Filtering for the Future: Blood Purification Technologies

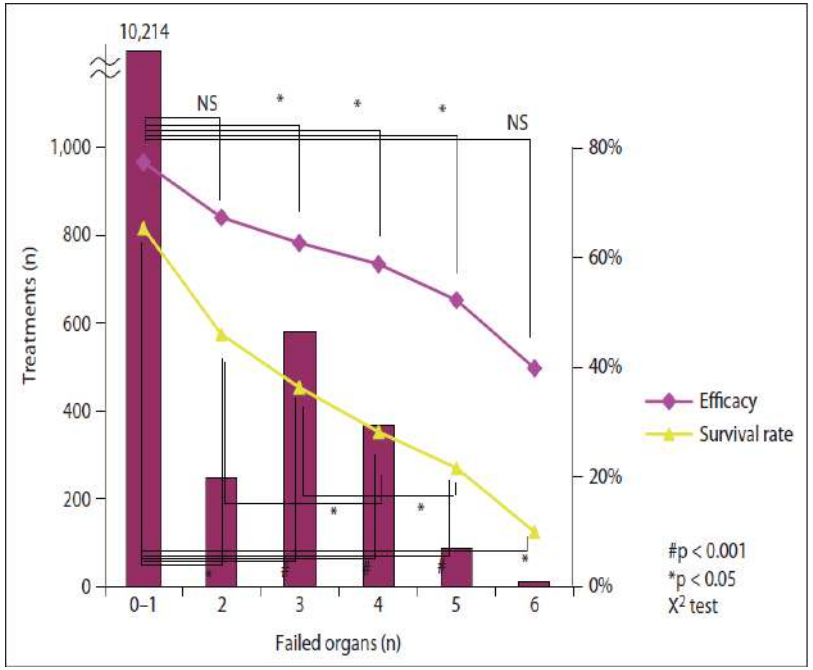
Ioannis Griveas, MD, PhD

Nephrologist

athens-NEPHROLOGY

Therapeutic Apheresis

- Extracorporeal procedure in removing abnormal blood cells and plasma constituents.
- Plasmaphersis, leukaphersis, erythrocytapheresis and thrombocytapheresis.
- Membrane or centrifugation.



Immune Cells as an Organ

Mass of immune cells = 2×10^{12} cell = about 2 kg

Lined up gives this a distance of $2 \times 10^{12} \times 10\ \mu$ =

20.000 km !

Life Time

- Granulocytes 8 hours
- Monocytes days….weeks
- Lymphocytes weeks….years
  (Memory cells) partly lifelong?

Dichotomy of Immune System

Humoral:

- **Immunoglobulins**
- **Complement system**

Cellular:

- **Lymphocytes**

Review Article
Volume 63, Issue 1103849 February 2024

Therapeutic Apheresis and Nephrologist: New and old aspects

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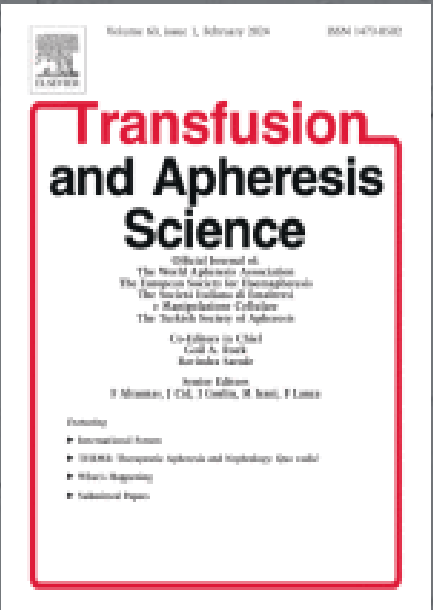


POWER

MARKETING

WEB DESIGN

SUPPORT

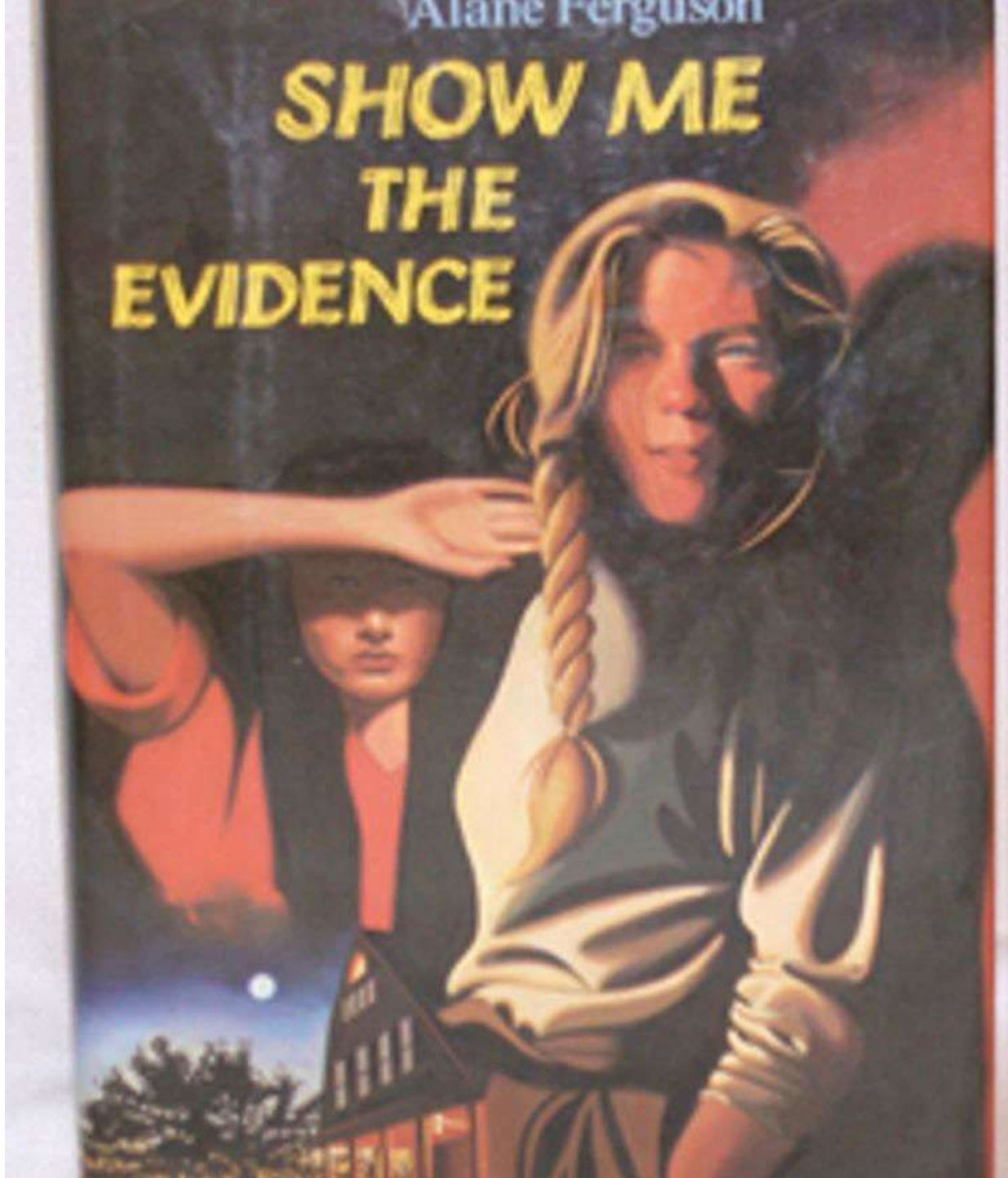
DEVELOP

IDEAS

TEAM CPO

2

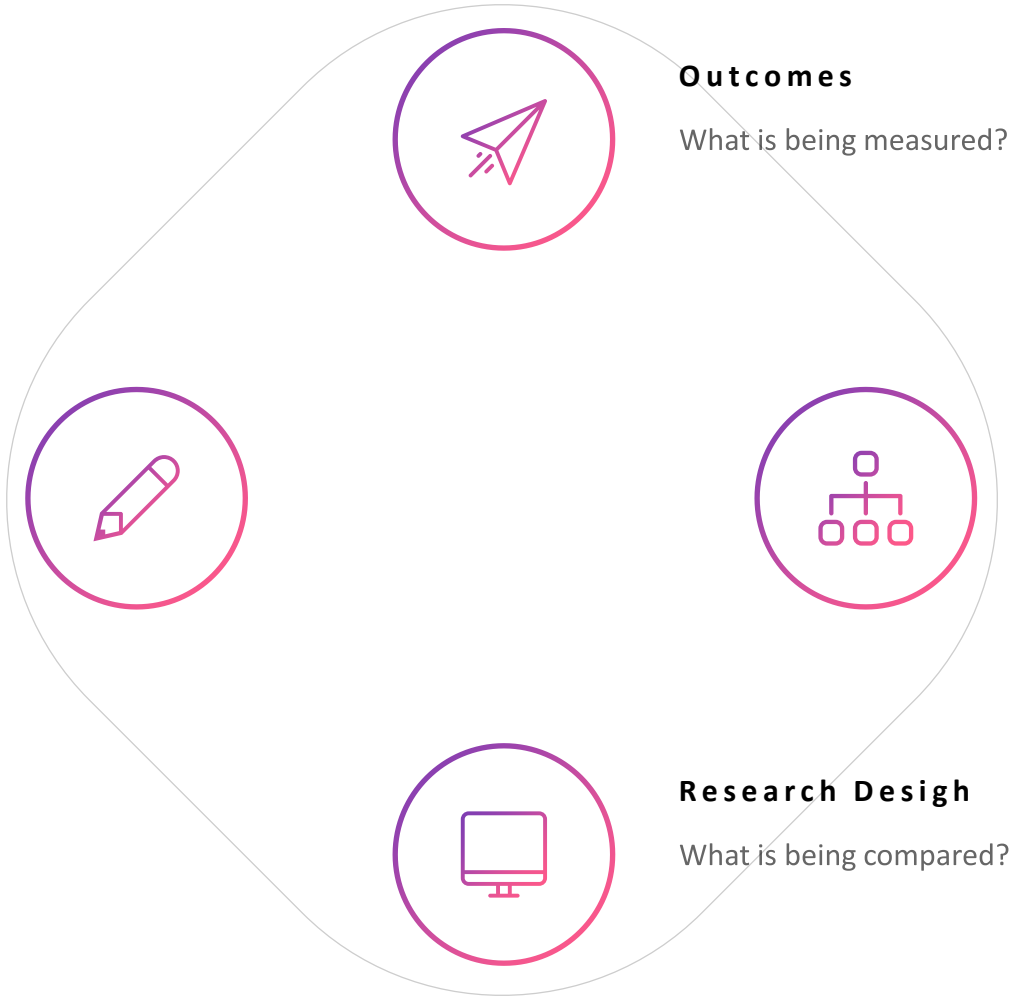
Various types of apheresis procedures have been performed on a clinical basis for many years, but the number of patients and types of diseases treated have risen significantly in the last 5 years. This increase is partially due to increased understanding of the disease and partially due to engineering advances in equipment technologies. By almost any standard, treatment by apheresis is still in relatively early stages of development—there are no ideal protocols based on a thorough understanding of reasons for its efficacy. Nevertheless, there is an increasing flow of clinical data, sometimes describing dramatic patient improvement, supporting the view that apheresis is a rapidly emerging technology with significant promise (117). Such evidence of treatment effec-



1981

L. F. Rothschild, Unterberg, Towbin, "Therapeutic Apheresis," unpublished, New York, Sept. 11, 1981.

*Effectiveness is the health benefit as measured under average conditions of use. *Efficacy* is the health benefit as measured under controlled conditions such as those in a randomized clinical trial (104).



Outcomes

What is being measured?

Treatment Desigh

What is being tested?

Patients Selection

Which subject population are involved in the research?

Research Desigh

What is being compared?

Treatment Desigh

01 | Procedure involves a single treatment?

02 | Combination of treatments?

03 | Combination of treatment and non-treatments factors?

04 | **Multivariant**

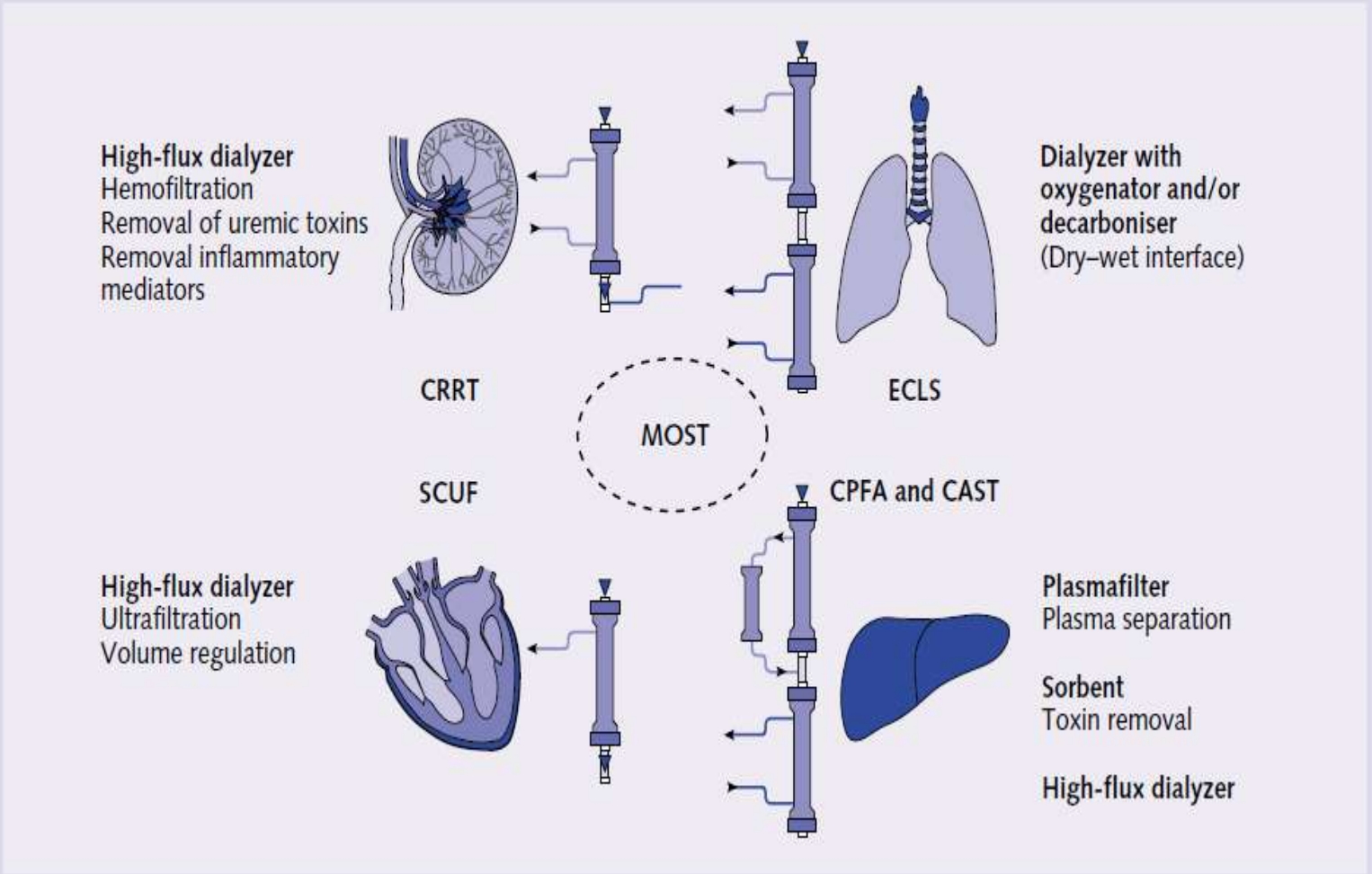
05 | The extent to which researchers can measure the impact of any one component of the procedure

06 | Clarity of design

Sepsis and MODS

- Extremely complex nature of inflammatory response in sepsis.
- Unlikely a single agent (e.g. anticytokine Rx) would work.
- Ronco proposed that '..unspecific removal of soluble mediators, be they pro or antiinflammatory, without completely eliminating their effect, may be the most logical and adequate approach to a complex and long-running process such as sepsis.'

