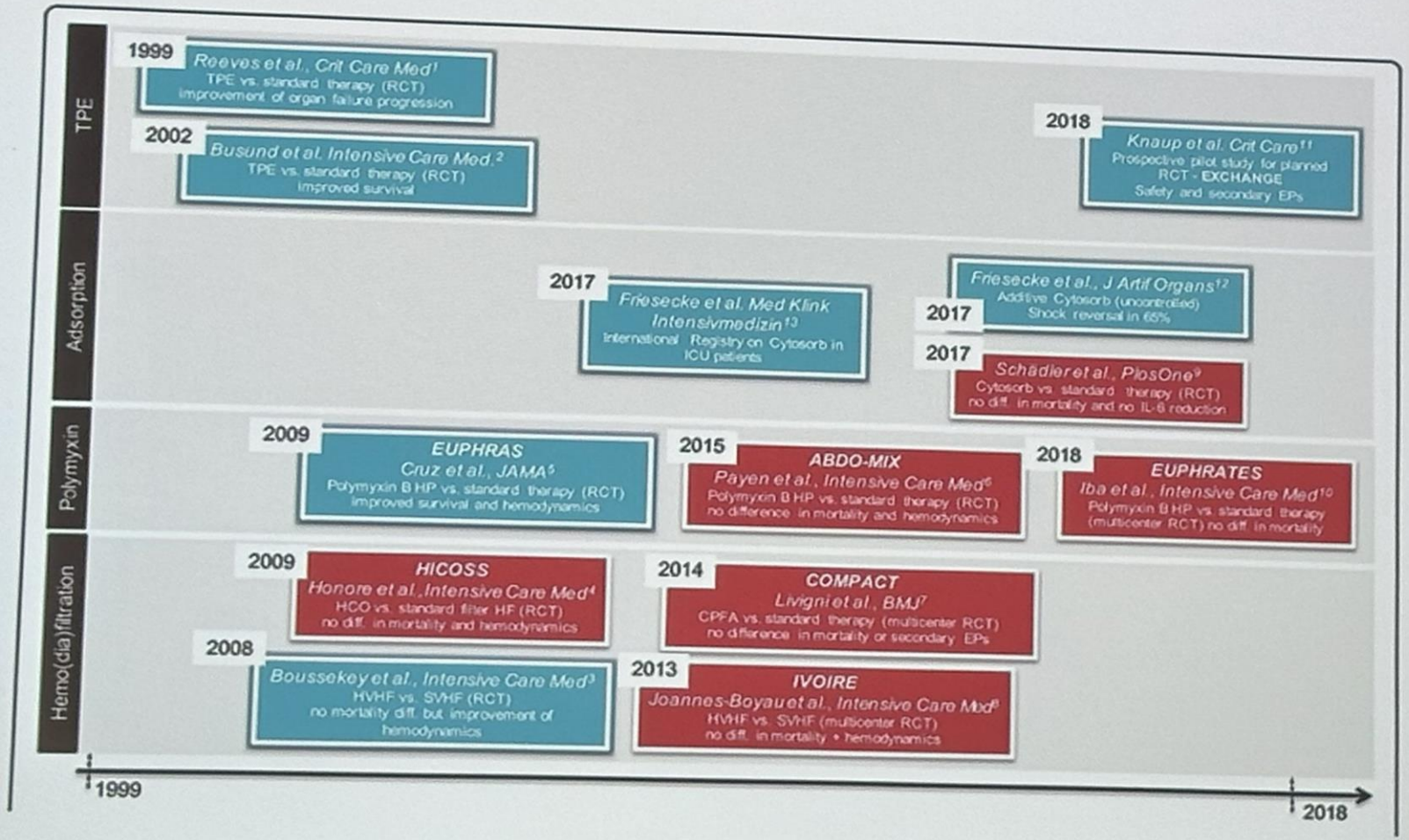


Figure 2: Kaplan-Meier analysis of survival in patients stratified for ICU admission < and > 60 hrs during 30 days (p log-rank test < 0.015).

Schmidt et al. NDT 2021

Medical literature on EBP: controversial findings



David et al. Crit Care 2019

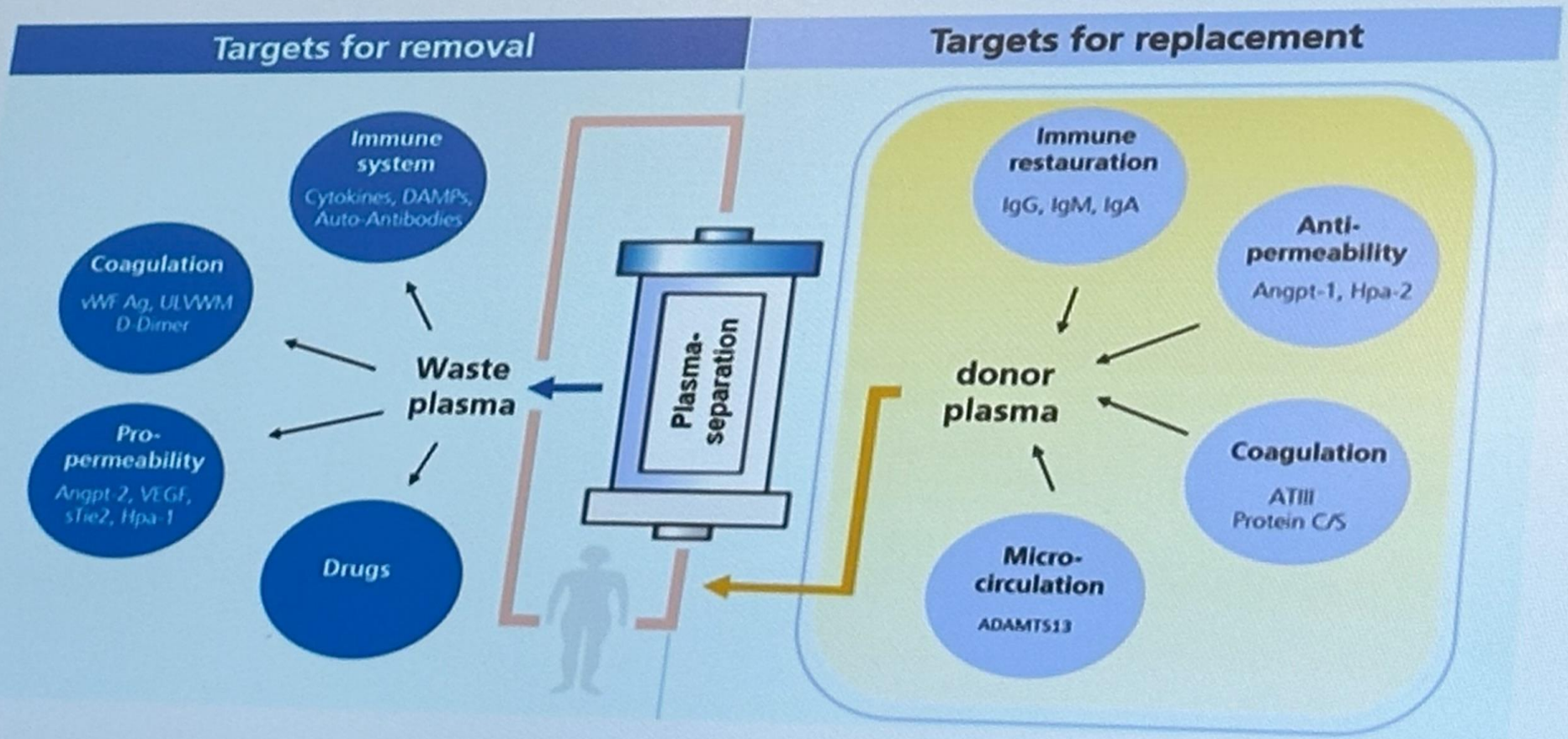
Conclusions: take-home messages

1) Adsorption is used in many types of EBP techniques

2) Adsorption-based blood purification techniques are under investigation, particularly in sepsis

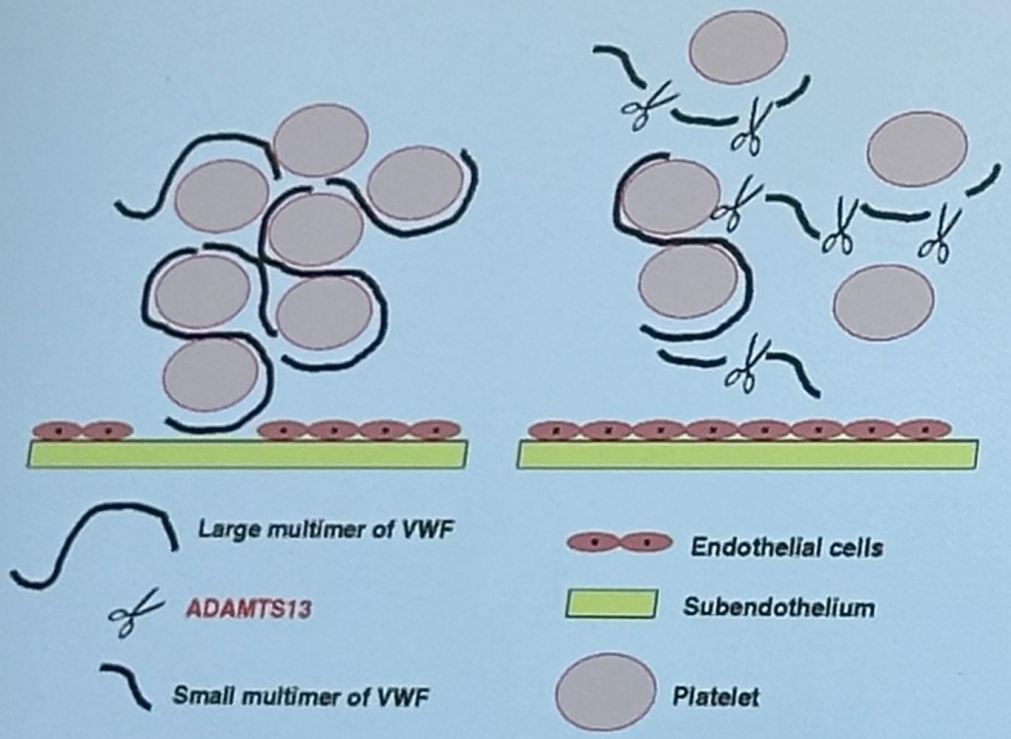
3) Conflicting results in the literature

Rationale for PE in septic shock

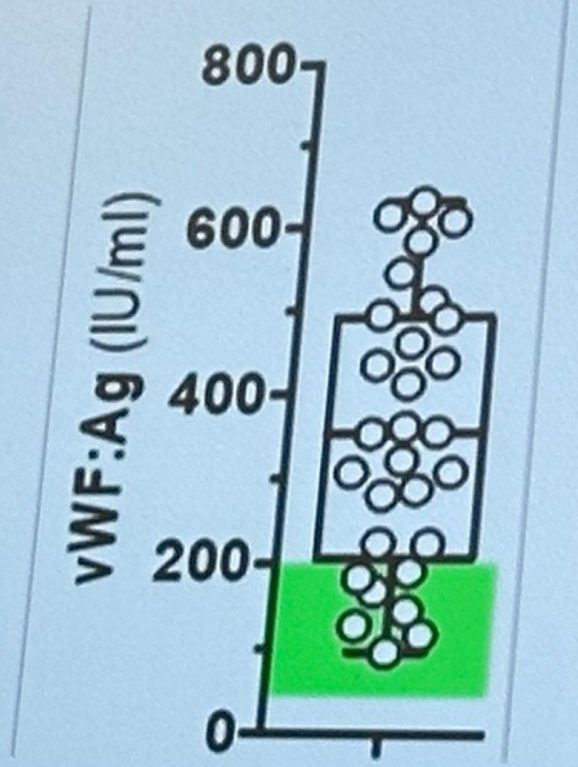


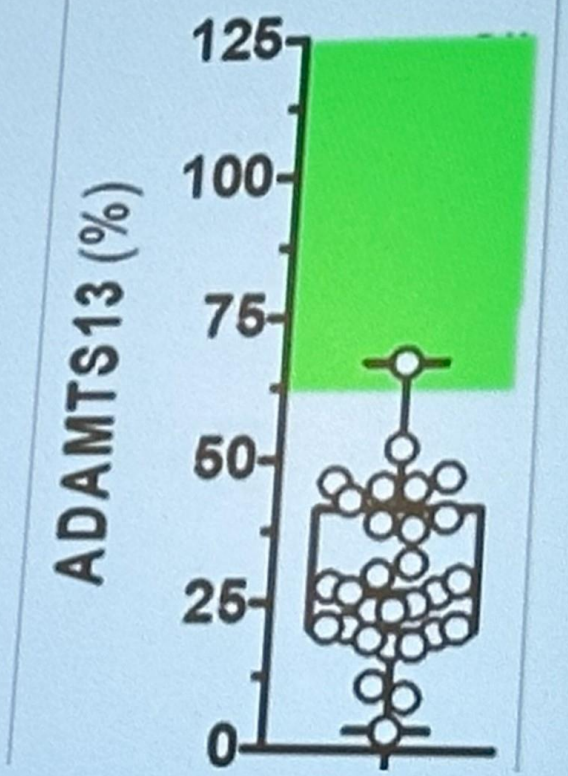
David et al, *Intensive Care Med Exp.* **2023**