Figure 4. The concept of MOST. Different organs can be supported by special modifications to the extracorporeal circuit. The kidney is supported by dialysis, the lung by extracorporeal CO_2 removal, the heart by optimal ultrafiltration and fluid balance, and the liver by specific filters and sorbents to remove liposoluble toxins.



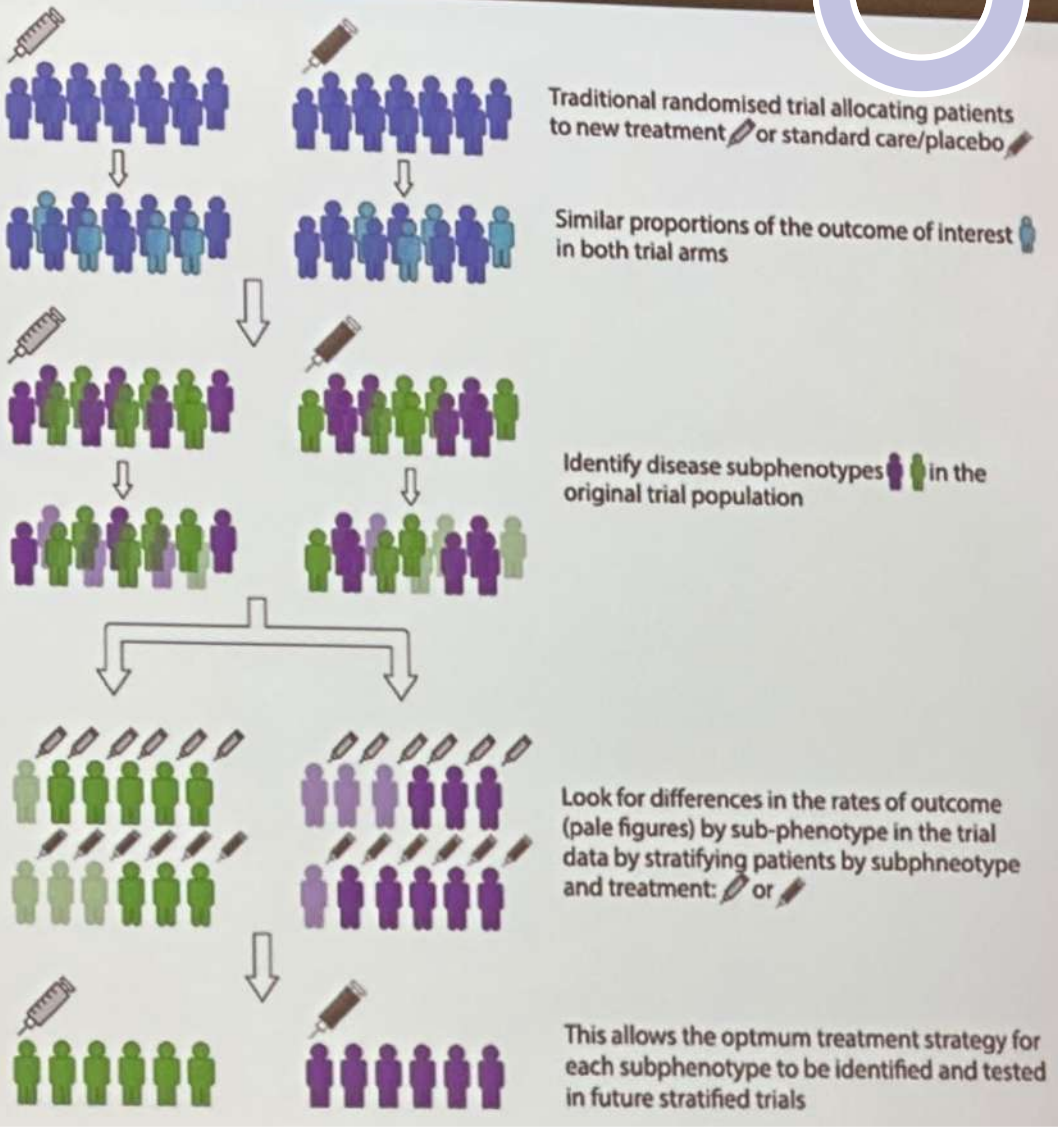
CAST: counter anti-inflammatory support therapy; CPFA: coupled plasmafiltration–absorption; CRRT: continuous renal replacement therapy; ECLS: extracorporeal life support; MOST: multiorgan support therapy; SCUF: slow continuous ultrafiltration.

Intensive Care Med
https://doi.org/10.1007/s00134-025-07873-6

Sepsis subphenotypes, theragnostics and personalized sepsis care

David B. Antcliffe[1,5*], Aidan Burrell[2], Andrew J. Boyle[3,4], Anthony C. Gordon[1], Daniel F. McAuley[3,4] and Jon Silversides[3,4*]

Heterogeneity between critically ill patients with sepsis is a major barrier to the discovery of effective therapies. The use of machine learning techniques, coupled with improved understanding of sepsis biology, has led to the identification of patient sub-phenotypes. This exciting development may help overcome the problem of patient heterogeneity and lead to the identification of patient subgroups with treatable traits



Web Data

EBP = Controversial literature

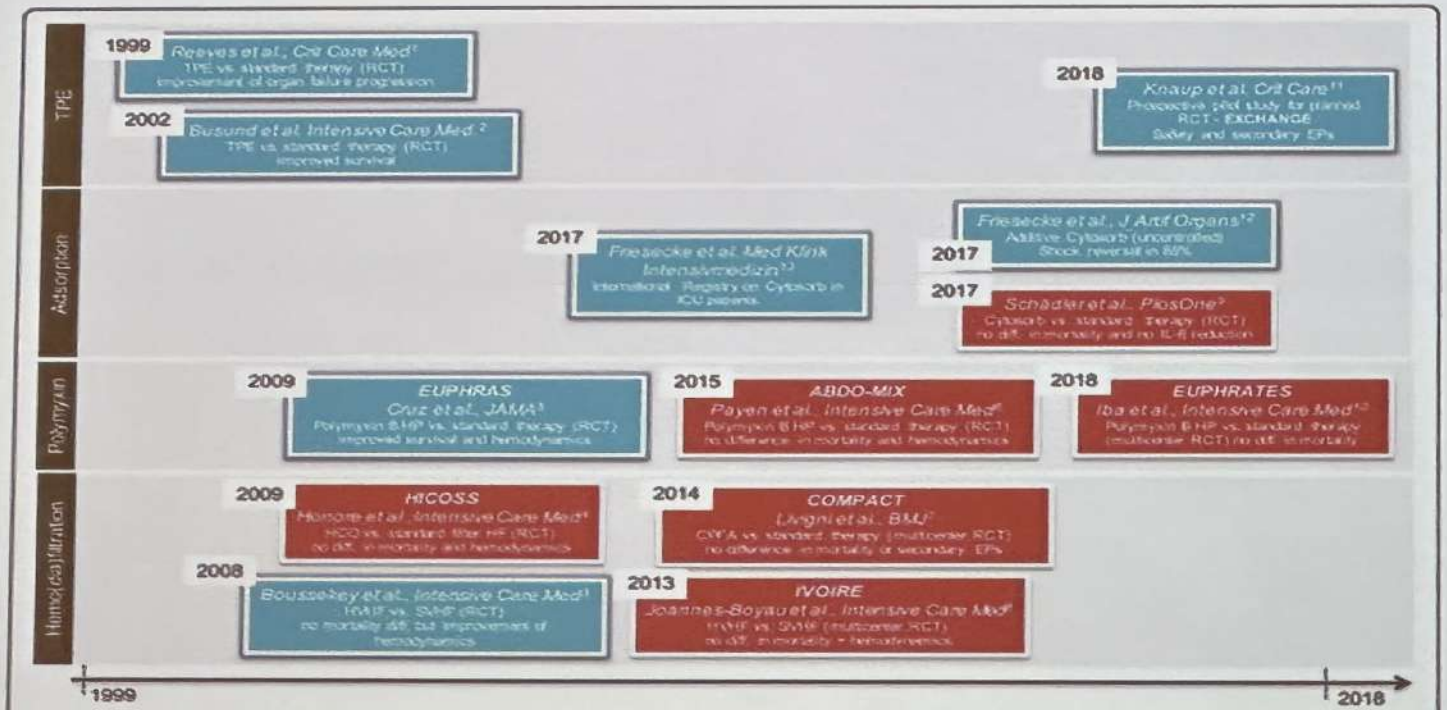
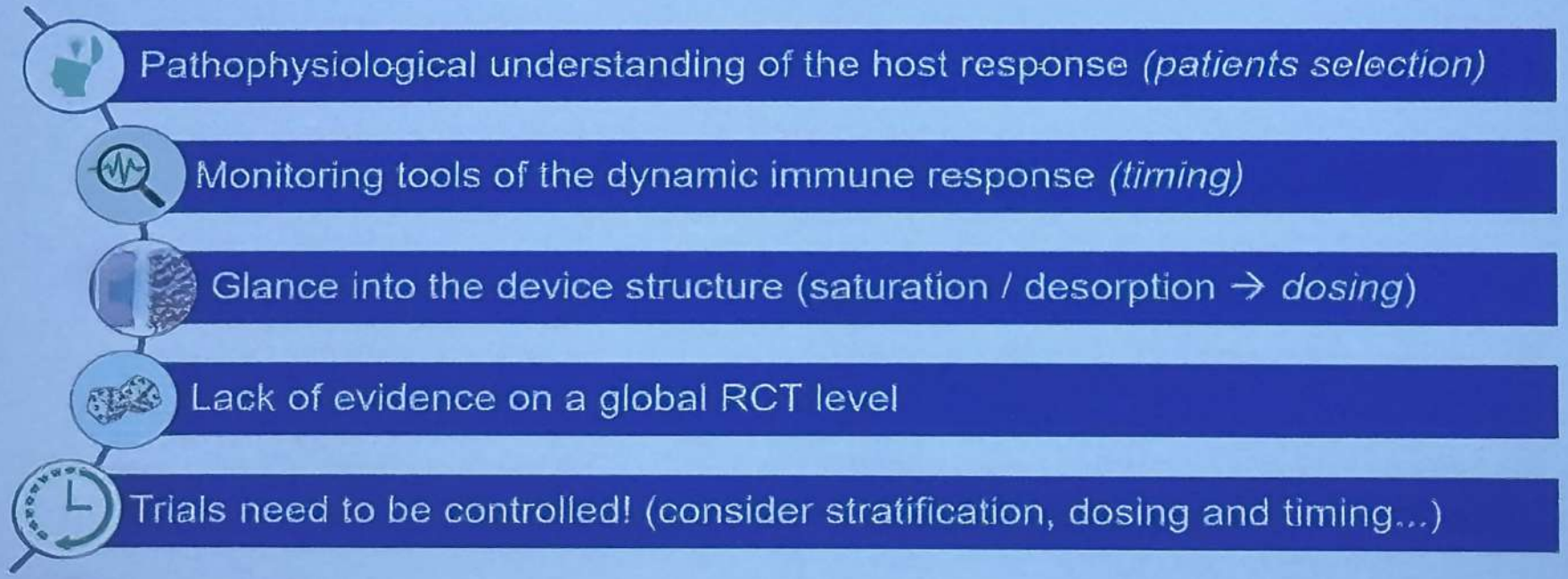


Fig. 1 Timeline of important prospective trials of various extracorporeal therapeutic strategies in sepsis. *Abbreviations*: *TPE* therapeutic plasmaexchange, *RCT* randomized controlled clinical trial, *HP* hemoperfusion, *HVHF* high volume hemofiltration, *SMHF* small volume hemofiltration, *HCO* high cut-off, *CPFA* combined plasma filtration adsorption. References: 1. Crit Care Med. Oct;27(10):2096–104. 2. Intensive Care Med. 2002;28(10):1434–9.; 3. Intensive Care Med. 2008;34(9):1646–53. 4. Crit Care Med. 2000;28(11):3581–7. 5. JAMA. 2009;301(23):2445–52. 6. Intensive Care Med. 2015;41(6):975–84. 7. BMJ Open. 2014 8;4(1):e003536. 8. Intensive Care Med. 2013;39(9):1535–46. 9. PLoS One. 2017;12(10):e0187015. 10. JAMA 2018;320(14):1455–1463. 11. Crit Care. 2018;22(1):285. 12. J Artif Organs. 2017;20(3):252–259. 13. Med Klin Intensivmed Notfmed. 2017, doi: https://doi.org/10.1007/s00063-017-0342-5

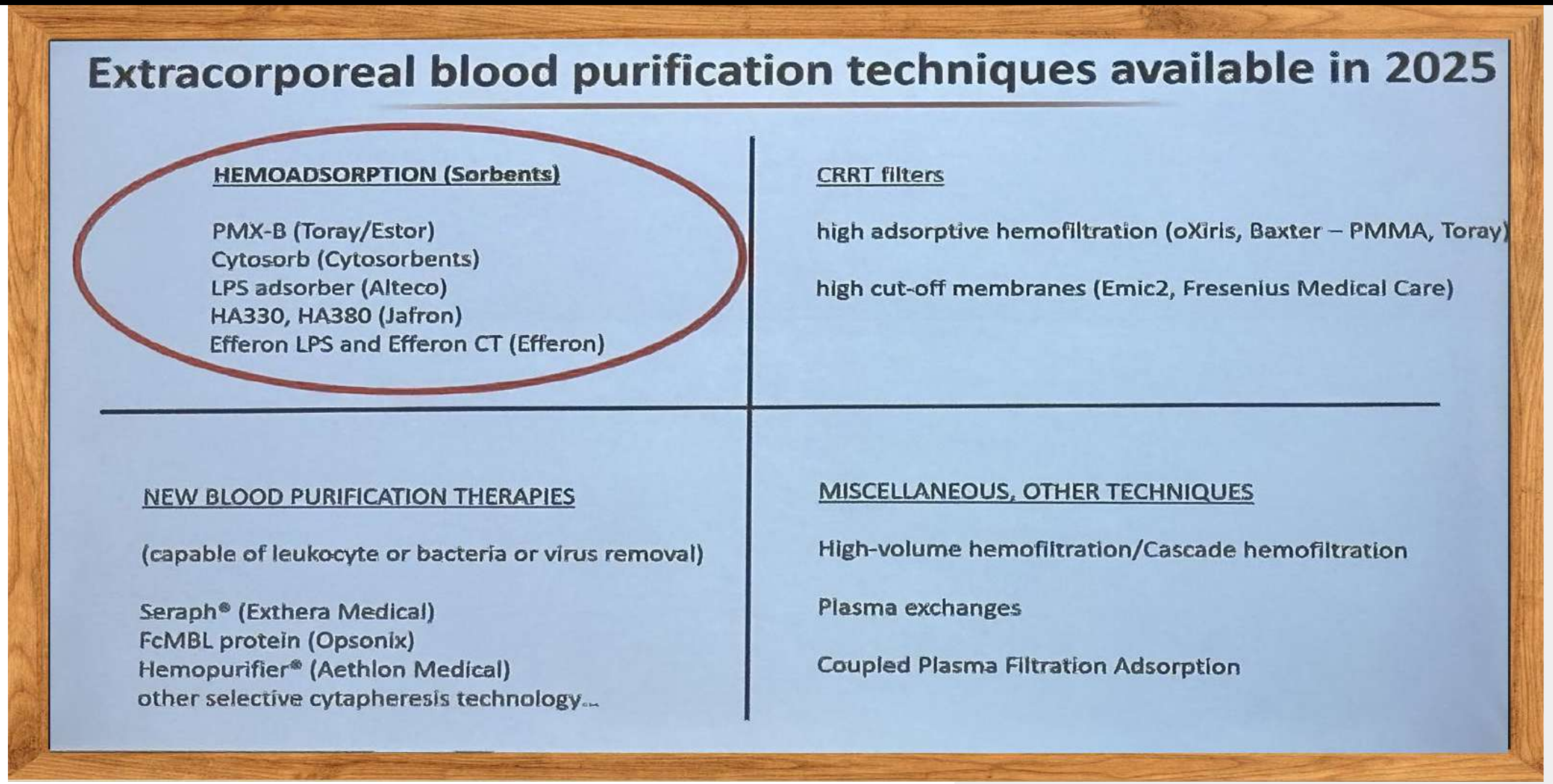
David et al. Crit Care 2019

Past-Present-Future

Summary - Areas in which we need more knowledge ...