Microcirculatory Clotting – VWF/ADAMTS13 Dysbalance in Sepsis



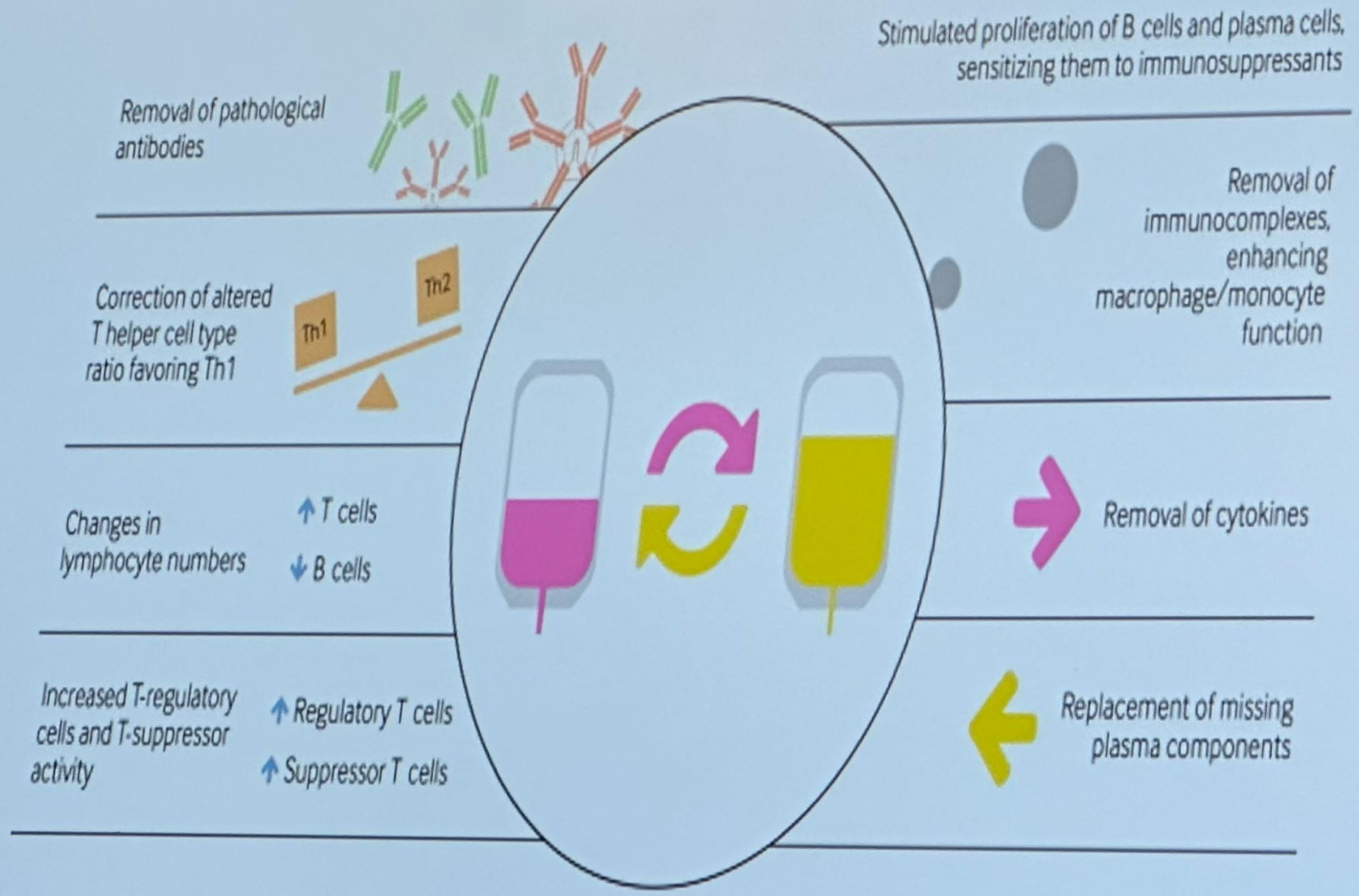
Moake et al, NEJM 182





David et al, ICM 2021

What is the effect of TPE on host immune response?



Jacob S, et al. J Neuroimmune Pharmacol 2021; 16:806–17 .

The timing and dose of TPE in critically ill

-To remove „undesired“ molecules, but to avoid removing concomitantly given therapeutics (IVIG, rituximab, cyclophosphamide…)

- To determine number and frequency of sessions which remove target molecules efficiently and/or to define stopping criteria for TPE

<u>Efficient removal</u>
- Low volume of distribution (<0.2L/Kg)
- high protein binding (80%)

-3-5 sessions every day or on alternate day
- disease specificity
- biologically driven markers (increase of platlates in TTP)

Table 6. Characteristics of Common Drugs Removed by TPE

Drug	Protein Binding, %	Volume of Distribution, L/kg
Acetaminophen	<3	0.1
Acetylsalicylic acid[a]	80-90	0.1-0.2
Azathioprine	30	0.6
Cefazolin[a]	80	0.13-0.22
Ceftriaxone[a]	90	0.12-0.18
Cyclosporine	90-98	13
Cyclophosphamide	23	0.8
Digoxin	20-30	5-8
Eculizumab	NA	5-8
Glyburide[a]	99	0.16-0.3
Heparin[a]	>90	0.06-0.1
Ibuprofen[a]	99	0.15-0.17
Levothyroxine[a]	90	0.1-0.2
Prednisone-prednisolone	90-95	0.6-0.7
Rituximab	NA	3.1-4.5
Valproic acid[a]	90	0.19-0.23
Tobramycin	10	0.25
Vancomycin	70	0.39
Verapamil[a]	90	NA
Warfarin[a]	97-99	0.11-0.15

Cervantes CE, et al. Am J Kidney Dis. 2023; 81(4):475-92.

Continuum of Septic Shock

Extracorporeal Blood Purification

Extracorporeal Pathogen Removal

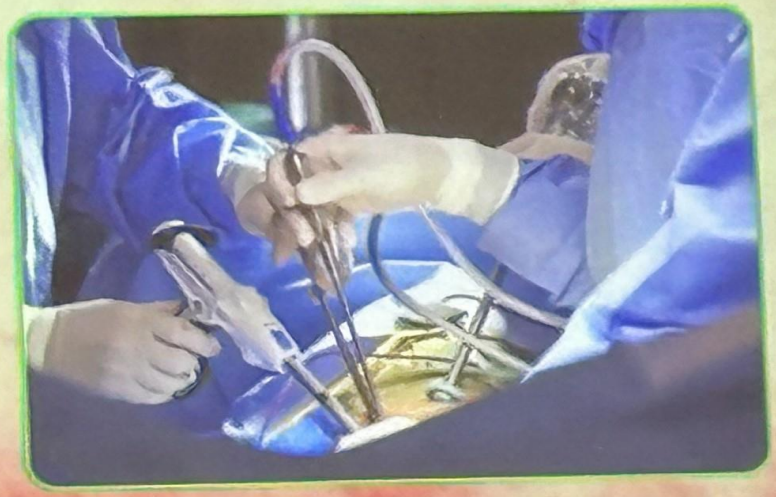
Endotoxemia

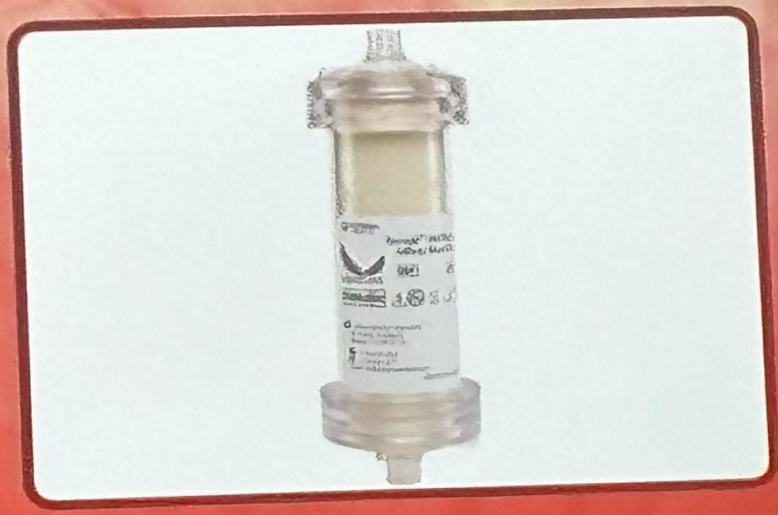
Neutrophil Activation

Cytokine Storm

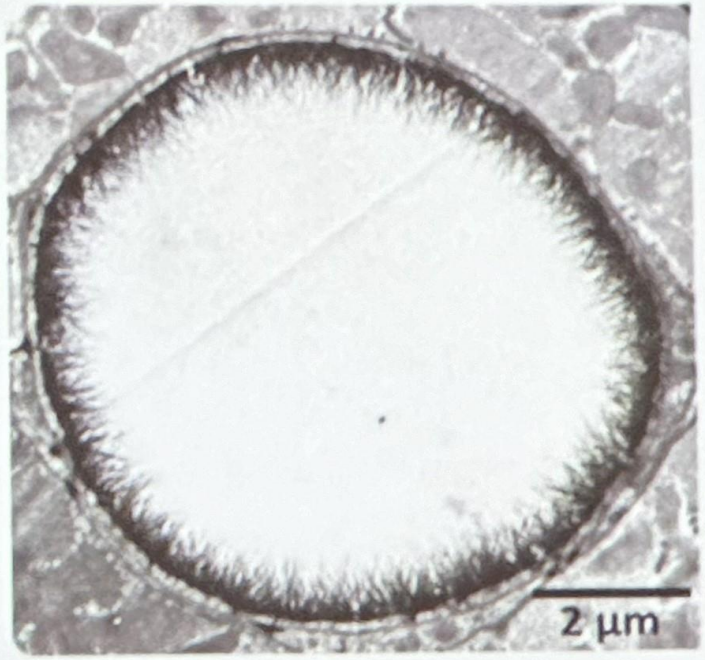
Infection → Sepsis → Septic Shock → Multi-System Organ Failure → Death