Blood Purification Up date 2025



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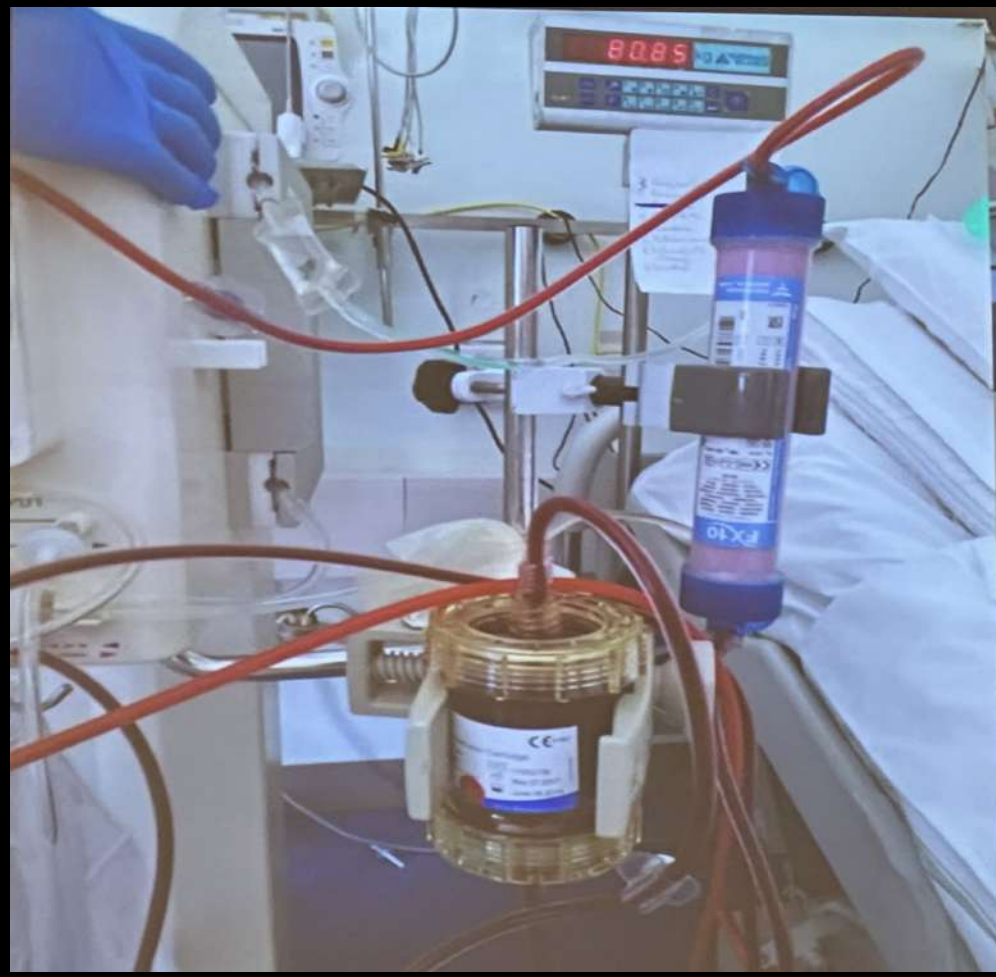
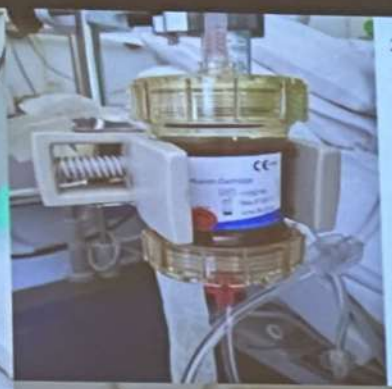
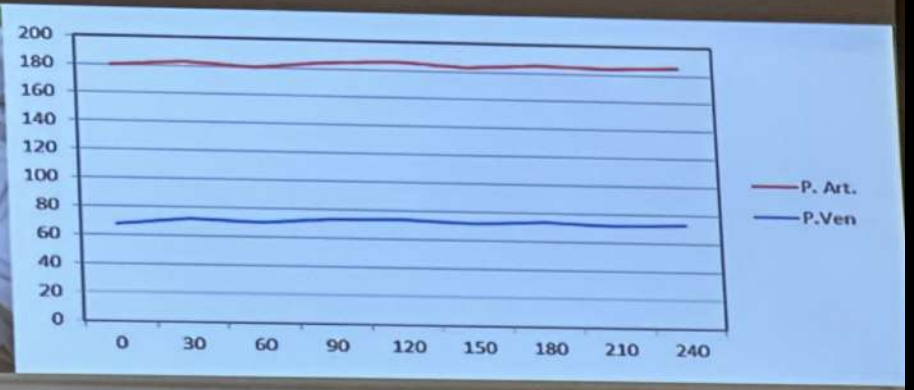
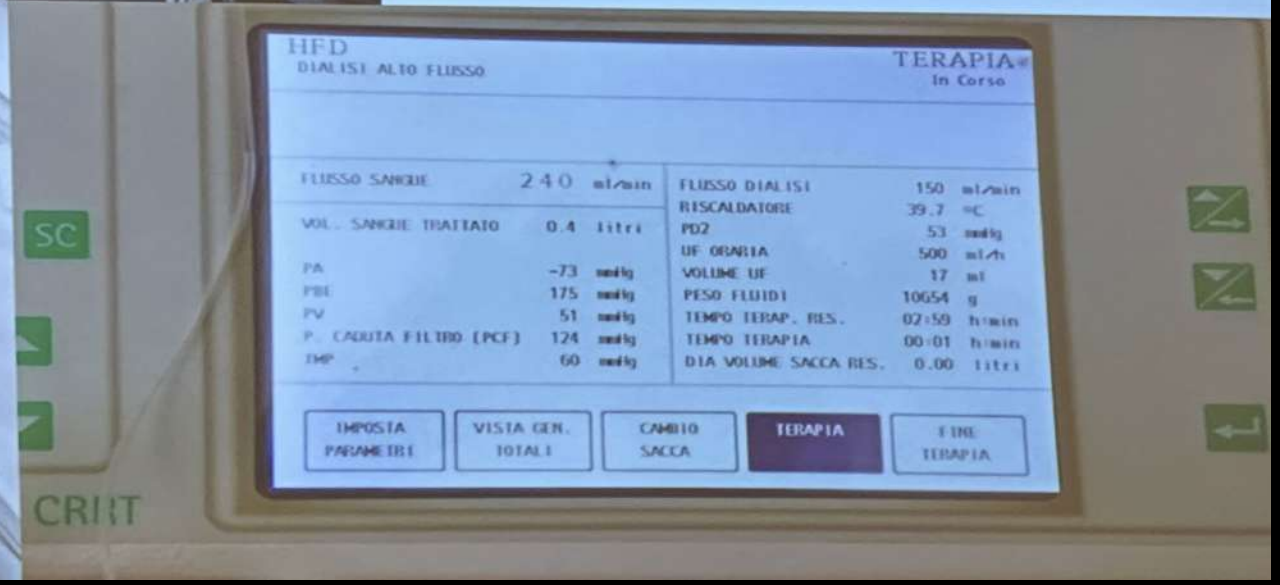
Technology









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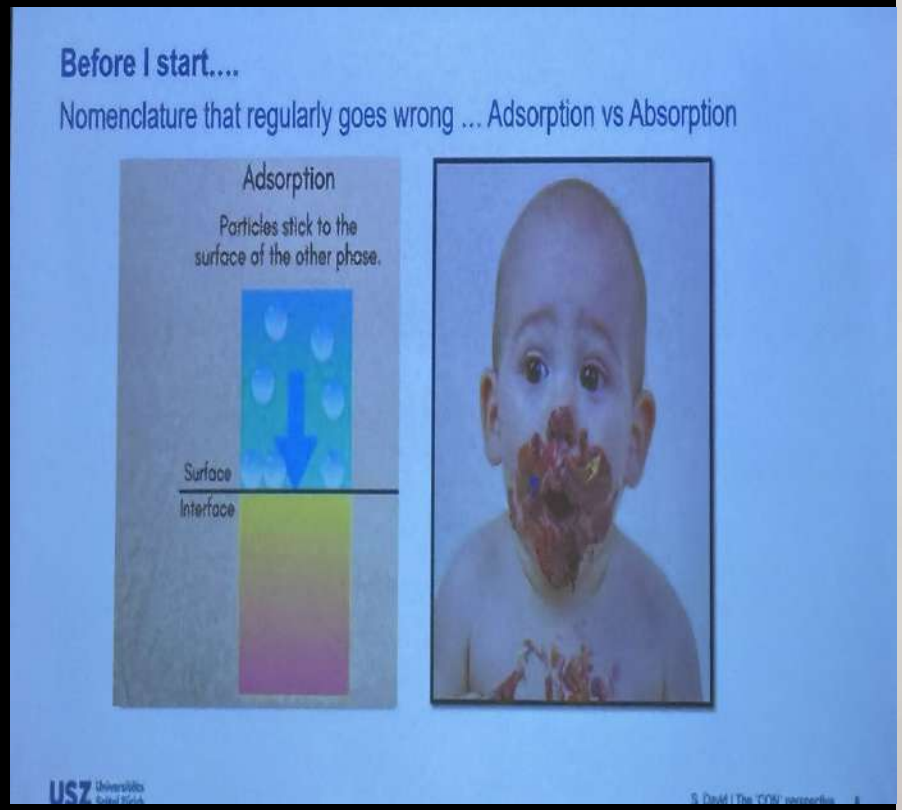
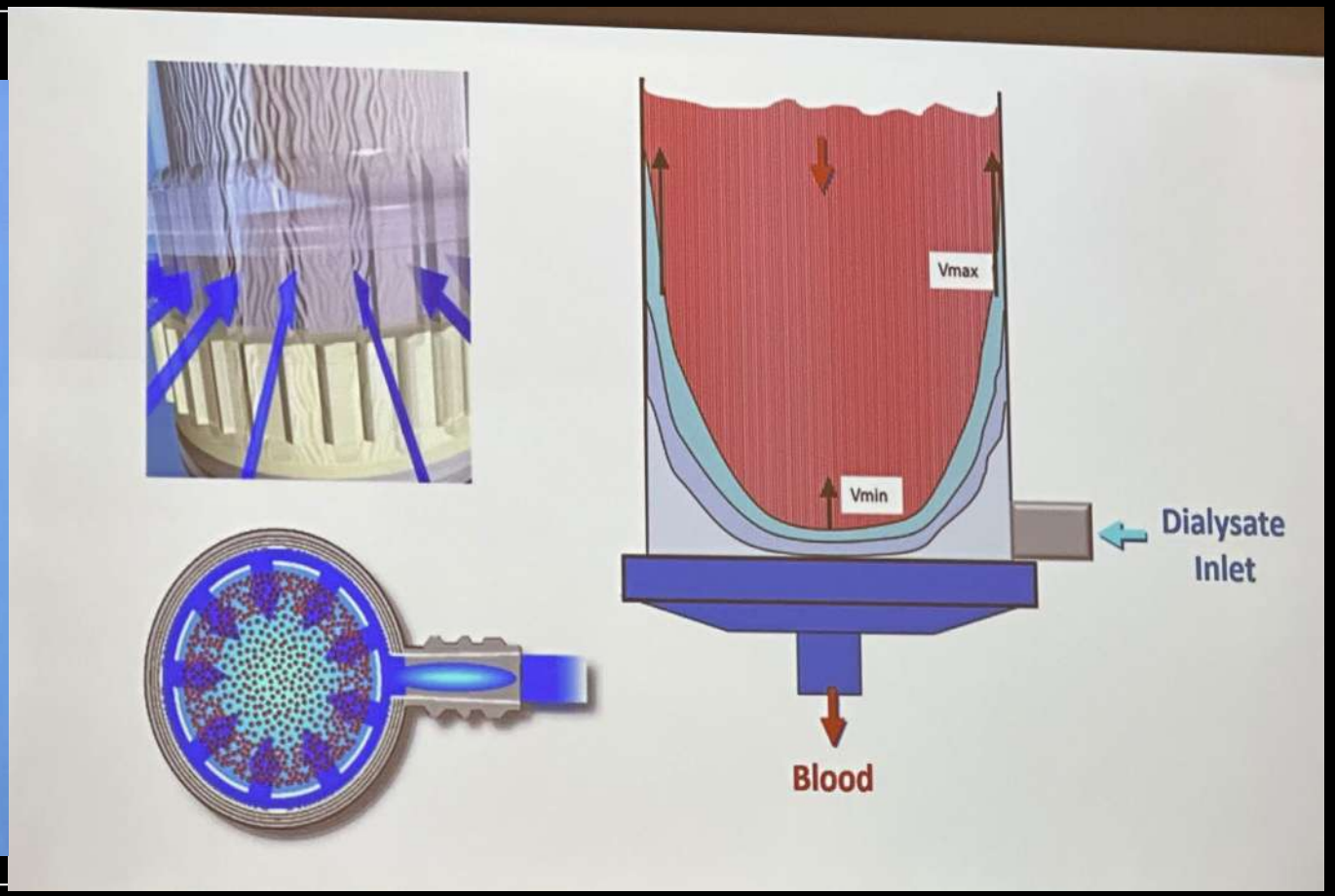
Technology





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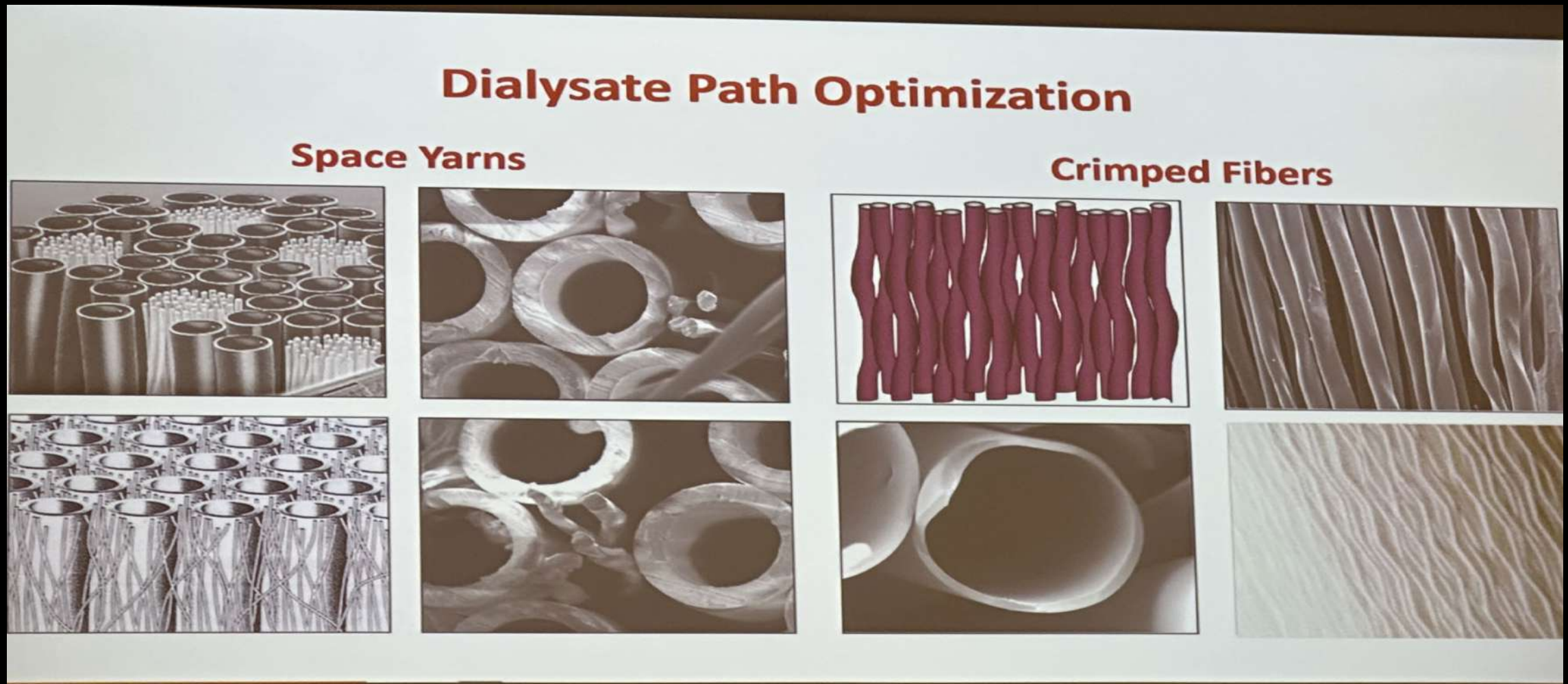
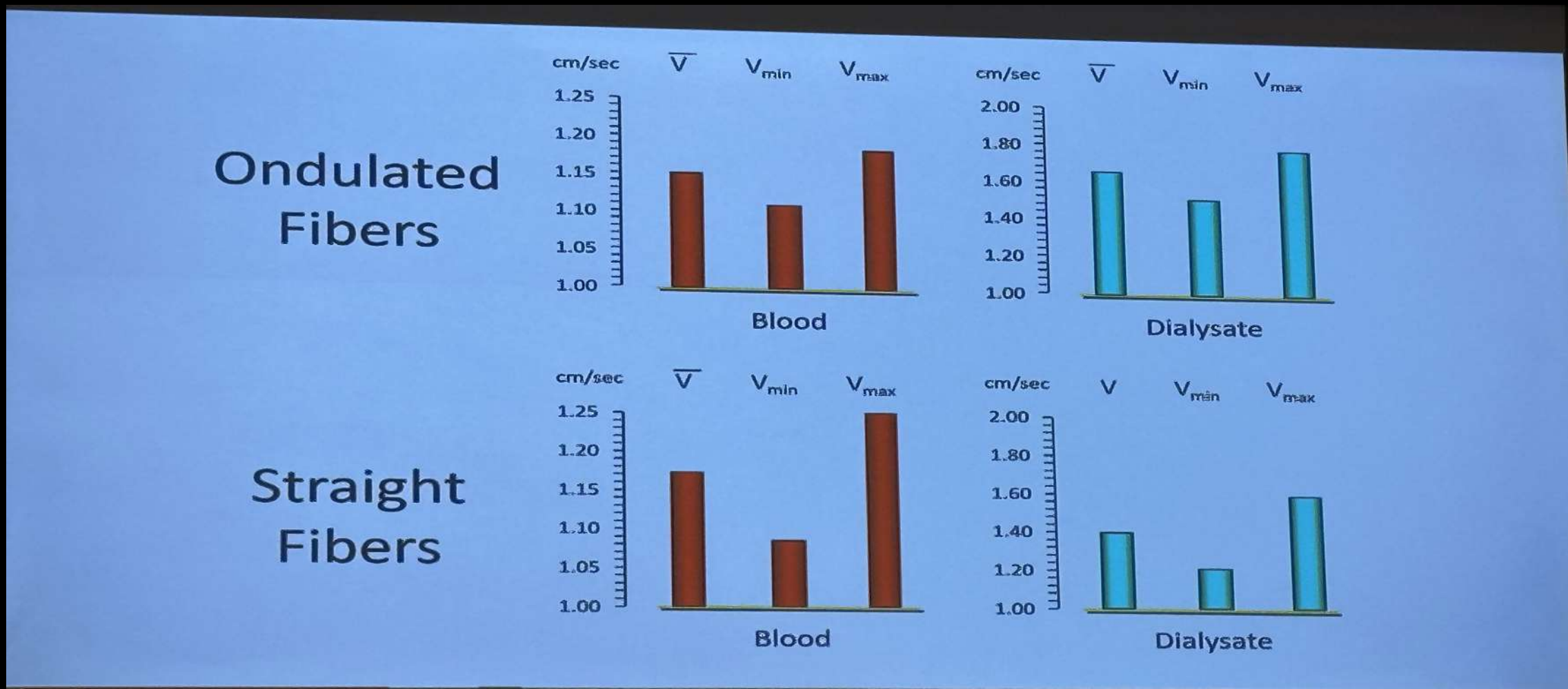


Technology



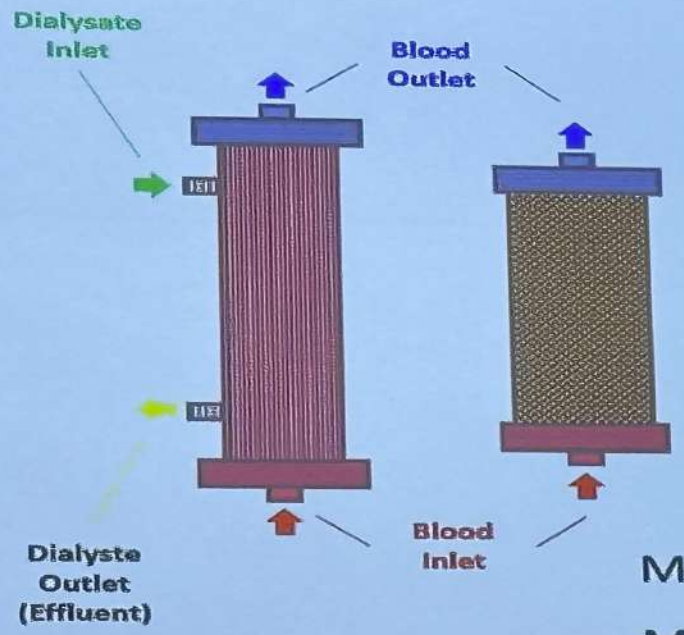
Menu

Technology

Dialyzer vs sorbent cartridge

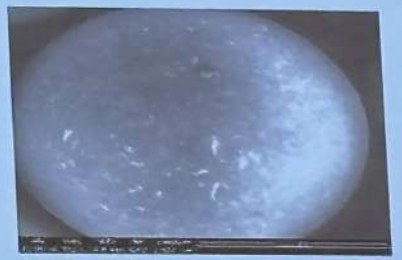
Dialyzer:

- 2 compartments (blood and dialysate/effluent)
- Removal of solutes and plasma water
- Removal based on molecular dimension



Cartridge:

- 1 compartment (blood)
- Removal of solutes based on chemical interaction



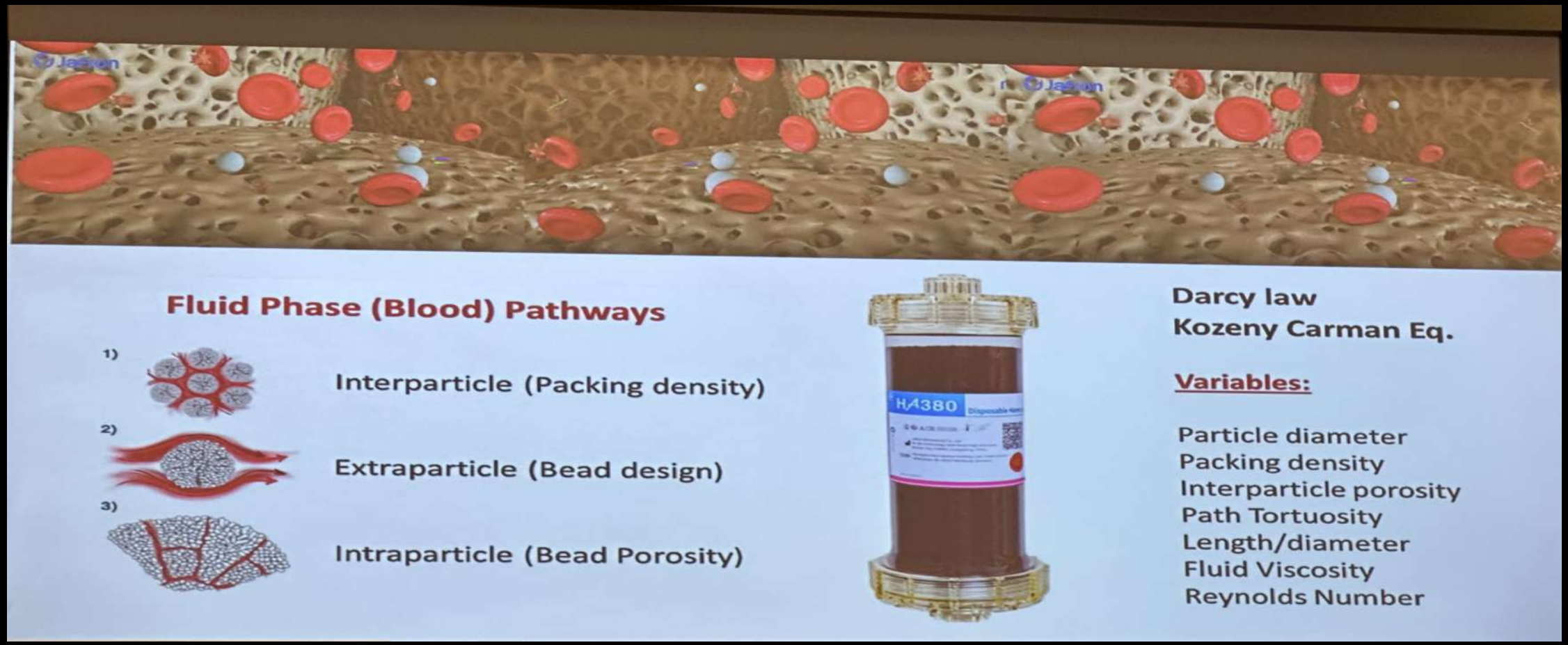
Macroporous = Pore size > 500 Å (50 nm)

Mesoporous = Pore size 20-500 Å

Microporous = Pore size < 20 Å

Menu

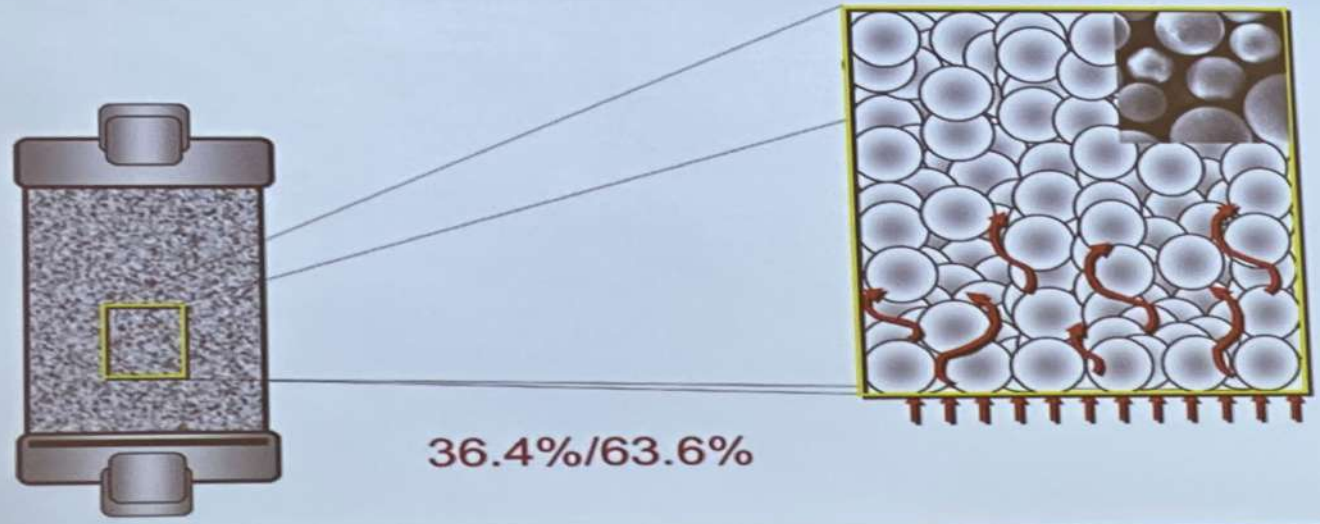
Technology



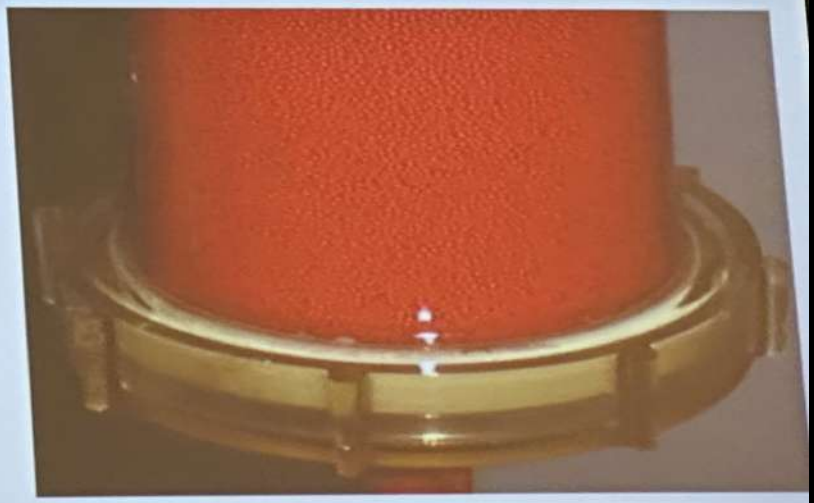
Technology

External (interphase) mass transfer

The most uniform flow profile can be obtained when beds are packed carefully with spherical particles of equal size.