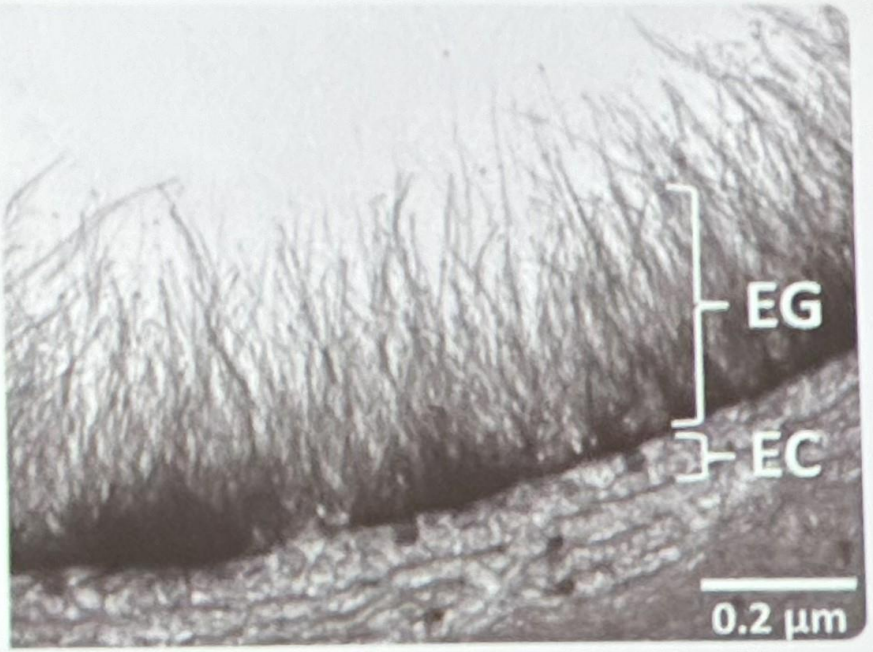
Source Control





Mechanism of Action: The Endothelial Glycocalyx

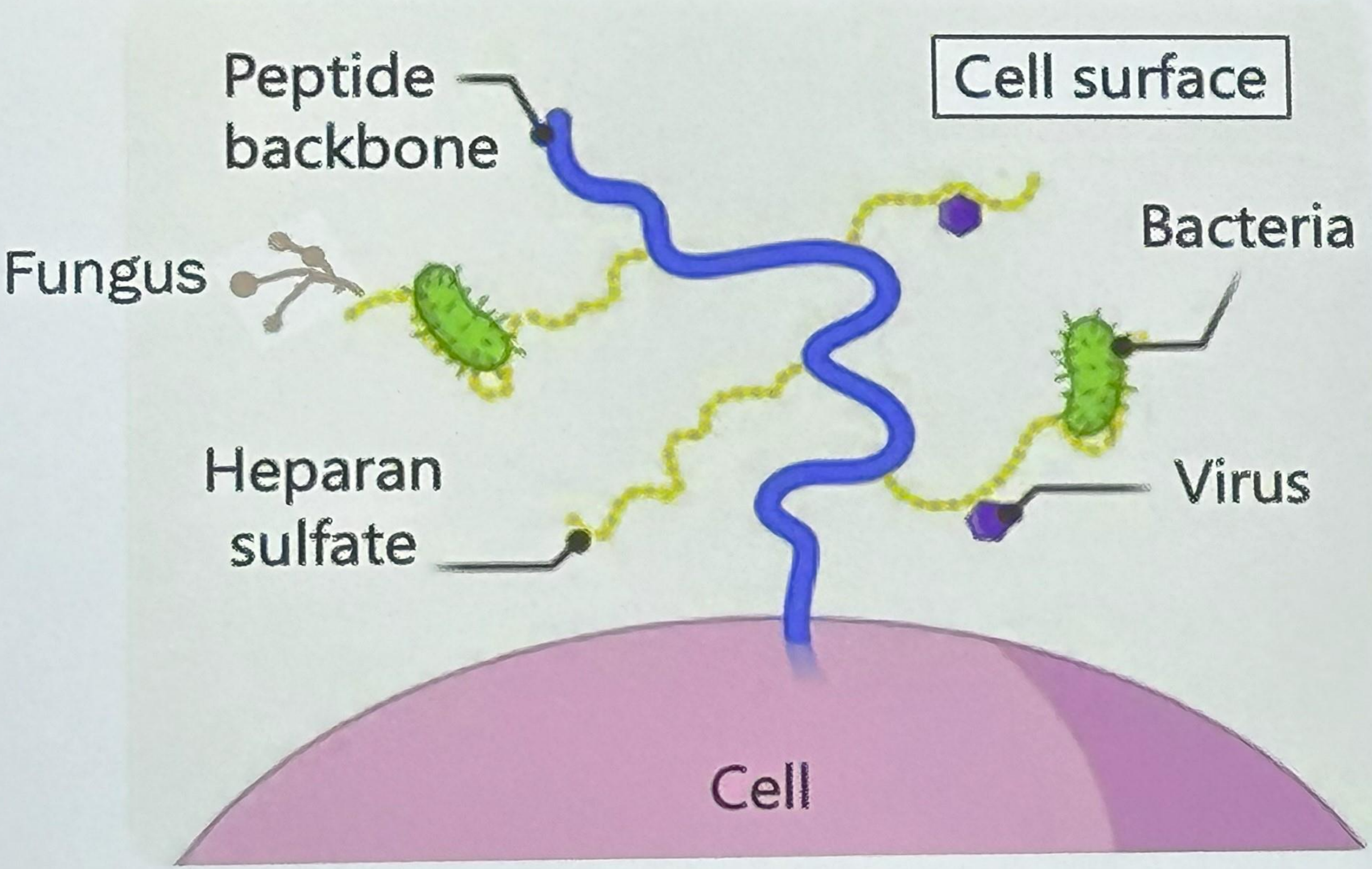




- A matrix lining the vascular endothelium, regulates vascular permeability
- Pathogens bind to *heparan sulfate* proteoglycans which facilitates initial pathogen attachment and promotes infection

Biddle C. Like a slippery fish, a little slime is a good thing: the glycocalyx revealed. AANA J. 2013 Dec;81(6):473-80. PMID: 24597010
Bartlett et Al , Heparan Sulfate Proteoglycans in Infection, in: Pavao M. (eds) Glycans in Diseases and Therapeutics. Biology of Extracellular Matrix. Springer, 2011

Mechanism of Action: The Endothelial Glycocalyx

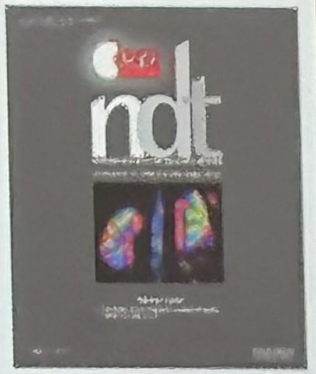


Adapted from Seffer et al. Heparin 2.0: A New Approach to the Infection Crisis, [illegible] Publications (2020); Jul 2, 1-7

Interim analysis of the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry

Schmidt J, Borchina D, Kielstein J, et al for the COSA Investigators

Hannover Medical School, Hannover, Germany
Academic Teaching Hospital Braunschweig, Braunschweig, Germany
KRH Klinikum Siloah, Hannover Germany



Nephrol Dial Transplant. (2022)

12 ICUs

6 countries

82 patients

Primary Outcome: 30-day survival

Secondary Outcome: Adverse events, clotting rates, time to ICU discharge

Interim analysis of the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry

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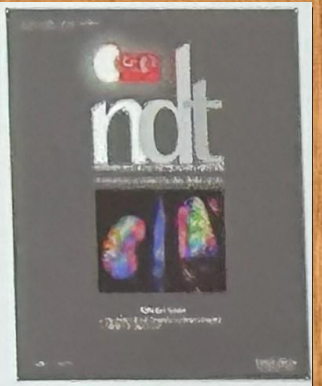

Nephrol Dial Transplant. (2022)

Treatment within 60 hrs

ICU to Seraph:
≤ 60 hours

Mortality:
34.5%
(predicted 51.7%)

vs.

p=0.04

Treatment after 60 hrs

ICU to Seraph:
> 60 hours

Mortality:
62.5%

Interim analysis of the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry

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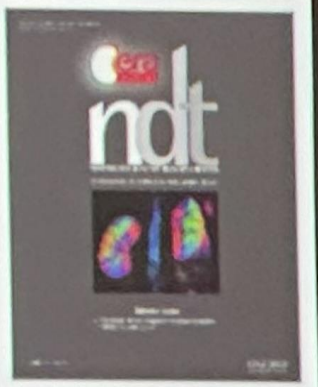
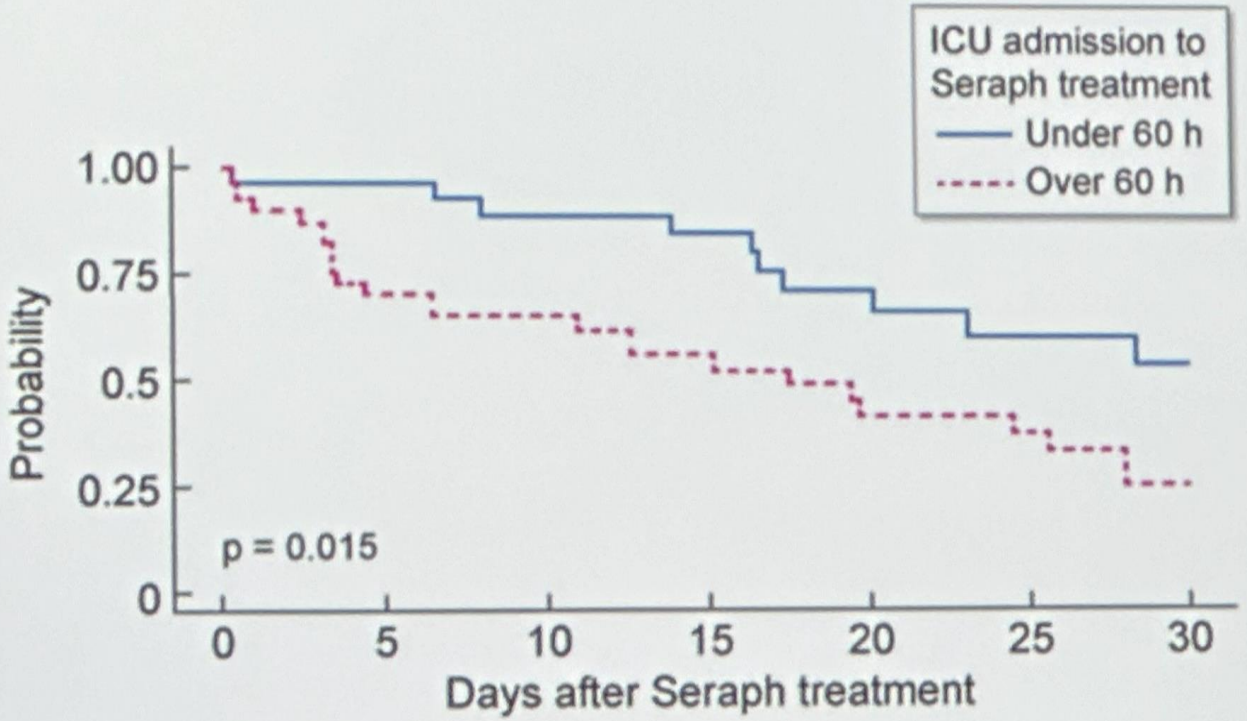


Nephrol Dial Transplant. (2022)



PURIFY-RCT: Blood Purification for the Treatment of Critically Ill Patients with Pathogen Associated Shock

PI: Ian Stewart

Department of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland

NIH

ClinicalTrials.gov

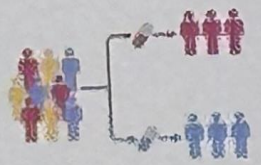
NCT05011656

Feasibility Study

Phase 1

N=14
Completed March 2023

Phase 2



N=45
Expanded study sites

PURIFY-RCT multicenter observational trial design: https://www.clinicaltrials.gov/ct2/show/NCT05011656

PURIFY-RCT: Blood Purification for the Treatment of Critically Ill Patients with Pathogen Associated Shock

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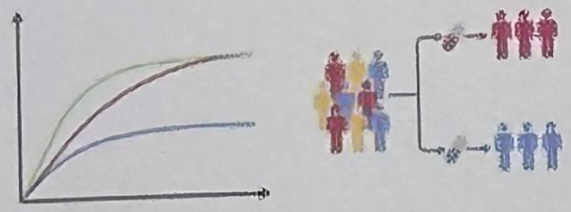
NCT05011656

Phase 1



N=14

Completed March 2023

Abstract submitted for presentation

Col Ian Stewart, MD, USAF, MC
Uniformed Services University of the Health Sciences

MILITARY HEALTH SYSTEM
MHSRS
RESEARCH SYMPOSIUM
2024

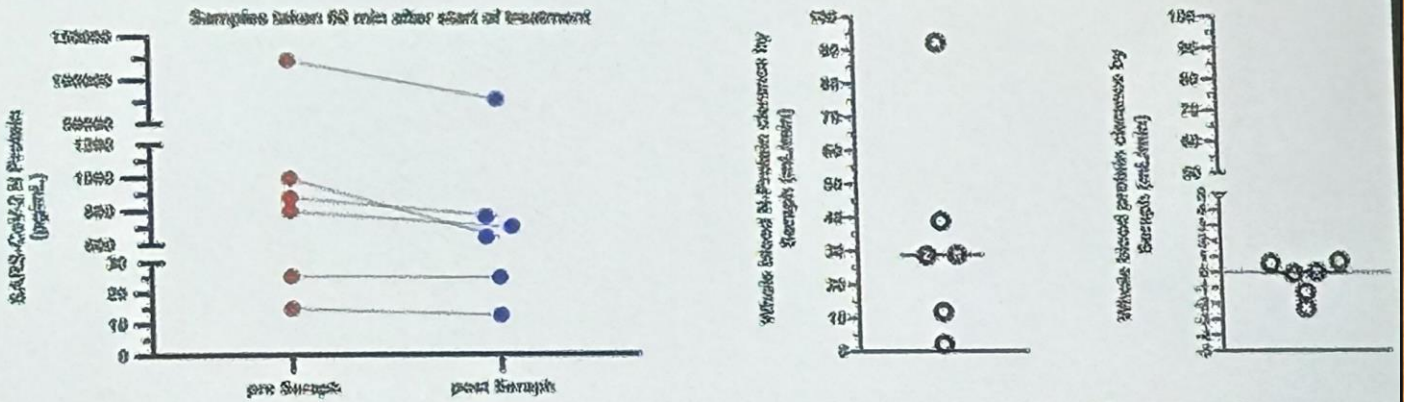
Seraph 100 Rapidly Reduces Viremia

Critical Care

Hemofiltration with the Seraph® 100 Microbind® Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill COVID-19 patients

Jan J. Kielstein ✉, Dan-Nicolae Boschina, Thomas Hüfner, Satyam Arora, Dawn Mattson & Andrew J. Ball

Critical Care 25, Article number 190 (2021) | Cite this article

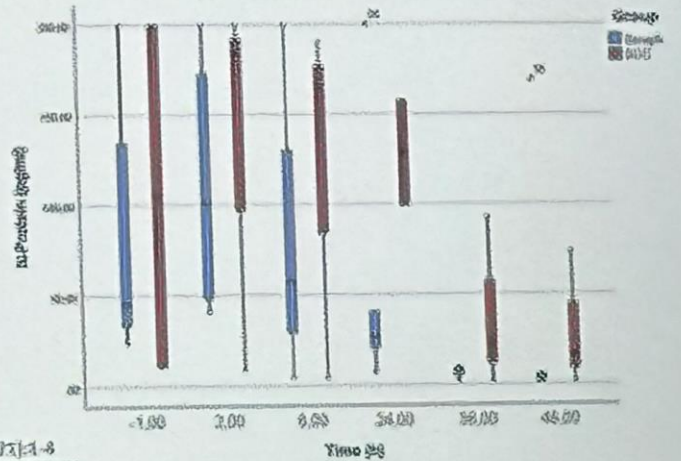


Concentration of the nucleocapsid protein pre (upstream) and post (downstream) of the Seraph® at 60 min of treatment (upper part of the figure) and the resulting device clearance for the N-protein as well as the total plasma protein (lower part of the figure)[15]