36.4%/63.6%



End-to-end pressure drop in different cartridges

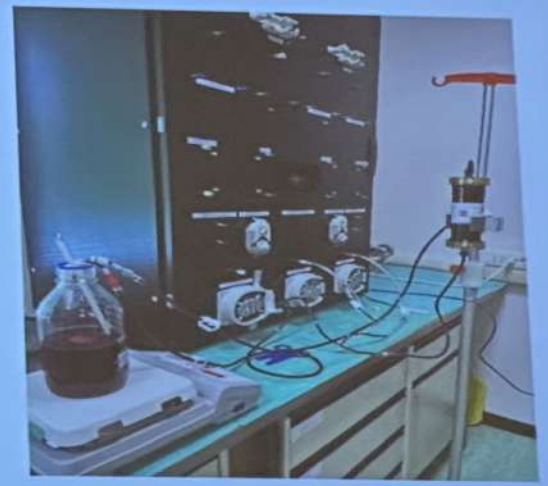
- 1000 mL of blood (Hct=31%)
- Blood flow rate from 100 to 400 mL/min, stepsize 50 mL/min
- Inlet pressure (P_{in}) and outlet pressure (P_{out}) were recorded
- Three different cartridges were tested:

HA130 $K = 1.66 \cdot 10^{-4}$ m/s

HA330 $K = 6.14 \cdot 10^{-4}$ m/s

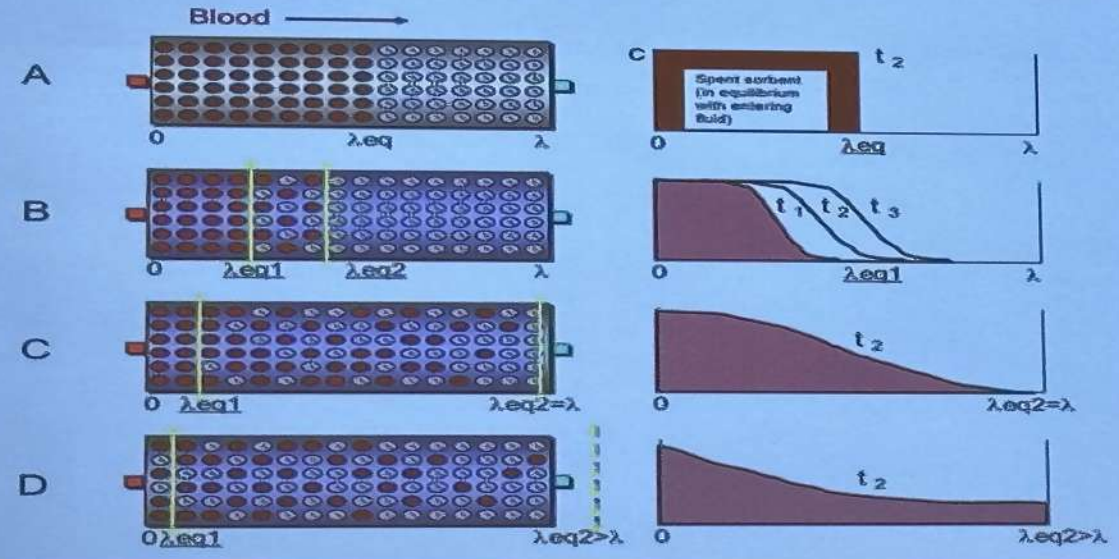
CA330 $K = 4.04 \cdot 10^{-4}$ m/s

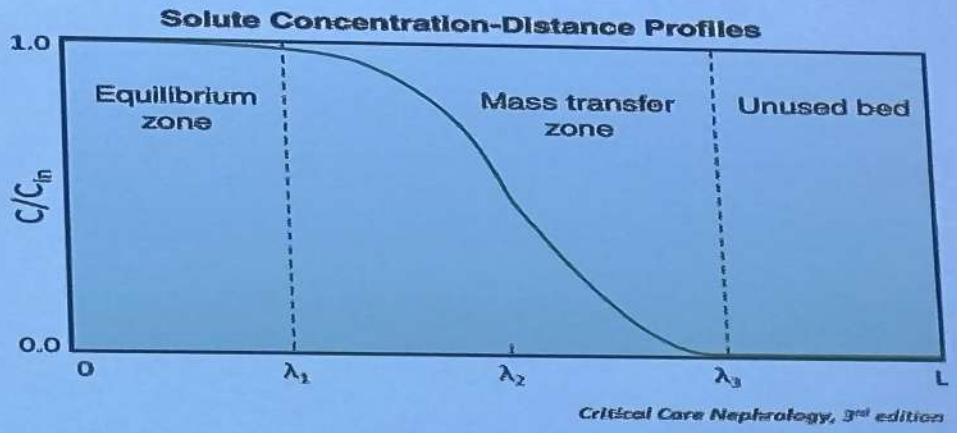
These values suggest important structural and functional differences among the cartridges and help design and configuration of future devices.



Mass Transfer Zone

Mass Transfer Zone: distance between the point (cross section) where all sorbent material is saturated, and the point with zero adsorbate.



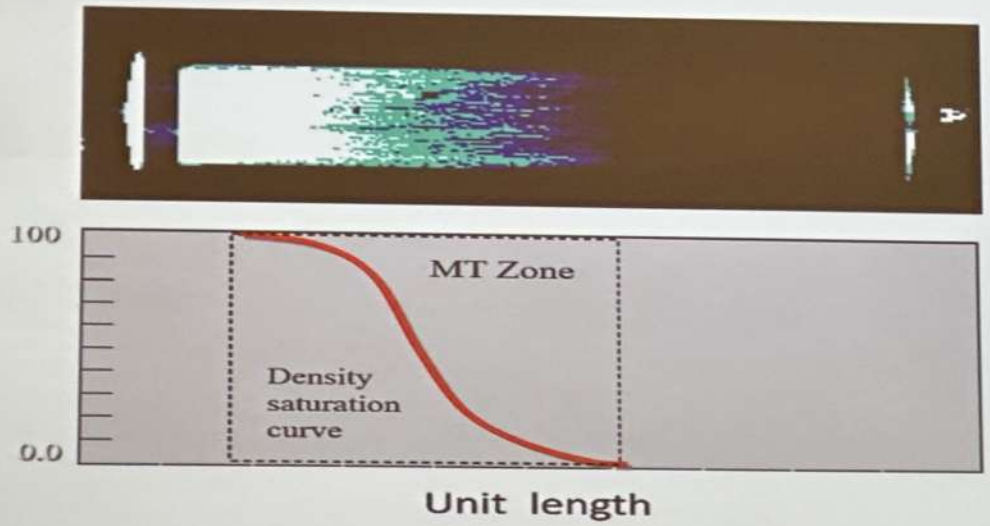


A. MTZ = 0 → ideal condition
B. MTZ < L → good design
C. MTZ = L → flow-through
D. MTZ > L → poor design

Technology

Average Velocity & Dye Density Transfer Zone

C. E. F. I.

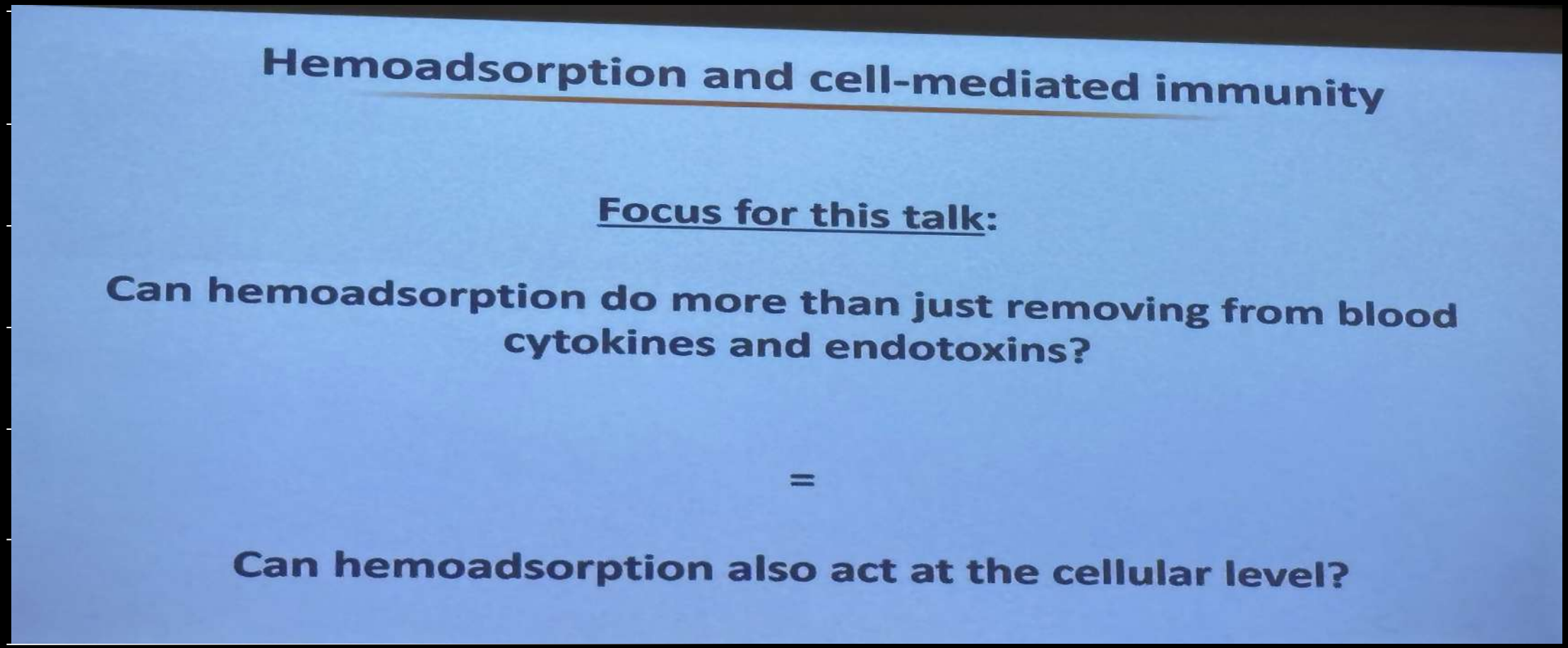


Adequate design is described by a color transfer zone shorter than 2/3 of unit length

Measured Average Velocity in the blood compartment slightly differ from the calculated average velocity of 1.35 cm/sec. This effect might be correlated to several factors including slight variation of the inner diameter of the fibers (cross sectional area 4,3 cm^2), slight variability of the blood compartment volume (113 ml) or, most likely, to internal filtration in the proximal portion of the dialyzer.

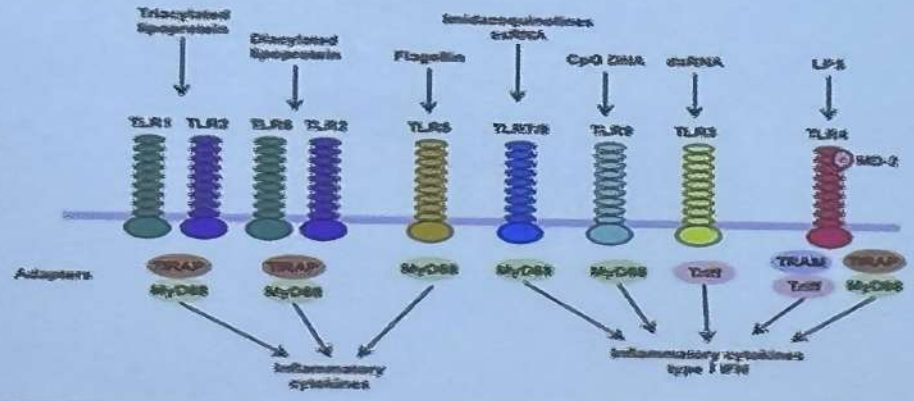
The analysis of the color transfer zones for density characterize the nature of flow present in the unit and the utilization of the hemodialyzer surface suggesting important clues for design modification.

Pathophysiology

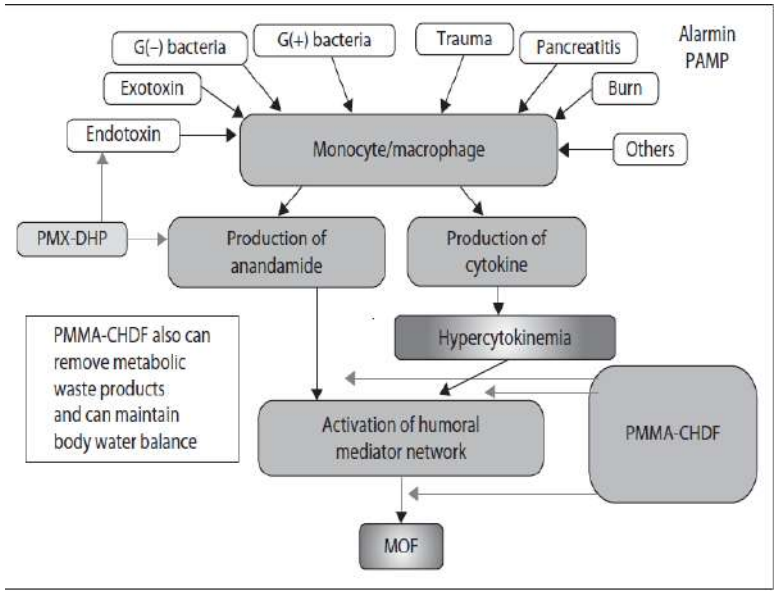


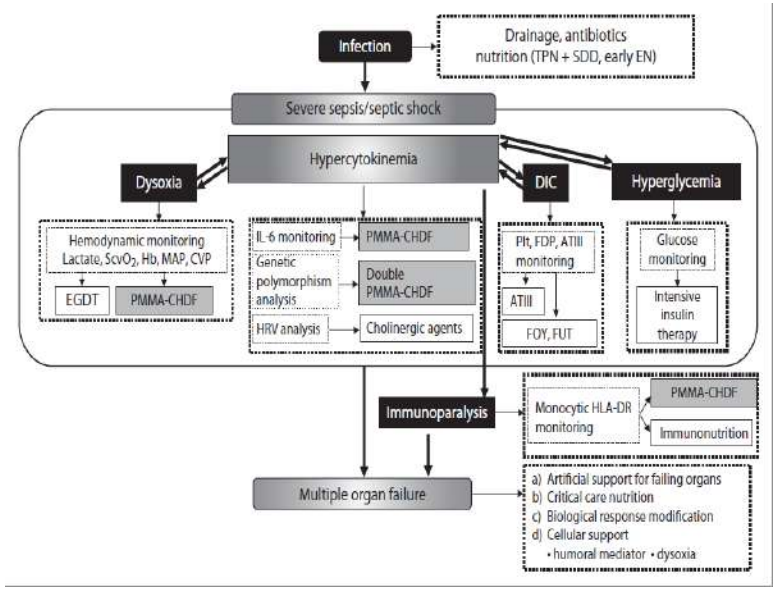
Environment: DAMPs and PAMPs

- Damage-Associated Molecular Patterns
  - HMGB1
  - Heat-shock Proteins
  - Hyaluronan fragments
  - Uric acid
  - Heparin sulfate
  - DNA

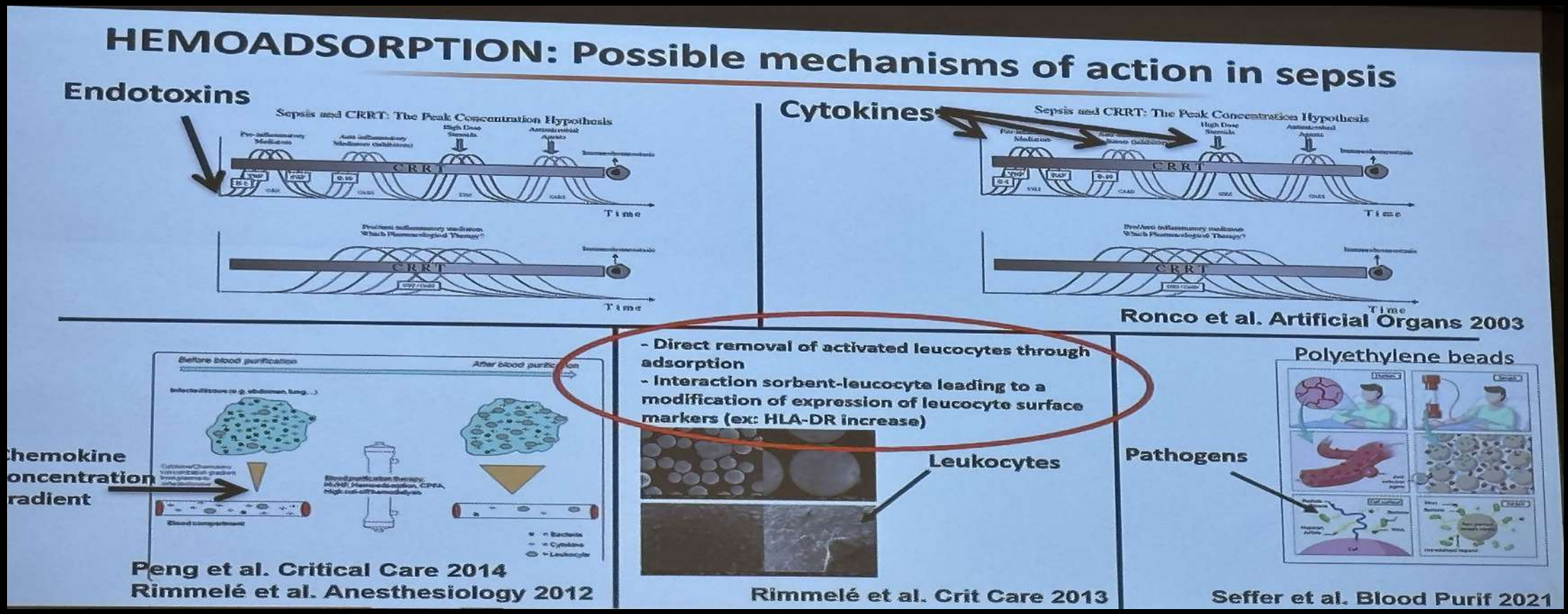


- Pathogen-Associated Molecular Patterns
  - Endotoxin
  - Flagellin
  - Lipoteichoic acid (gram-positive bacteria)
  - Peptidoglycan
  - Nucleic acid variants (viruses) e.g. double-stranded RNA (dsRNA), unmethylated CpG motifs


G(−) bacteria
G(+) bacteria
Trauma
Pancreatitis
Alarmin
PAMP
Exotoxin
Burn
Endotoxin
Monocyte/macrophage
Others
PMX-DHP
Production of anandamide
Production of cytokine
PMMA-CHDF also can remove metabolic waste products and can maintain body water balance
Hypercytokinemia
Activation of humoral mediator network
PMMA-CHDF
MOF


Infection
Drainage, antibiotics
nutrition (TPN + SDD, early EN)
Severe sepsis/septic shock
Hypercytokinemia
Dysoxia
DIC
Hyperglycemia
Hemodynamic monitoring
Lactate, ScvO2, Hb, MAP, CVP
EGDT
PMMA-CHDF
IL-6 monitoring
PMMA-CHDF
Genetic polymorphism analysis
Double PMMA-CHDF
HRV analysis
Cholinergic agents
Plt, FDP, ATIII monitoring
ATIII
FOY, FUT
Glucose monitoring
Intensive insulin therapy
Immunoparalysis
Monocytic HLA-DR monitoring
PMMA-CHDF
Immunonutrition
Multiple organ failure
a) Artificial support for failing organs
b) Critical care nutrition
c) Biological response modification
d) Cellular support
• humoral mediator • dysoxia

Pathophysiology



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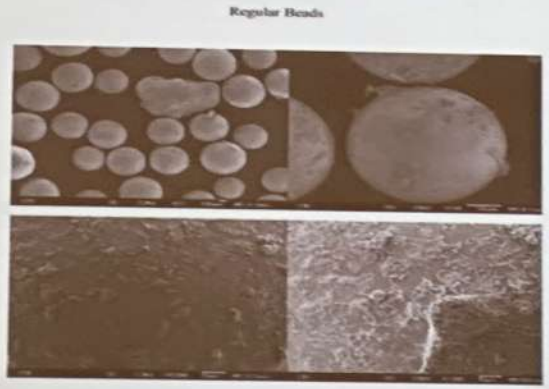
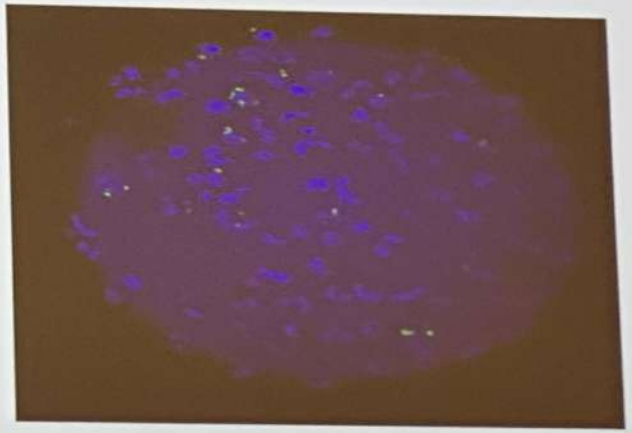
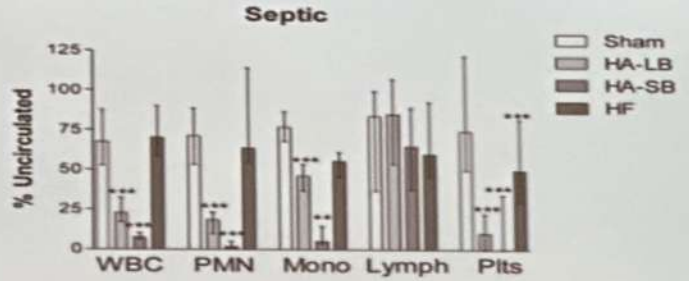
Pathophysiology

Leukocyte adsorption on the beads



Electronic microscopy and immunofluorescence pictures showing leucocytes adsorption on adsorptive polymer





Rimmelé et al. Crit Care 2013

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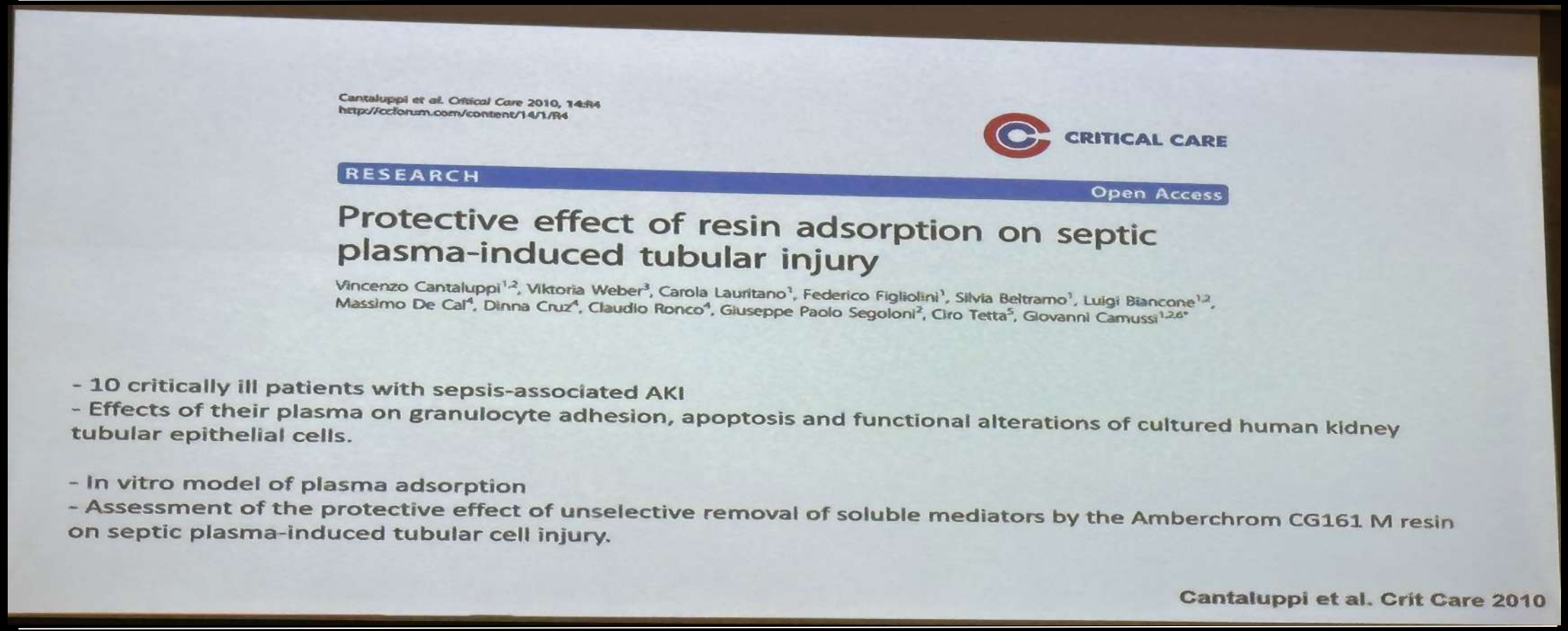
Pathophysiology



Cantaluppi et al. Critical Care 2010, 14:R4
http://ccforum.com/content/14/1/R4

CRITICAL CARE

RESEARCH

Open Access

Protective effect of resin adsorption on septic plasma-induced tubular injury

Vincenzo Cantaluppi[1,2], Viktoria Weber[3], Carola Lauritano[1], Federico Figliolini[1], Silvia Beltramo[1], Luigi Biancone[1,2], Massimo De Cal[4], Dinna Cruz[4], Claudio Ronco[4], Giuseppe Paolo Segoloni[2], Ciro Tetta[5], Giovanni Camussi[1,2,6*]

- 10 critically ill patients with sepsis-associated AKI
- Effects of their plasma on granulocyte adhesion, apoptosis and functional alterations of cultured human kidney tubular epithelial cells.

- In vitro model of plasma adsorption
- Assessment of the protective effect of unselective removal of soluble mediators by the Amberchrom CG161 M resin on septic plasma-induced tubular cell injury.

Cantaluppi et al. Crit Care 2010

Pathophysiology

CONCLUSION

1) Hemoadsorption may be helpful in sepsis via the direct removal of DAMPS and PAMPS (LPS, cytokines)

2) Thanks to technological improvements, new hemadsorption devices can adsorb leukocytes (monocytes and polynuclear cells +++) and pathogens

3) Hemoadsorption does also act at the cellular level through complex mechanisms
- Modification of leukocyte surface markers
- Modification of leukocyte function
- Modification of other cells (TECs) function

4) Both INNATE and ADAPTIVE immunity seem accessible to modulation via hemoadsorption

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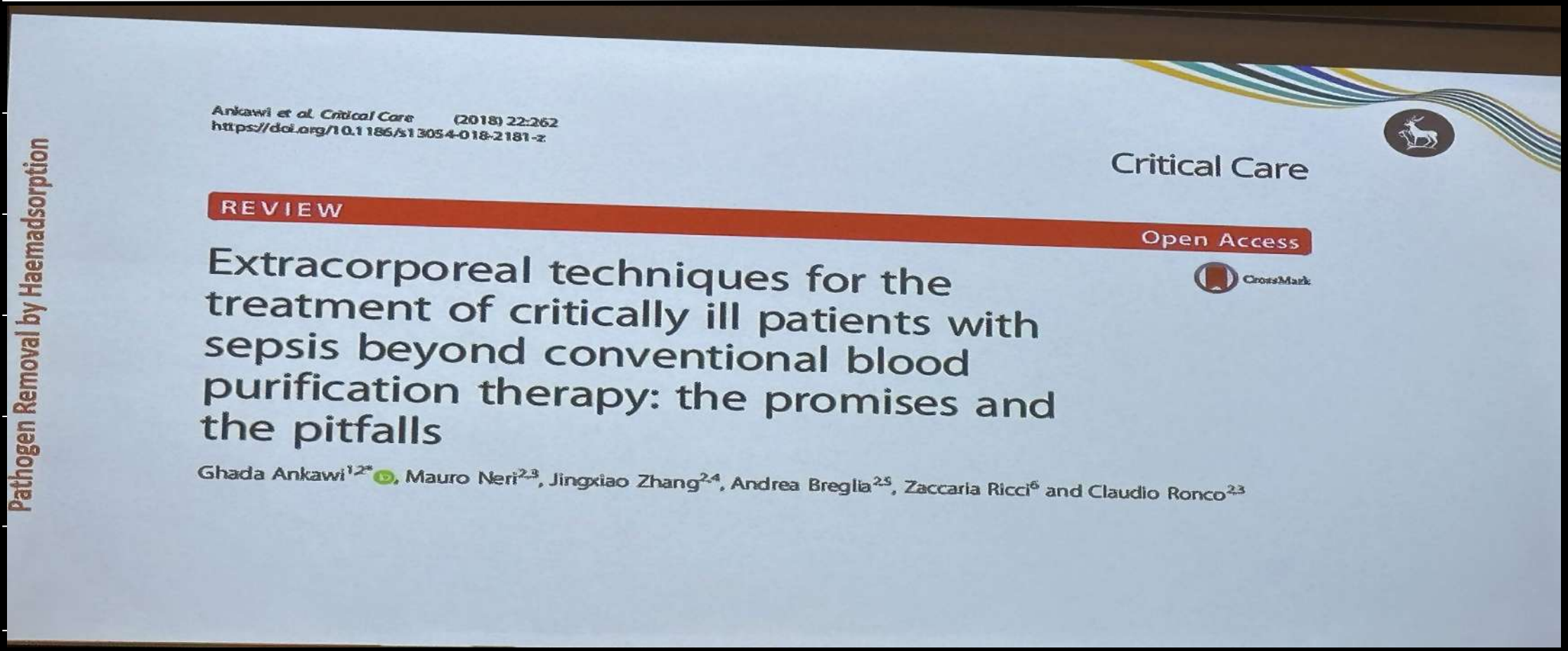
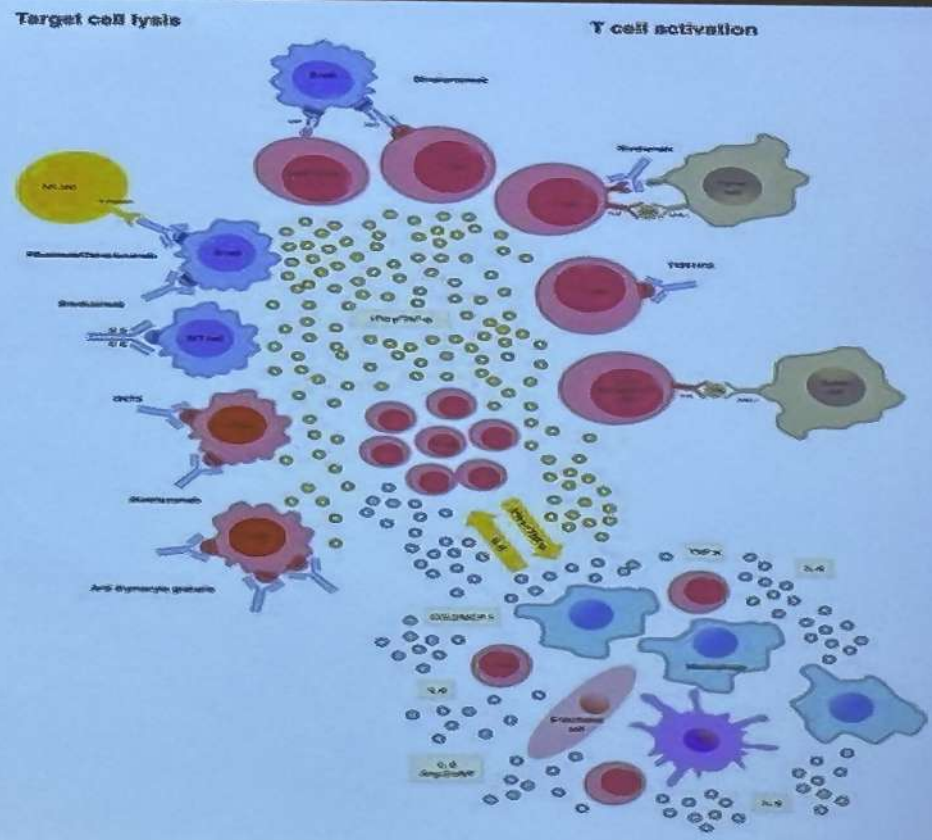
Modality