Preliminary Results on SARS-CoV-2 Clearance from the Blood

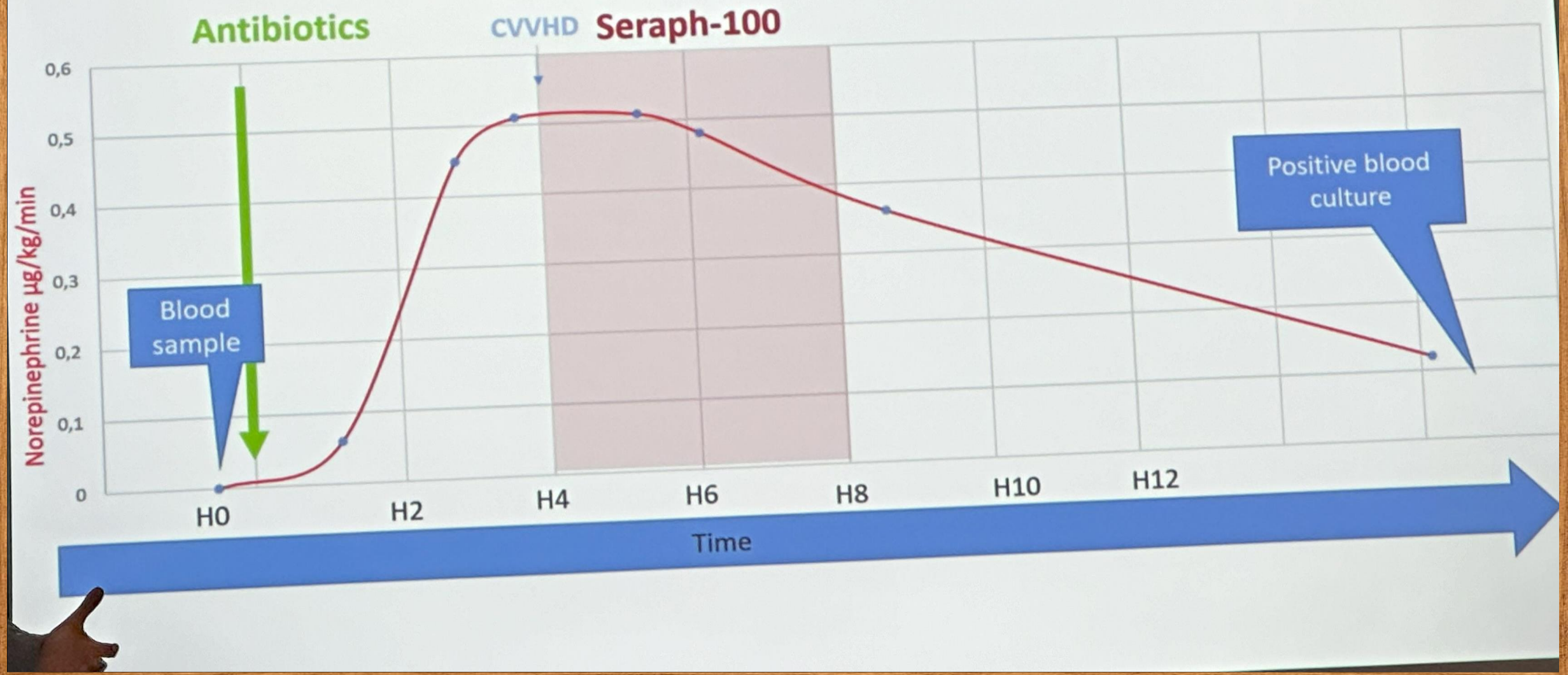
SARS-CoV-2 RCT study in Europe[16]

Sample analysis from the first 8 enrolled patients shows trending data indicating more rapid viral clearance in Seraph treated patients compared to standard of care control patients. This is after only a single 4-hour Seraph 100 treatment.



15. Kielstein et al. Hemofiltration with Seraph 100® Microbind Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill.... Critical Care 25.1(2021):1-8
16. Safety & Effectiveness Evaluation of Seraph 100 in Treatment of Pts With COVID-19 (CP012) – Protein Data on file: https://clinicaltrials.gov/ct2/show/NCT04547257

Treatment with a 4-hour session of Seraph-100



ICU Case 2 : Post operative Peritonitis

- Male, 74yo
- Hypertension
- Cardiovascular disease
- CKD

- July 2nd : Colectomy
- July 6th : Septic shock

CT -> Post operative peritonitis

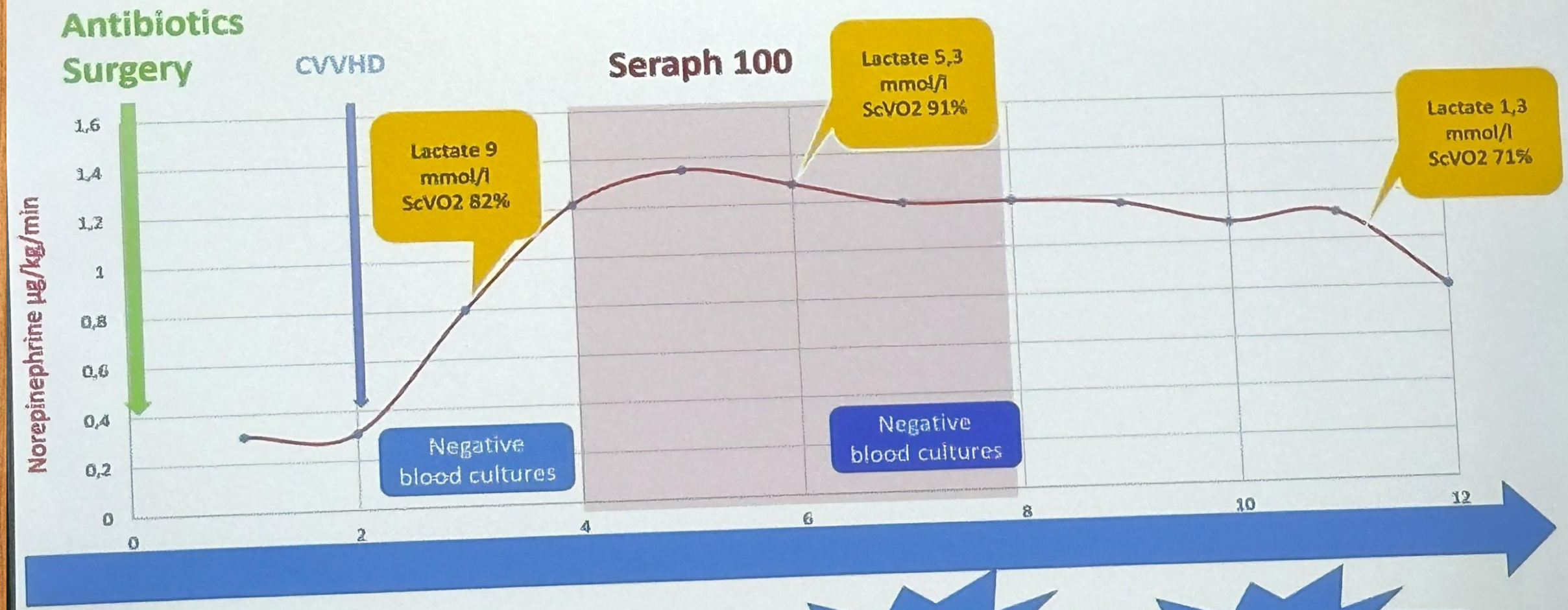
- Surgery
- ICU admission

- **Multi Organ Failure**
- Microcirculatory dysfunction
- Antimicrobials
- Supportive measures including a 4-h Seraph session

- Initial recovery
- Norepinephrine weaning in 48h
- Extubation on day 4

- Gut perforation on day 5
- Complications
- Death on day 30

Treatment with Seraph-100



Negative blood cultures but positive effect of Seraph-100 → ???

PAMPS Removal ?

Cytokines Removal ?

What we do NOT want to remove!

Reduction Ratio
0-5 min

Table 1. Summary of the in vitro anti-infective drug elimination profile of the Seraph® 100

Drug	C_0	Cl_0	$Cl_{5'}$	Cl_{30}	Cl_{60}	RR_{0-5}	RR_{5-60}	RR_{0-60}
Aciclovir	58.6 ± 8.3	−2.12	1.07	10.73	−2.3	20	0	22
Amphotericin B	12 ± 2.1	8.45	8.5	−5.52	−20.69	19	8	26
Ceftazidime	276 ± 22.8	−2.07	−7.23	29.09	−4.12	14	2	11
Cefazolin	828.8 ± 86.7	0.52	−2.09	17.78	−2.35	20	0	15
Clindamycin	9.9 ± 3.3	3.53	5.51	17.77	3.19	−1	−2	20
Daptomycin	68.5 ± 3.5	17.32	−22	0	−2.17	−4	19	15
Fluconazole	28.5 ± 4.9	−5.35	−20.41	−40	60.05	19	−25	−1
Fosfomycin	953.9 ± 427.8	−14.1	−4.9	2	−8	14	−3	10
Gentamycin	6.4 ± 0.1	24.6	−30.61	−9.09	−14.15	54	12	59
Levofloxacin	89.6 ± 17.9	−1.51	−2.08	9.11	−13.21	9	3	9
Linezolid	109.4 ± 10.9	−1.51	−2.08	10.12	−13.21	11	3	14
Meropenem	125.6 ± 17.9	−3.48	11.36	12.39	−6.05	13	−2	15
Moxifloxacin	67.4 ± 7.1	0.8	2.48	9.65	−11.78	9	3	11
Piperacillin	1364.3 ± 193	18.87	16.44	9.93	−50.08	11	5	16
Rifampicin	109.4 ± 4.4	−0.97	−5	9.86	0.99	7	1	7
Tazobactam	142.3 ± 16.7	11.33	7.89	44.92	−36.6	12	5	17
Tobramycin	18.8 ± 6.5	48.7	−4.19	−25.07	−4.56	62	7	62
Vancomycin	179.8 ± 23.8	0.46	−1.63	13.48	−1.05	20	2	23

C_0 = plasma drug concentration at the beginning of the experiment (mg/l). $Cl_{\dots}$ = mean drug plasma Cl of the seraph adsorber at different investigated measure time points in milliliters per minute. RR (%) of the investigated drug during the first 5 min and during the rest of the experiment.

In vitro study

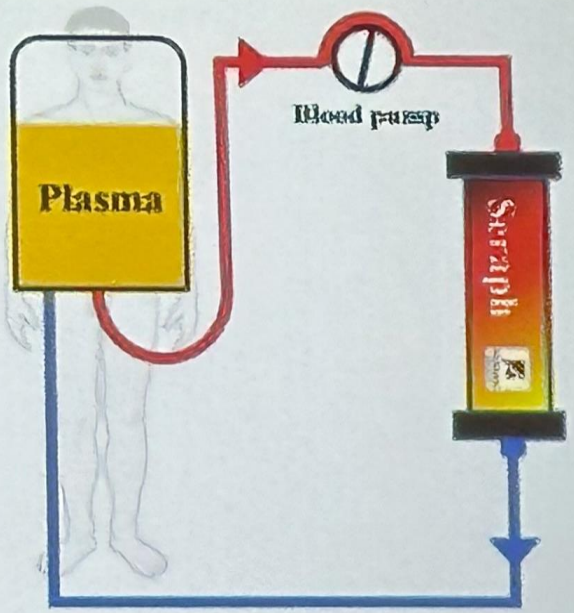


FIGURE 1 Schematic overview of the experimental setup. Plasma was circled through the Seraph cartridge by a roller pump. Plasma samples were obtained before and after passing through the Seraph device.

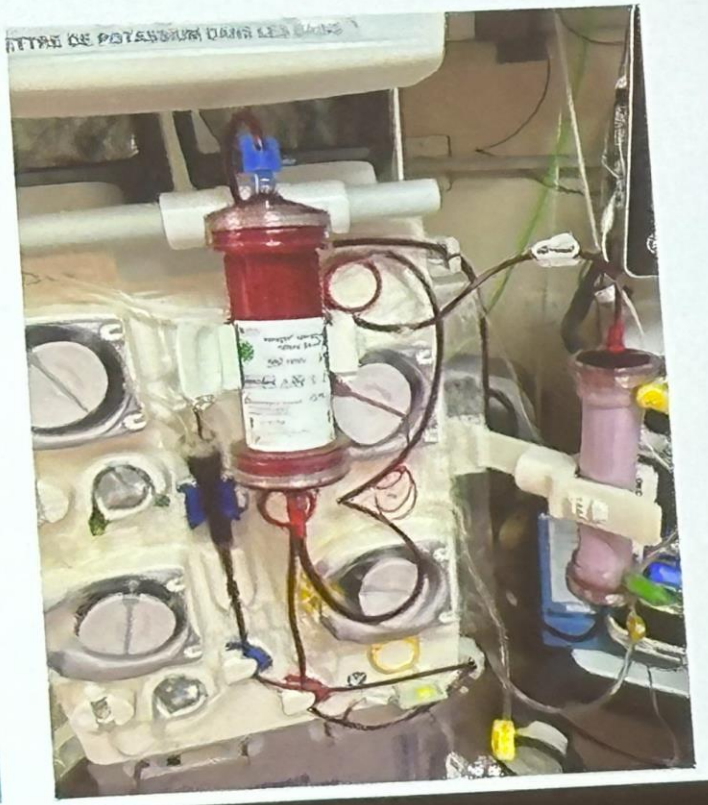
- Therapeutic Drug Monitoring
- Administer Aminoglycosides after the Seraph session

Schmidt et al. Clin Kidney Journal 2020

CORRESPONDENCE Open Access

Intraoperative extracorporeal blood purification therapy during major septic vascular surgery

Céline Monard[1,3*], Philippe Tresson[2,4], Antoine Lamblin[1], Farida Benatir[1], Xavier-Jean Taverna[1] and Thomas Rimmelé[1,3]



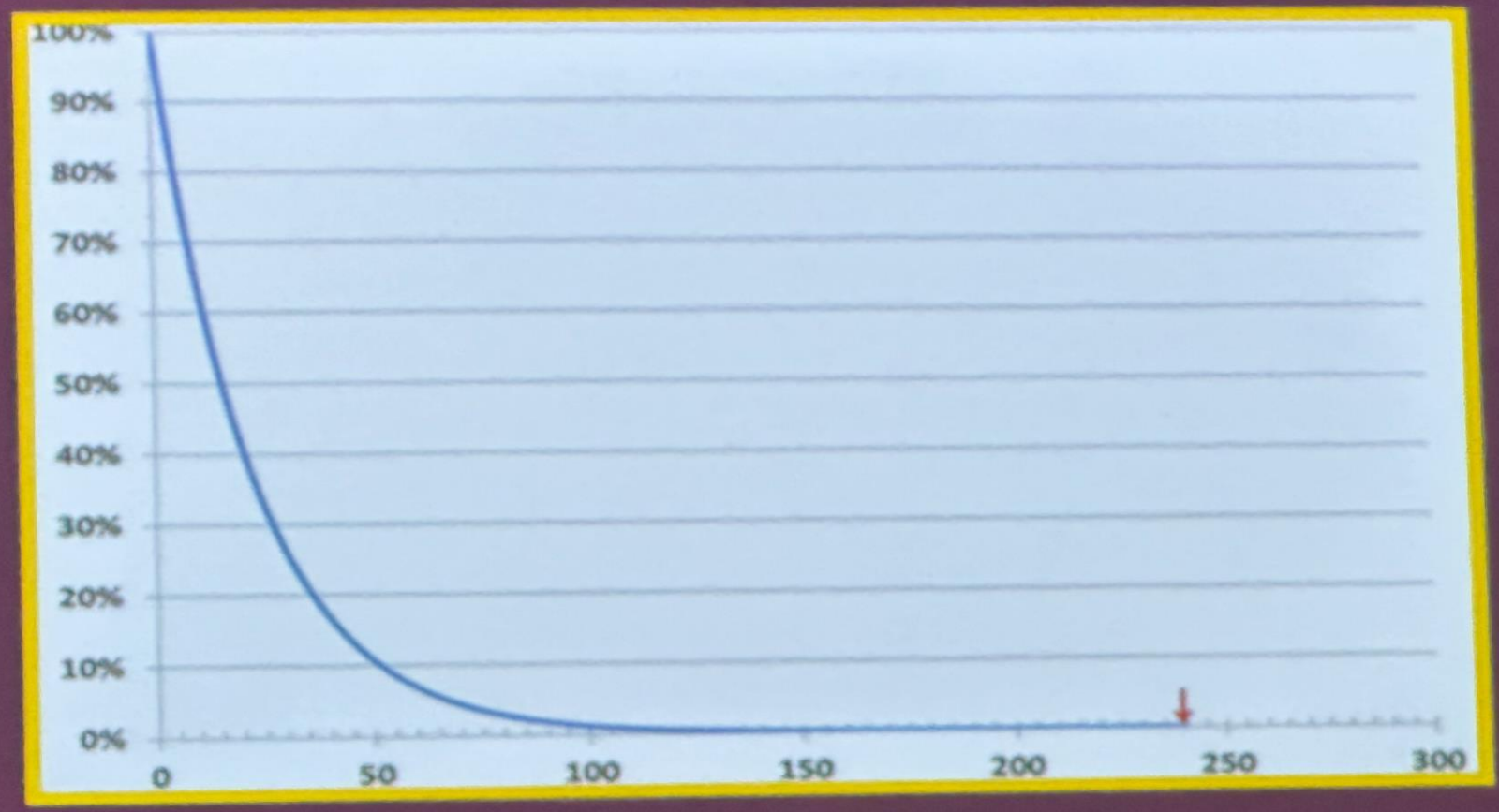
Monard et al. Crit Care 2022

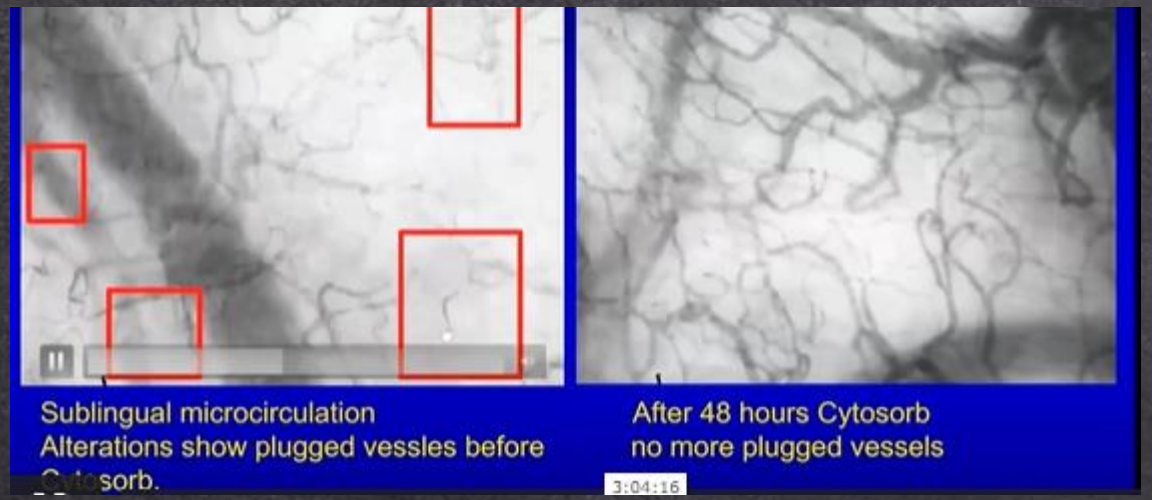
Conclusions / Take Home Messages

- Historic targets for EBP in sepsis include cytokines and endotoxins.
- Seraph 100 acts at a different level: it directly removes pathogens from the blood.
- Seraph 100 is easy to use either as a stand-alone therapy or within a RRT circuit.
- Outside the ICU, Seraph 100 looks also very promising in the OR for complex surgical procedures releasing bacterial components in the blood.

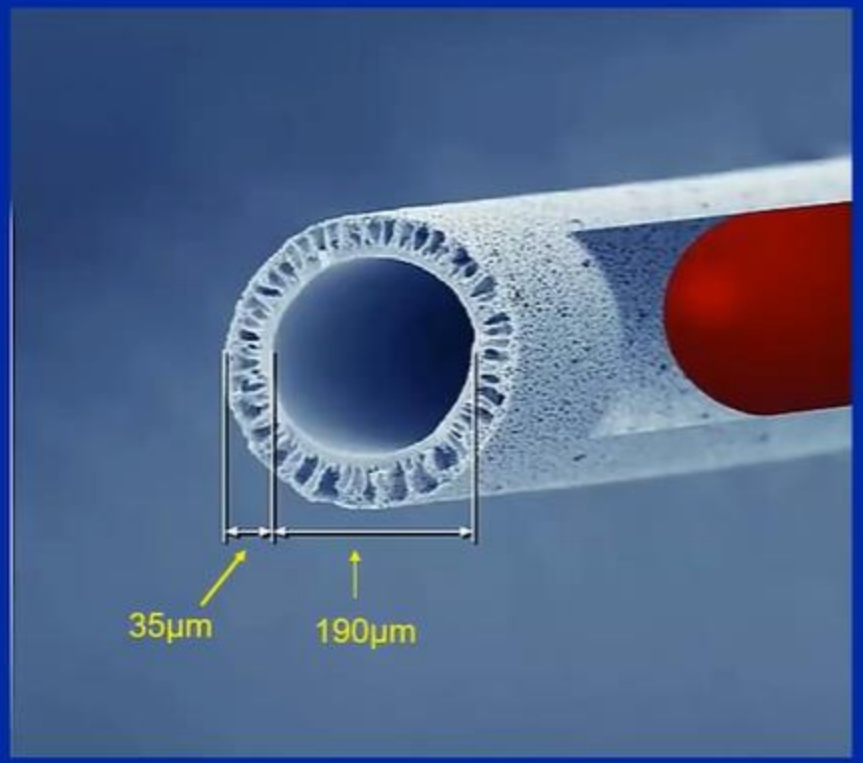
Pathogen Removal by Hemadsorption

Maximum Pathogen Clearance by Seraph w. Source Control @ 73% Per Pass & 300 mL/min





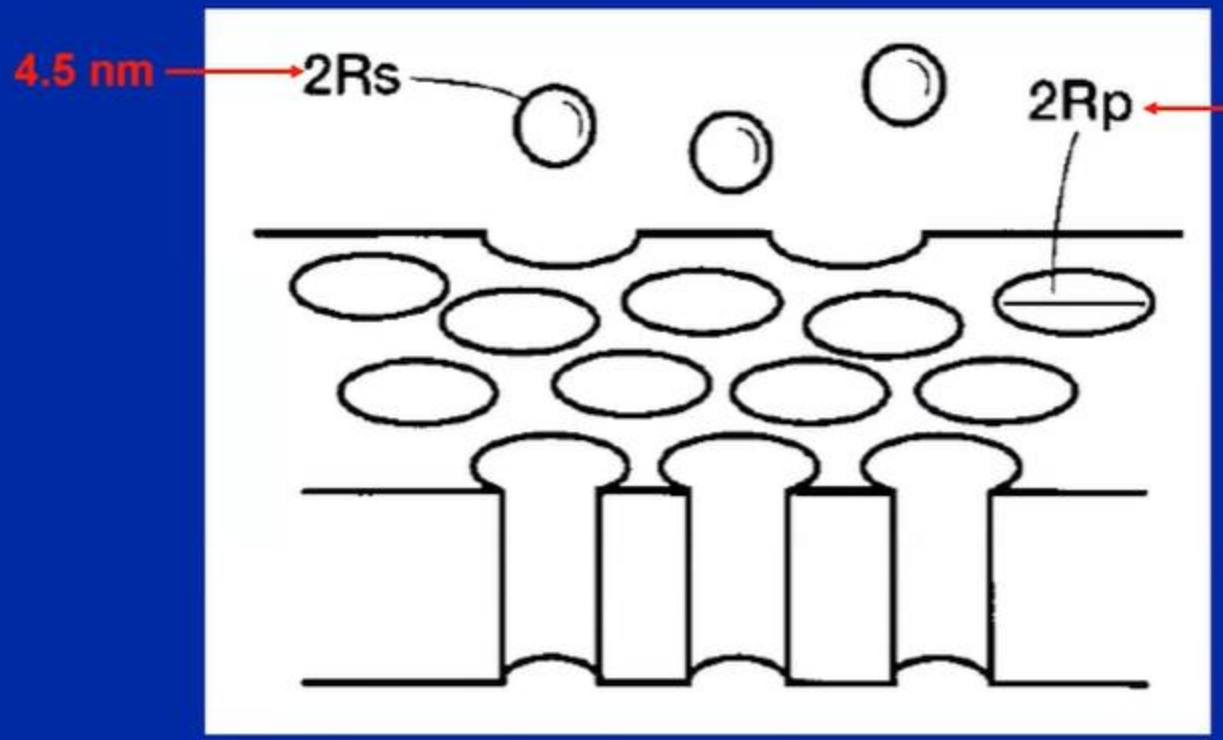
Principle of the Hollow Fiber Membrane



A human hair has a thickness of about 0.09 mm = 90µm

Idealized Membrane

Takeyama and Sakai, Contrib Nephrol 1998



Fiber and Filter Dimensions

Conventional HD[a]

Hemodialyzer	Fiber inner diameter, µm	Fiber effective length, mm	Number of fibers	Module length, mm	DK_{UF}, mL/h/mm Hg	Surface area, m^2	Priming volume, mL
Theranova 400	180	236	12,960	260	48	1.7	91
Theranova 500	180	236	15,120	260	59	2.0	105