CRS:
Triggers and Mechanisms

CRS can be induced by direct target cell lysis with consecutive release of cytokines like IFN-γ or TNF-α) or by activation of T cells due to therapeutic stimuli with subsequent cytokine release. These cytokines trigger a chain reaction due to the activation of innate immune cells like macrophages and endothelial cells with further cytokine release.



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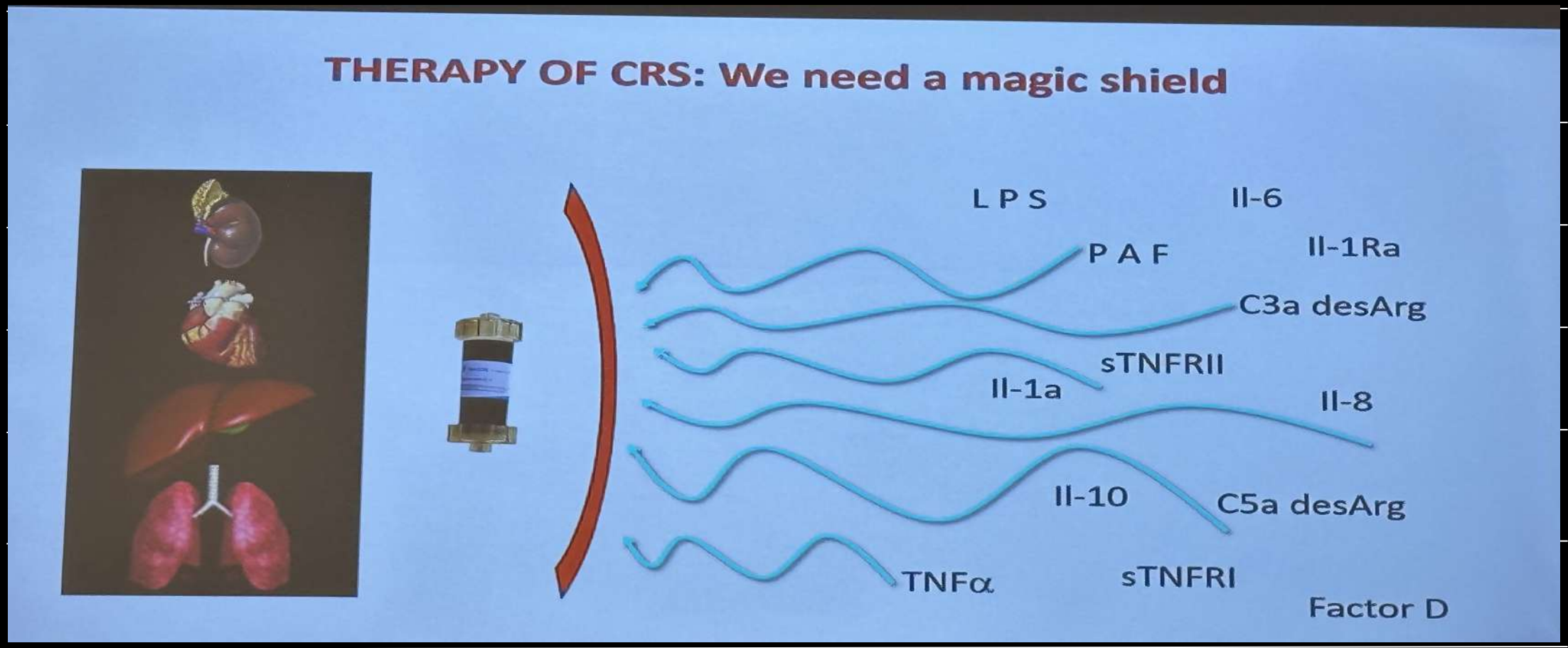
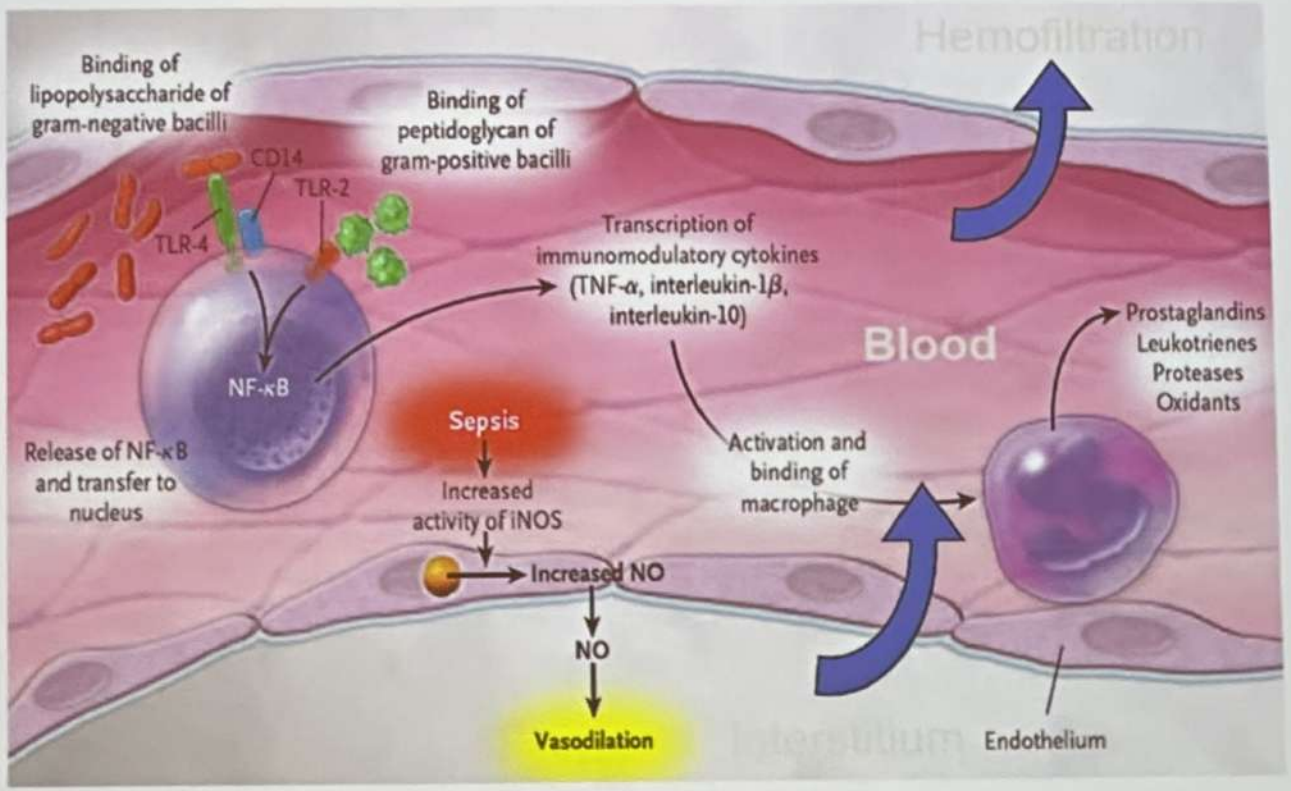
Modality



The "Threshold Immunomodulation" hypothesis



In spite the clinical effectiveness of extracorporeal therapies is likely to be only at the blood level, a possible effect is envisaged at tissue level. The model hypothesizes that mediator removal from blood is coupled to changes in tissues.

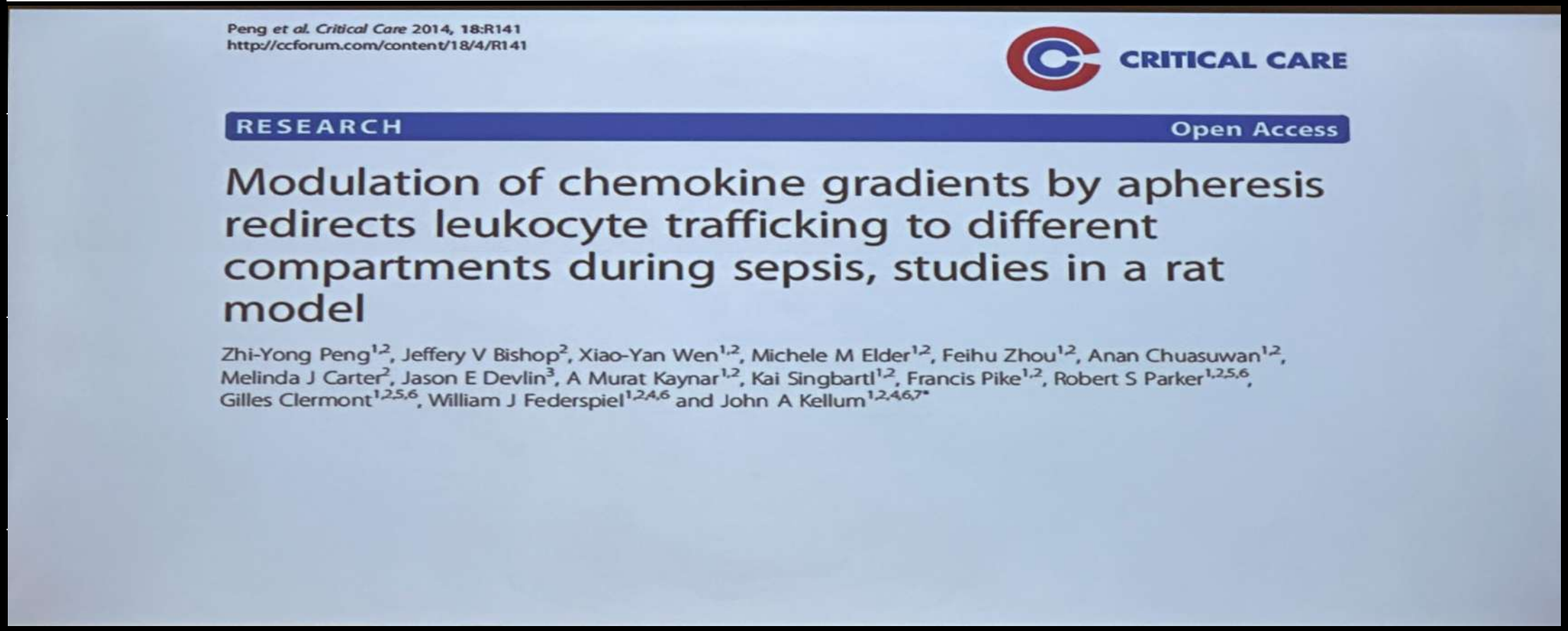
Menu

Modality

Endothelial protection with hemoadsorption

Menu

Modality



Peng et al. Critical Care 2014, 18:R141
http://ccforum.com/content/18/4/R141

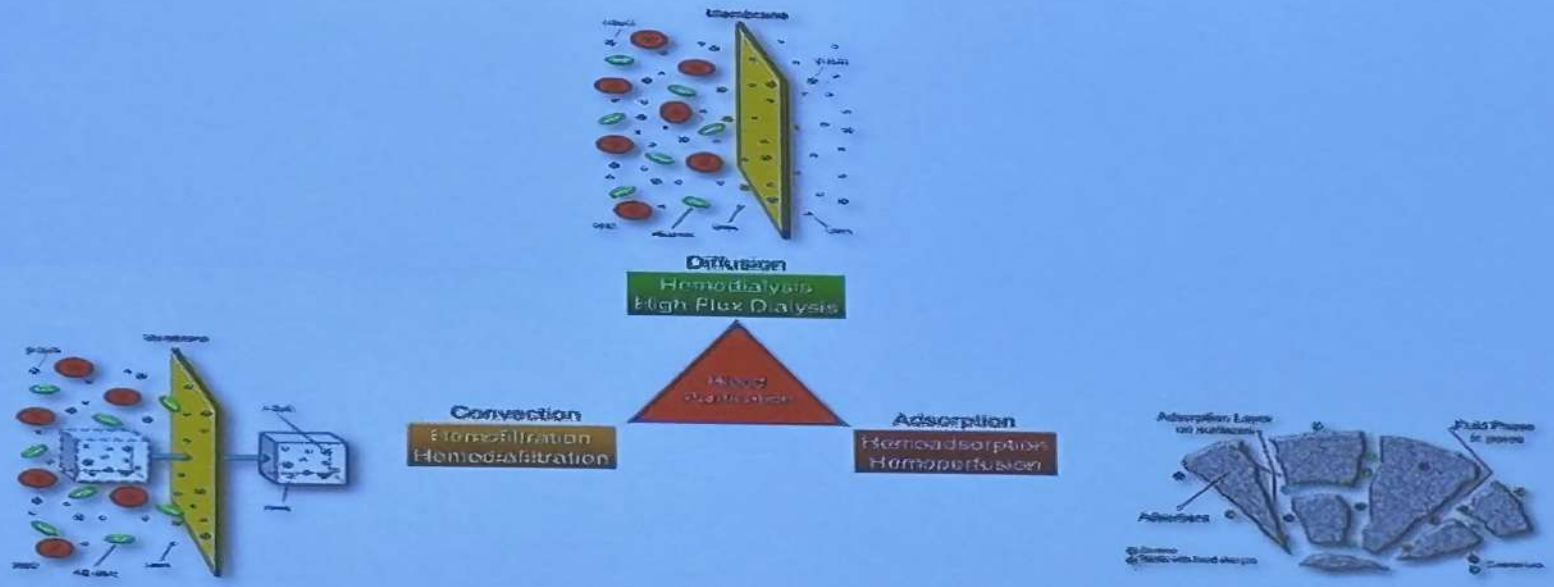
CRITICAL CARE

RESEARCH Open Access

Modulation of chemokine gradients by apheresis redirects leukocyte trafficking to different compartments during sepsis, studies in a rat model