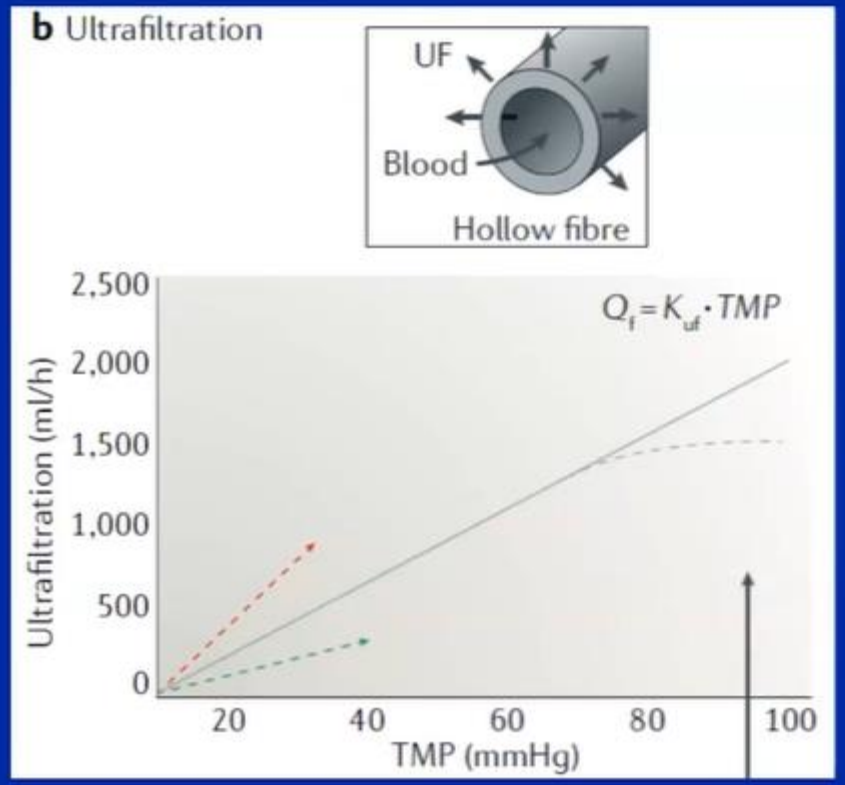
CRRT[b,c]

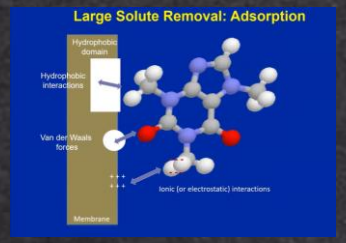
	Fiber inner diameter, [µm]	Wall thickness [µm]	Fiber effective length, L [mm]	Number of fibers, N	Module length, L [cm]	UF coefficient [ml/(h*mmHg)]	Surface area [m²]	Priming volume [ml]
HF1000	215	50	218	7,500	245	35	1.1	81
HF1400	215	50	218	9,500	245	46	1.4	102

a: from Lorenzin et al, Blood Purif 2018
b: data provided Dr. Markus Storr (Baxter)
c: HF1000 and HF1400 surface area = 1.1 and 1.4 m^2, respectively

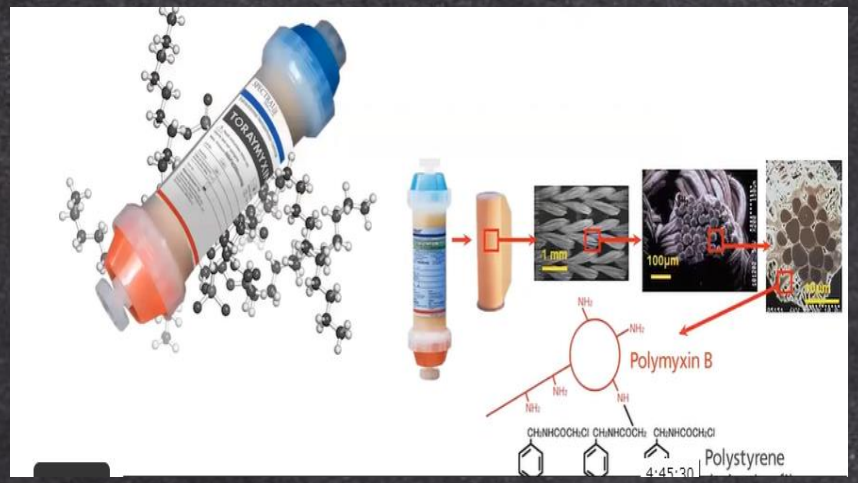
Membrane/Filter: Ultrafiltration

Ronco and Clark, Nature Revs Nephrol 2018





oXiris Membrane



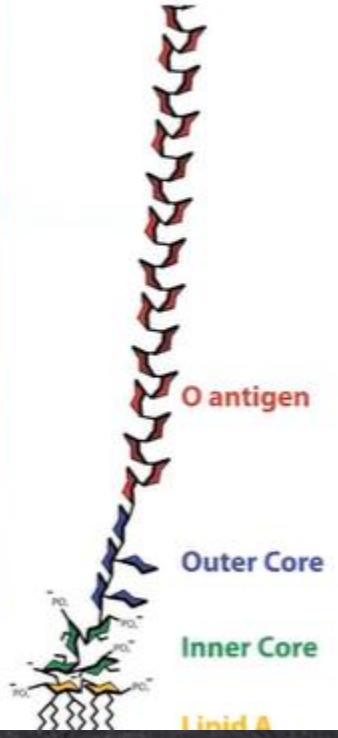
Endotoxemia ≠ bacteremia

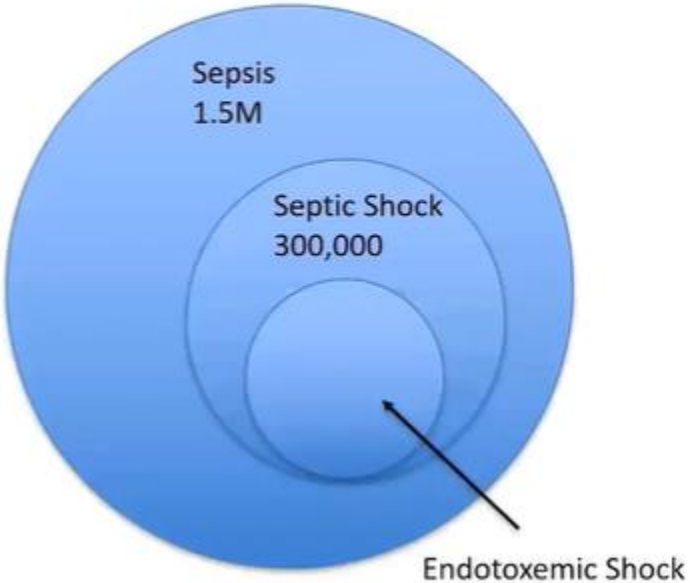
- Endotoxin in bloodstream does not equate to primary or secondary blood stream infections.
- >70% of patients with sepsis with high endotoxin activity have negative blood cultures.[1]
- Endotoxemia can result from…
  - Active infections gram negative bacteria
  - **Infections with various types of organisms (including COVID-19) that compromise gut barrier function (resulting in translocation of endotoxin)[2]**
  - Antibiotics can release endotoxin as they kill bacteria[3]

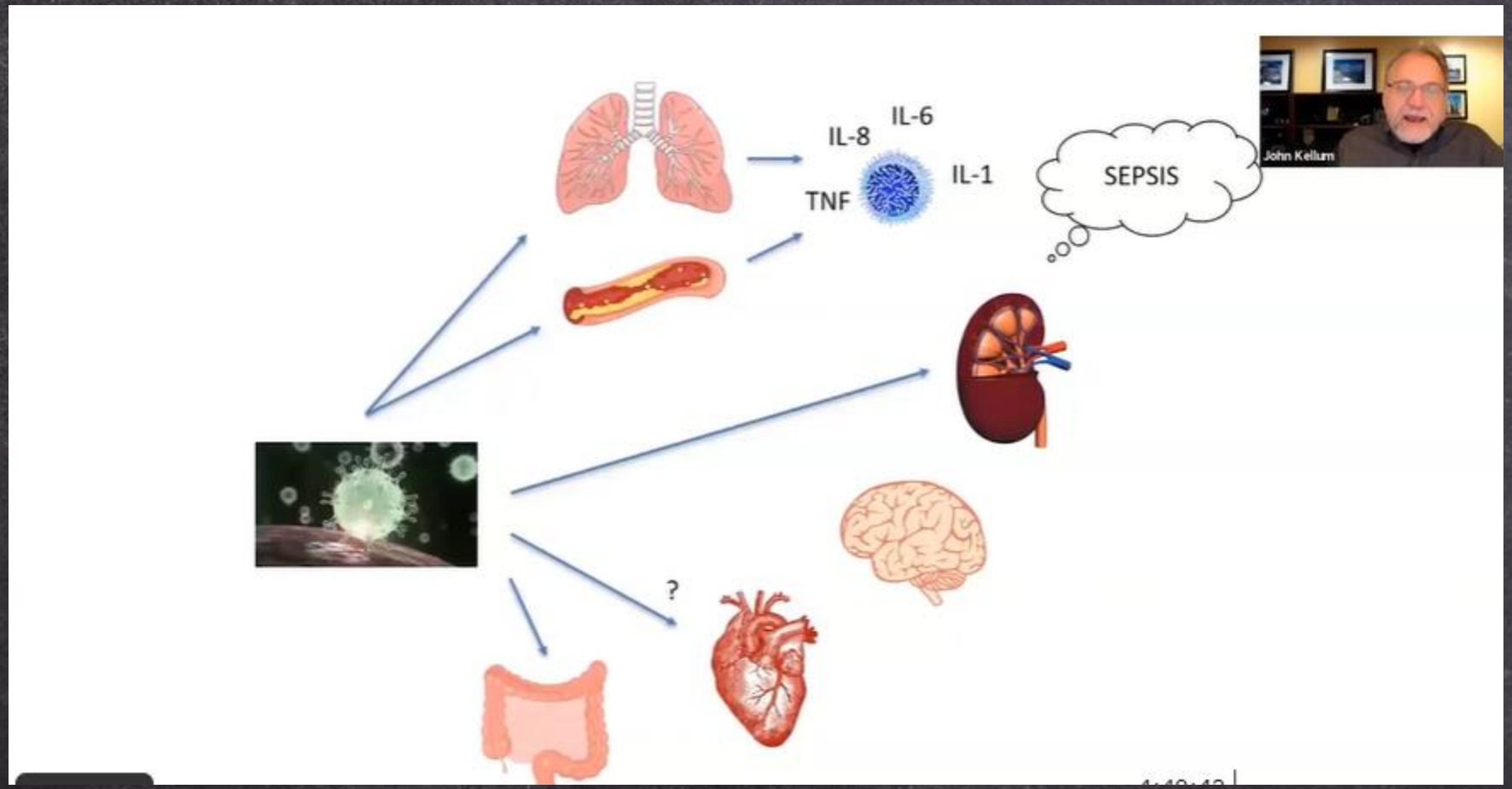
The Gut contains more than 1 million times the lethal dose of endotoxin

[1]Dellinger RP et al. JAMA. 2018;320(14):1455-1463

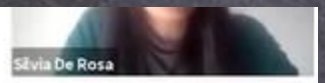
Endotoxin and Endotoxemia





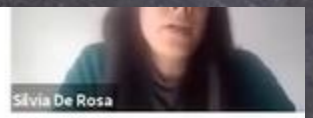


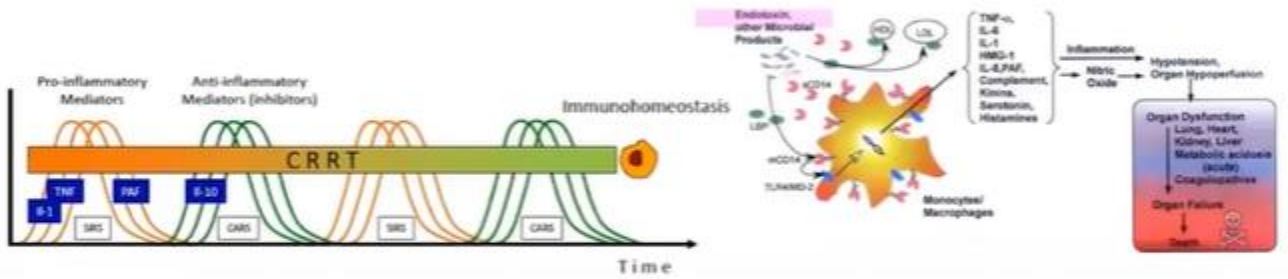
WHAT WE KNOW?

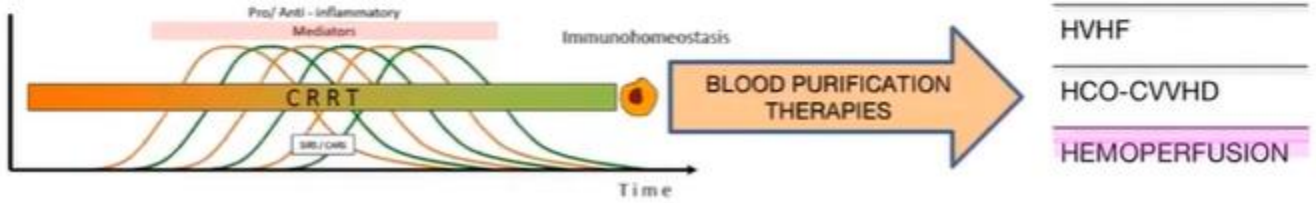


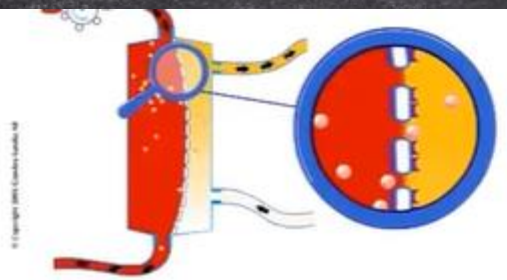
- During episode of severe endotoxemia, concentrations of both lipopolysaccharide and its lipid A-core subfraction are liberated from gram-negative bacteria and become elevated within the systemic circulation
- Lipid-A core is the most homogeneous and physiologically toxic segment of the lipopolysaccharide molecule
- Polymyxin-B has profound binding avidity for the lipid A-core subfraction of lipopolysaccharide
- The mechanism of this binding avidity involves the development of attractive forces between the cationic groups of polymyxin-B and the anionic groups of the lipid A-core moiety of lipopolysaccharide.
- Complementary attractive forces include hydrophobic interactions which additionally become established between the octylheptanoyl group of polymyxin-B and the saturated carbon chains of the lipid A-core moiety

Beyond “PEAK CONCENTRATION” HYPOTHESIS







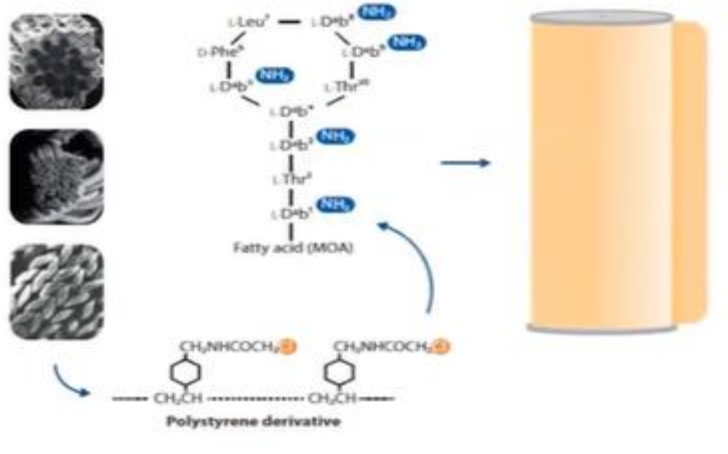


ADSORPTION: beyond filtration

..... is an extracorporeal process in which molecules dissolved in plasma or blood (in particular peptides and proteins) bind to the membrane structure or to other adsorbing substances such as resins or gels.....

- The characteristics that influence molecule-membrane interaction are typical for each molecule (i.e., dimension, charge, etc.) and for each particular membrane (i.e., porosity, hydrophobicity, etc.)
- **Adsorption cartridges should be evaluated in terms of their device adsorption capability (DAC) and their selectivity**
- DAC represents the total quantity of a specific molecule that the device is able to adsorb
- Selectivity is a safety parameter, as it defines what the device does not adsorb

In the mid-1970s, polymyxin B was discovered to be protective against endotoxin-induced hemodynamic shock b
time, was demonstrated to be extremely toxic for the kidney and central nervous system, which precludes its systemic use

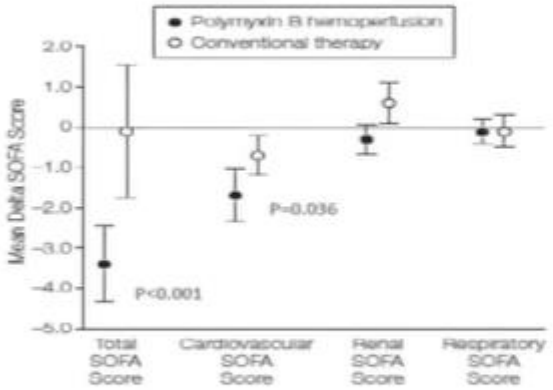


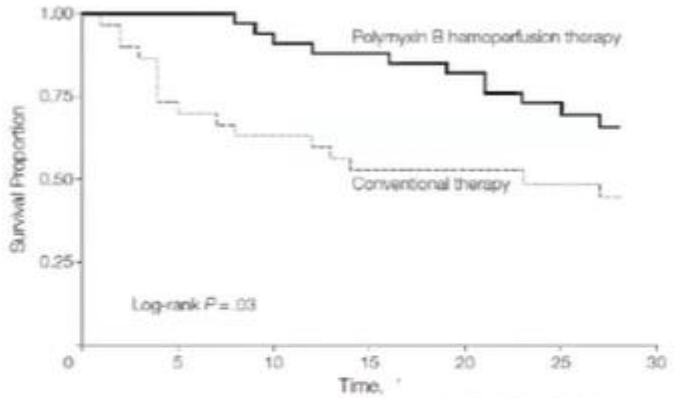
PMX is composed of
polymyxin B (PL-B) covalently bonded to
polystyrene-derivative fibers.

Since 1994, polymyxin B has been bound
and immobilized to polystyrene fibers

The EUPHAS Randomized Control Trial

- Randomized unblinded study of 10 tertiary Italian ICU
- 64 patients





The absolute risk of death at 28 days improved significantly from 53% in the conventional therapy group to 32% in the PMX-HP treated group.

JAMA®

LIMITS: the trial was not blinded. Patients were selected for therapy based on evidence of septic shock from an intra-abdominal source to hopefully enrich the patient population with likely endotoxemic patients, but the EAA was not measured.

Cruz D, Et al. JAMA. 2009

Management of Sepsis (Shock)

Source Control	Host Response	Hemodynamic Stability
Debridement Abscess Drainage	Inflammation Coagulopathy	Fluids Vasopressors
		
• Removes Pathogens from the Bloodstream	• Removes DAMPS and PAMPS • Impacts coagulopathy	• Case reports show improved hemodynamics

Decreases pro-inflammatory cytokines

Seraph 100 is Effective at Removing COVID19

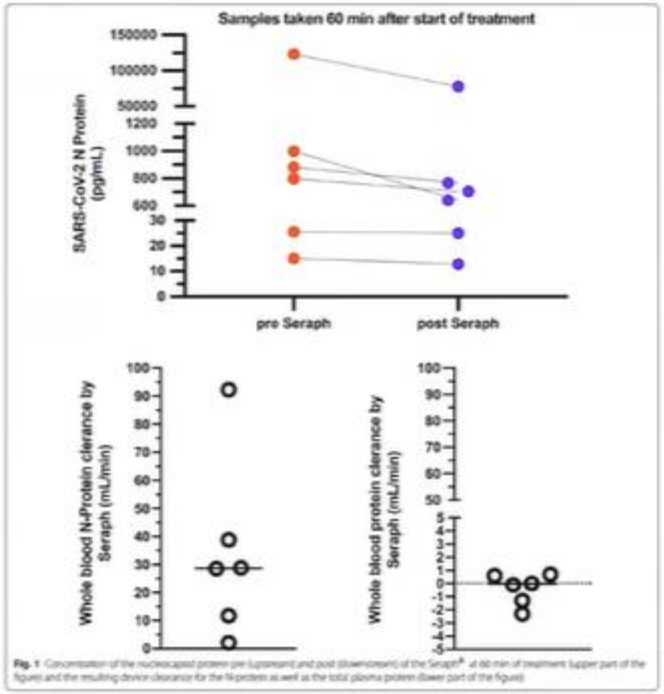
Kielstein et al. Crit Care (2021) 25:190
https://doi.org/10.1186/s13054-021-03597-3

Critical Care

RESEARCH LETTER Open Access

Hemofiltration with the Seraph® 100 Microbind® Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill COVID-19 patients

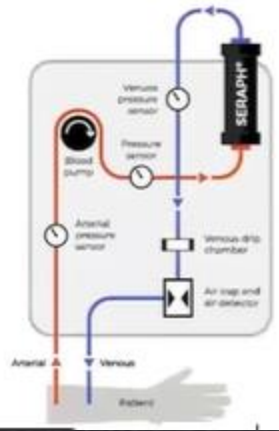
Jan T. Kielstein[1*], Dan-Nicolae Borchina[1], Thomas Führer[2], Soyoon Hwang[3], Dawn Mattoon[3†] and Andrew J. Ball[3†]



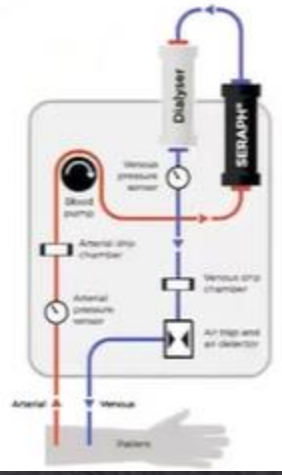
SERAPH® 100 USE IN EXTRACORPOREAL EQUIPMENT

Setup With RRT & Hemoperfusion Machines[1]

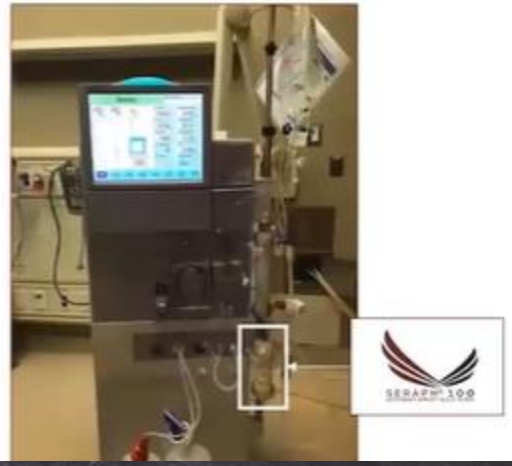
Seraph® 100 in Stand-Alone Configuration



Seraph® 100 and Dialyser In Combination Configuration



Therapy Sessions Match Life of Main Circuit & Used With Commercially Available Bloodlines & Luers

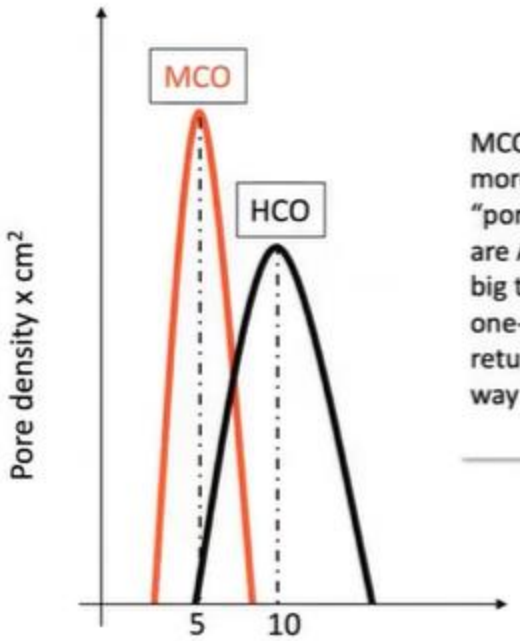


Devices for Seraph 100

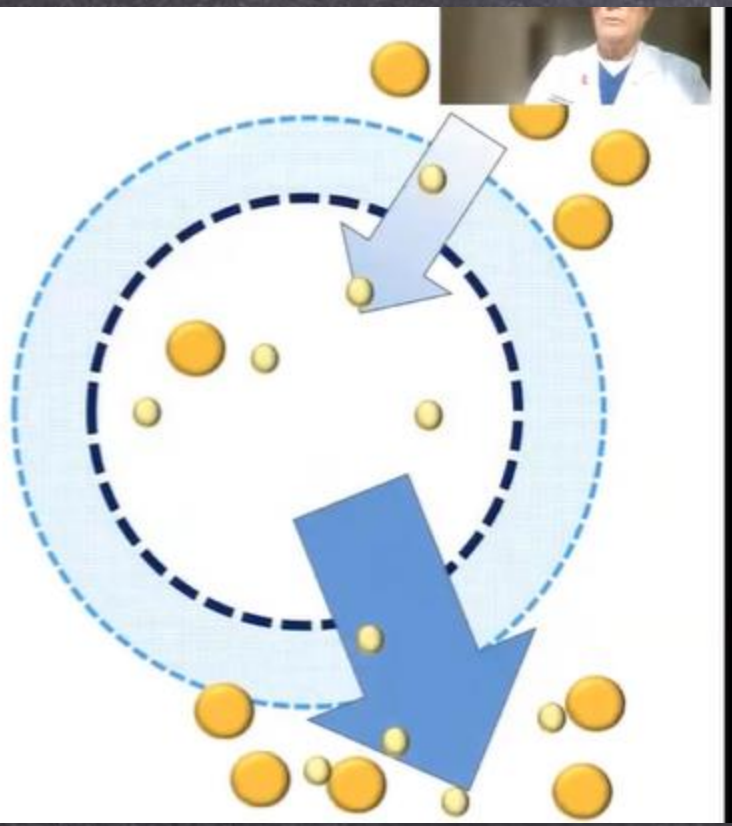
Summary

- High levels of SARS-CoV-2 viremia are common in critically ill patients with COVID-19
- Viremia appears to be an important modulator of multi-system organs failure
- Pathogen Removal is a Strategy to Improve Outcomes
- Early Intervention is Critical
- Seraph 100 effectively removes SARS-CoV-2
- Seraph 100 has been safely administered to over 700 patients with COVID-19
- Seraph 100 may fill an important gap for critically ill patients with COVID-19

NEWER MEMBRANES



MCO membranes have more homogeneous "pores" and are ASYMMETRICAL: big things go across one-way, but can't return in the opposite way



HEMADSORPTION

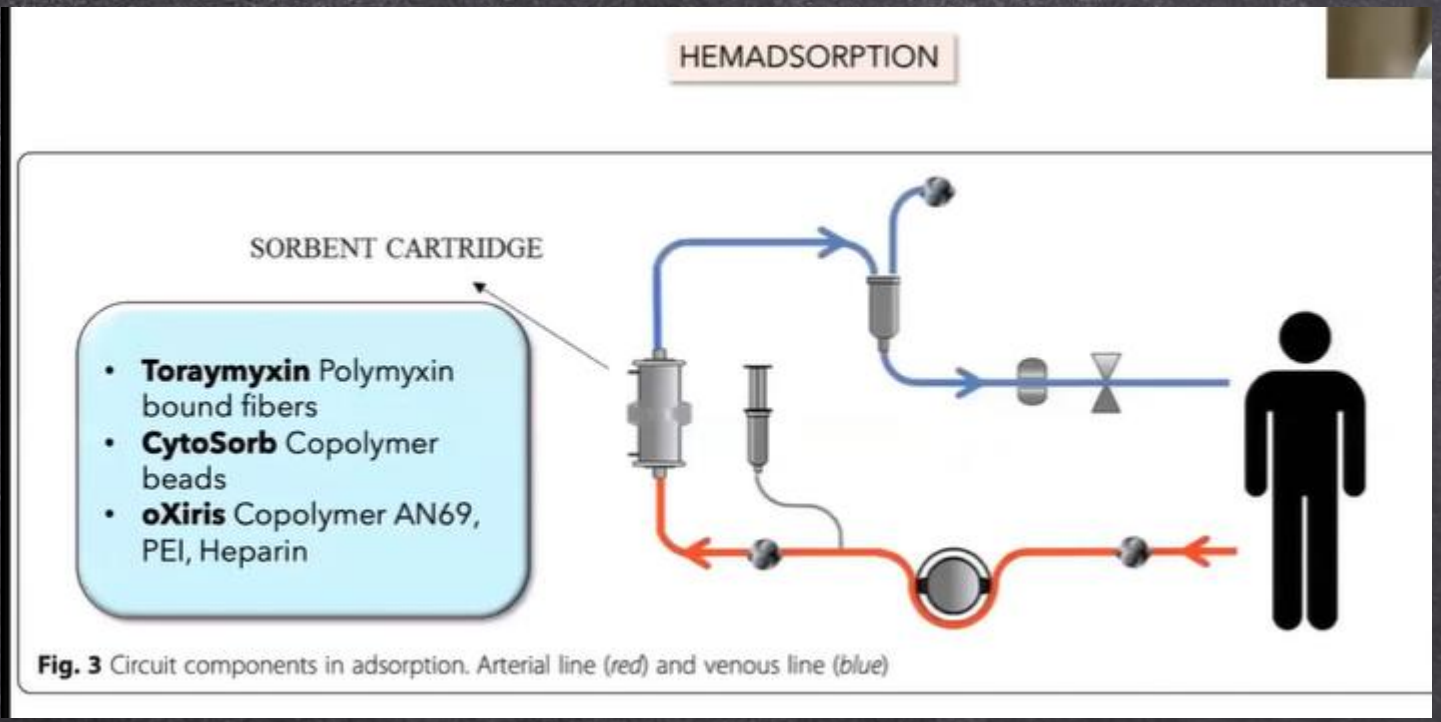
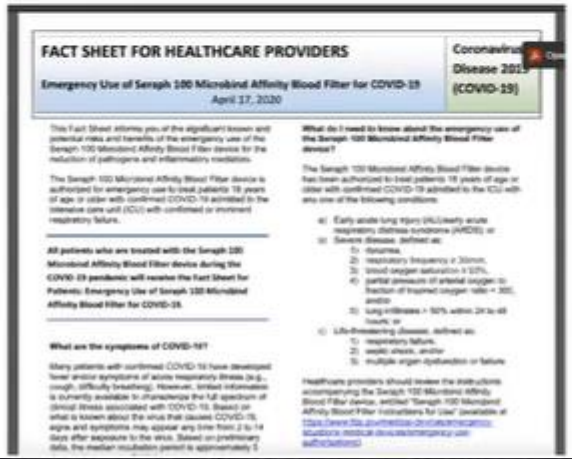


Fig. 3 Circuit components in adsorption. Arterial line (*red*) and venous line (*blue*)

SERAPH™ MICROBIND AFFINITY BLOOD FILTER:

Microbial removal device

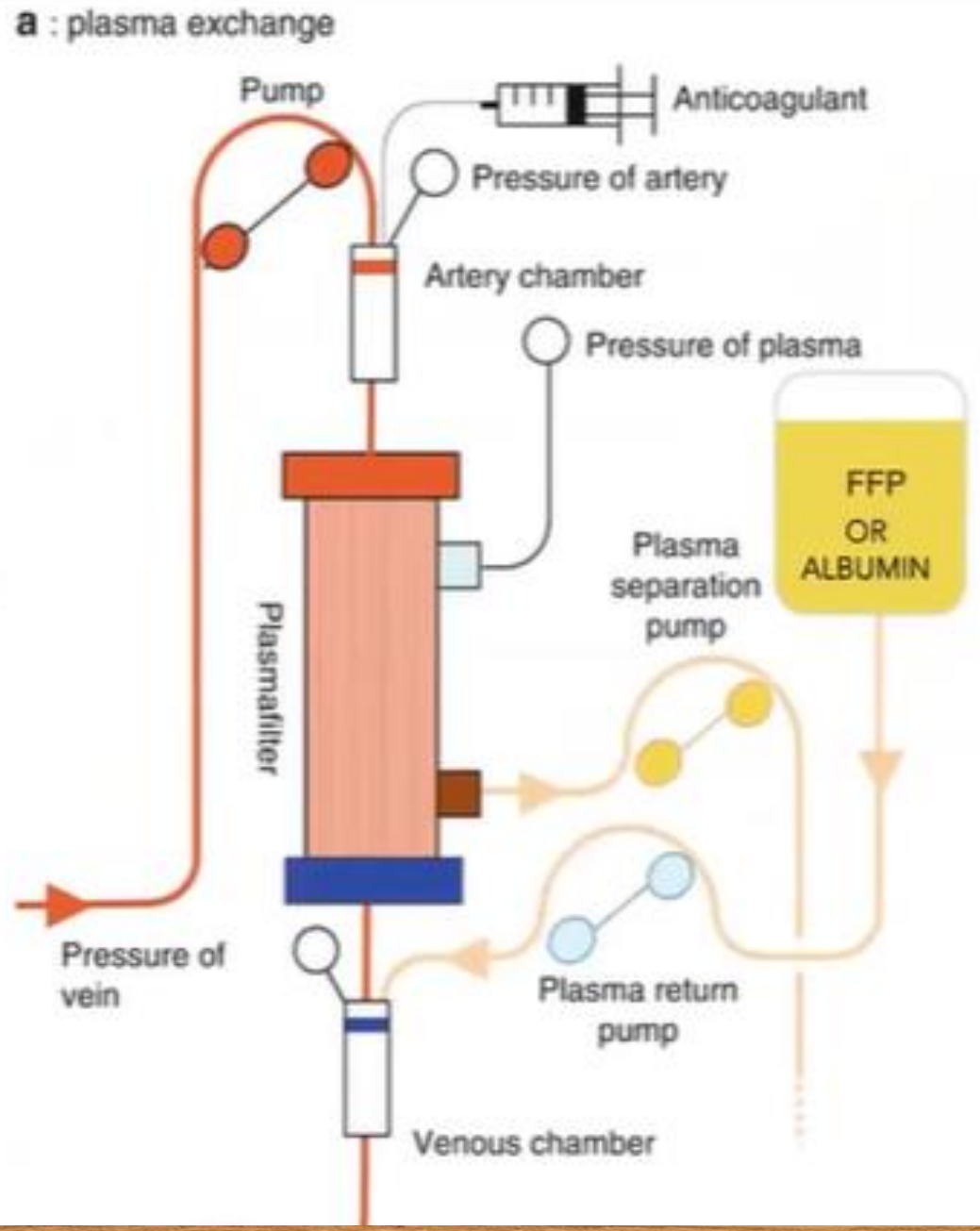


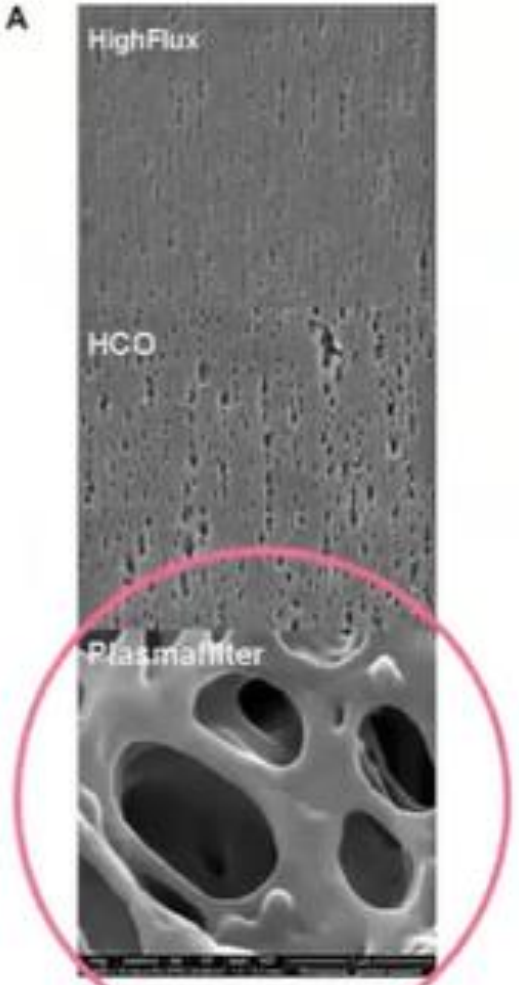
FACT SHEET FOR HEALTHCARE PROVIDERS

Emergency Use of Seraph 100 Microbind Affinity Blood Filter for COVID-19
April 17, 2020

Coronavirus Disease 2019 (COVID-19)

THERAPEUTIC PLASMA EXCHANGE



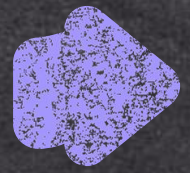


Hello!

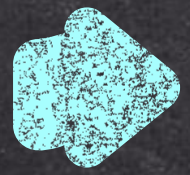
Here is where you introduce yourself.

You can add your name, title and a little background. Right click the image and replace it with your own.

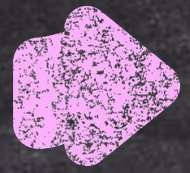
Here is where you add your talking points.



We will talk about this first.



We will talk about this second.



We will talk about this last.

We will talk about this first.

Add a brief introduction of your section here.

Let's dive in and get to know some interesting facts about animals!

Did you know?

Elephants and storms.

Did you know that elephants can sense storms?

Elephants may be able to detect a thunderstorm from hundreds of miles away, and will head towards it, looking for water.

Did you know?

A man's best friend...

Did you know that dogs can smell your feelings?

Dogs can pick up on subtle changes in your scent, which can help him figure out how you are feeling, such as by smelling your perspiration when you become nervous or fearful.

Mmm, can I fit in?...

Did you know that a cat uses its whiskers as feelers to determine if a space is too small to squeeze through?

Also, cats love to sleep. A fifteen-year-old cat has probably spent ten years of its life sleeping.

“Clearly, animals know more than we think, and think a great deal more than we know.

— Irene M. Pepperberg

Did you know?

Pandas don't hibernate.

When winter approaches, they head lower down their mountain homes to warmer temperatures, where they continue to chomp away on bamboo!

There are more kangaroos than humans in Australia.

It is estimated that more than 50 million kangaroos live there. They are Australia's national symbol and appear on postage stamps, coins, and airplanes.

Koalas are even more lazy than cats.

Koalas don't have much energy and, when not feasting on leaves, they spend their time dozing in the branches. Believe it or not, they can sleep for up to 18 hours a day!

Very interesting facts!

This is where you section ends. Duplicate this set of slides as many times you need to go over all your sections.

Sometimes it only takes one image...

...to tell the story.

Some facts about my cats.

Of my cats are adorable.

Traveled by plane. Twice!

Are females.

Let's review some facts.

Elephants

Elephants can sense storms.

Pandas

Pandas don't hibernate.

Kangaroos

There are more kangaroos than humans in Australia.

Dogs

Dogs can smell your feelings.

Cats

Cats use their whiskers as feelers to determine if a space is too small to squeeze through.

Koalas

Koalas are even more lazy than cats.

Meet the dream team!

Carlos V.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

Mariel S.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

Oscar M.

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Aenean commodo ligula eget dolor.

This is an editable world map.

Showcase places

You can use maps to show your offices or markets. Or as charts, highlighting the countries and adding your data.

100% Editable

You can double click on the desired country and change fill color.

And this is a timeline or process

Monday	Tuesday	Wednesday	Thursday	Friday
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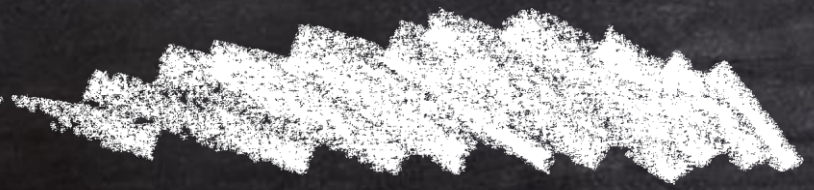

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