Zhi-Yong Peng[1,2], Jeffery V Bishop[2], Xiao-Yan Wen[1,2], Michele M Elder[1,2], Feihu Zhou[1,2], Anan Chuasuwan[1,2], Melinda J Carter[2], Jason E Devlin[3], A Murat Kaynar[1,2], Kai Singbartl[1,2], Francis Pike[1,2], Robert S Parker[1,2,5,6], Gilles Clermont[1,2,5,6], William J Federspiel[1,2,4,6] and John A Kellum[1,2,4,6,7*]

Mass Separation Process

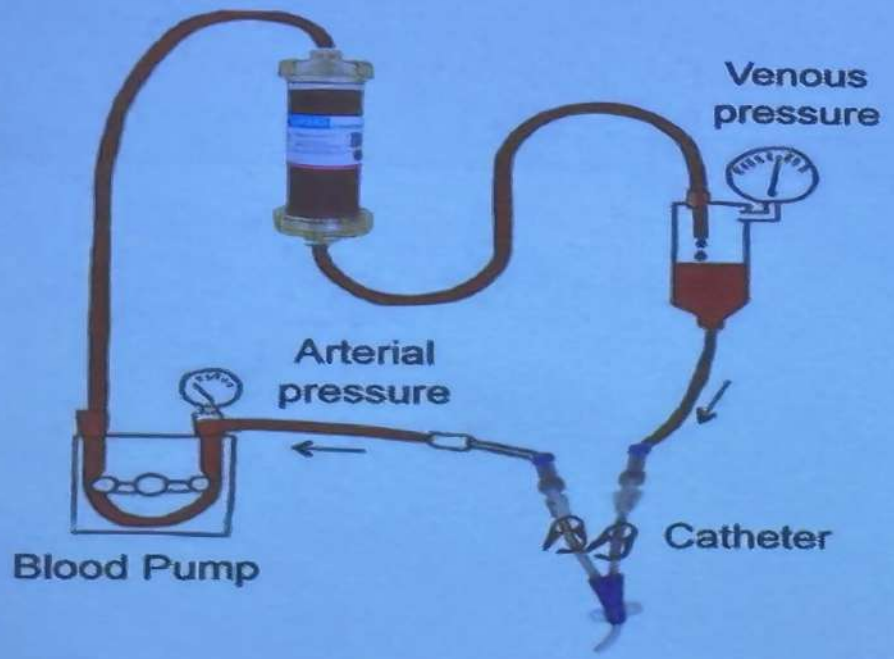


a) **Separation by barrier** (CRRT: CVVH-CVVHD-CVVHDF)

b) **Separation by solid agent** (Hemoadsorption)

Modality

HEMOADSORPTION



Advantages and Rationale

- Overcoming limitations of HD membranes
- Potential selectivity of the removal
- Placement of sorbent in contact with blood
- No alteration of anticoagulation regime
- No problems of circuit pressure profile

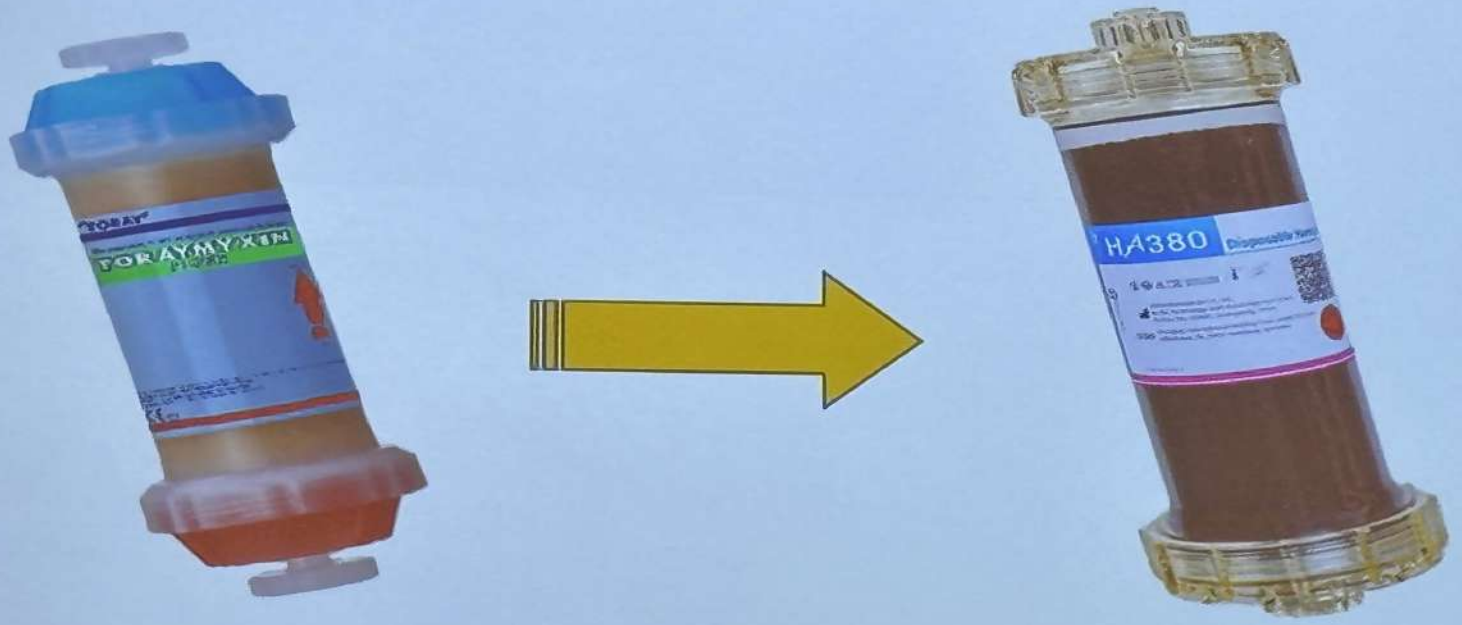
Requirements

- Demonstrated effectiveness
  Hemocompatibility
- Mechanical strength
- No fouling or clotting activation
- Well designed cartridge

Menu

Modality

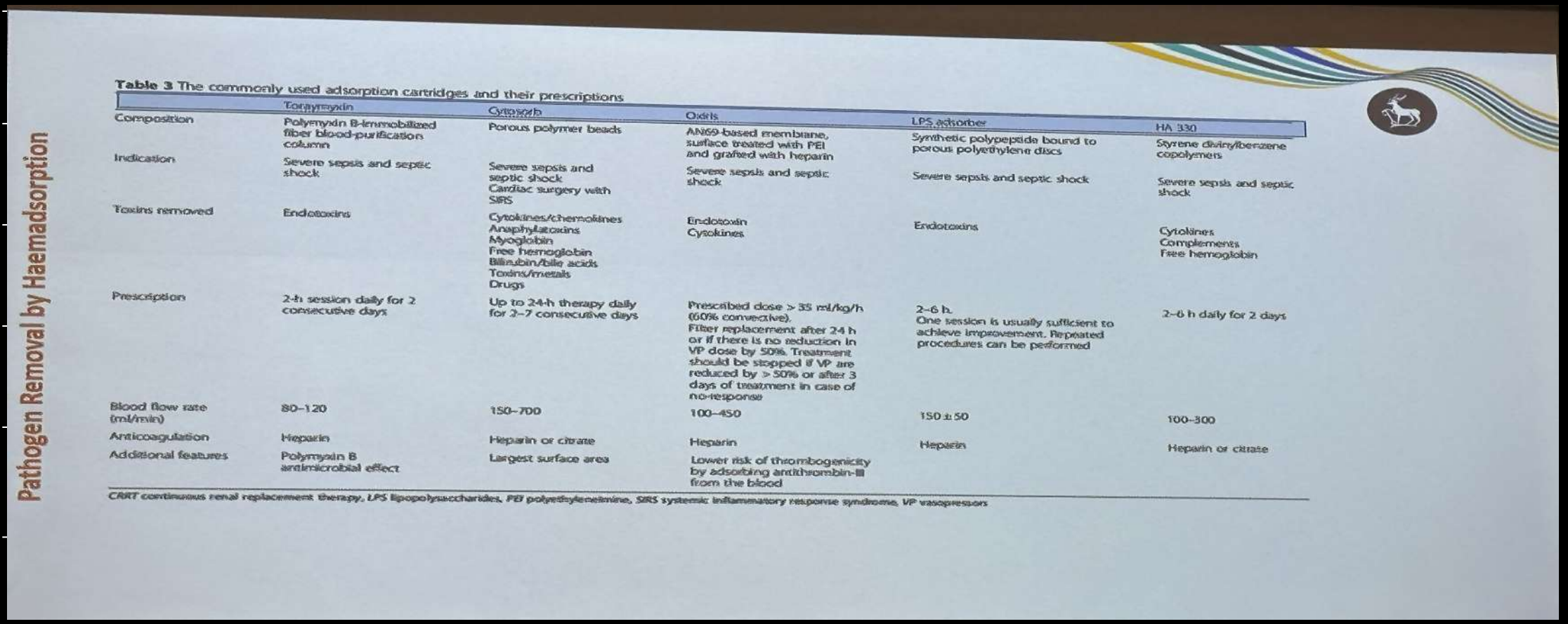
From Endotoxin to Cytokine adsorption



- ✓ Indicated for critical conditions such as CRS, sepsis, trauma, burns, pancreatitis, cardiac surgery.
- ✓ Biocompatible, Neutral macro- porous polymer bead.
- ✓ Adsorb cytokines in the ~ 10–60 kDa range.

Menu

Modality



Pathogen Removal by Haemadsorption

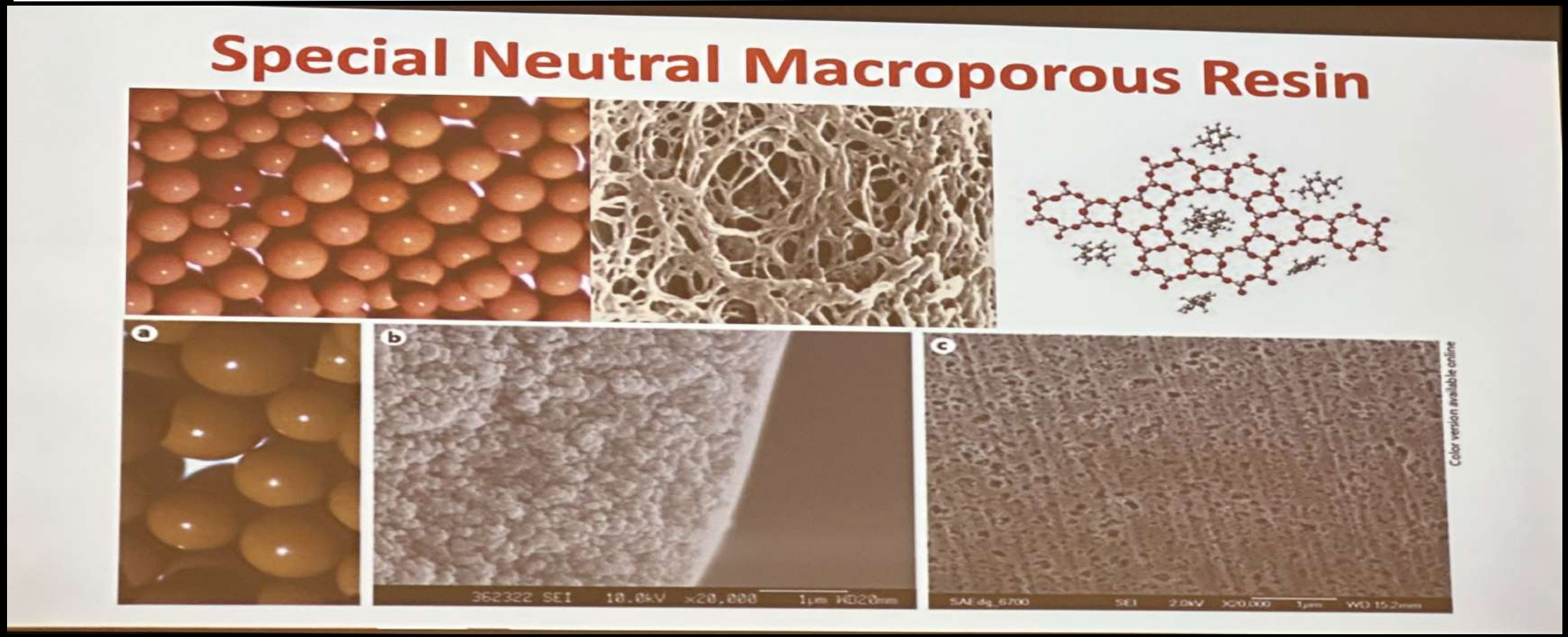
Table 3 The commonly used adsorption cartridges and their prescriptions

	Toraymyxin	Cytosorb	Oxiris	LPS adsorber	HA 330
Composition	Polymyxin B-immobilized fiber blood-purification column	Porous polymer beads	AN69-based membrane, surface treated with PEI and grafted with heparin	Synthetic polypeptide bound to porous polyethylene discs	Styrene divinylbenzene copolymers
Indication	Severe sepsis and sepsc shock	Severe sepsis and septic shock Cardiac surgery with SIRS	Severe sepsis and septic shock	Severe sepsis and septic shock	Severe sepsis and septic shock
Toxins removed	Endotoxins	Cytokines/chemokines Anaphylatoxins Myoglobin Free hemoglobin Bilirubin/bile acids Toxins/metals Drugs	Endotoxin Cytokines	Endotoxins	Cytokines Complements Free hemoglobin
Prescription	2-h session daily for 2 consecutive days	Up to 24-h therapy daily for 2–7 consecutive days	Prescribed dose > 35 ml/kg/h (60% convective). Filter replacement after 24 h or if there is no reduction in VP dose by 50%. Treatment should be stopped if VP are reduced by > 50% or after 3 days of treatment in case of no-response	2–6 h. One session is usually sufficient to achieve improvement. Repeated procedures can be performed	2–6 h daily for 2 days
Blood flow rate (ml/min)	80–120	150–700	100–450	150 ± 50	100–300
Anticoagulation	Heparin	Heparin or citrate	Heparin	Heparin	Heparin or citrate
Additional features	Polymyxin B antimicrobial effect	Largest surface area	Lower risk of thrombogenicity by adsorbing antithrombin-III from the blood		

CRRT continuous renal replacement therapy, *LPS* lipopolysaccharides, *PEI* polyethyleneimine, *SIRS* systemic inflammatory response syndrome, *VP* vasopressors

Menu

Modality



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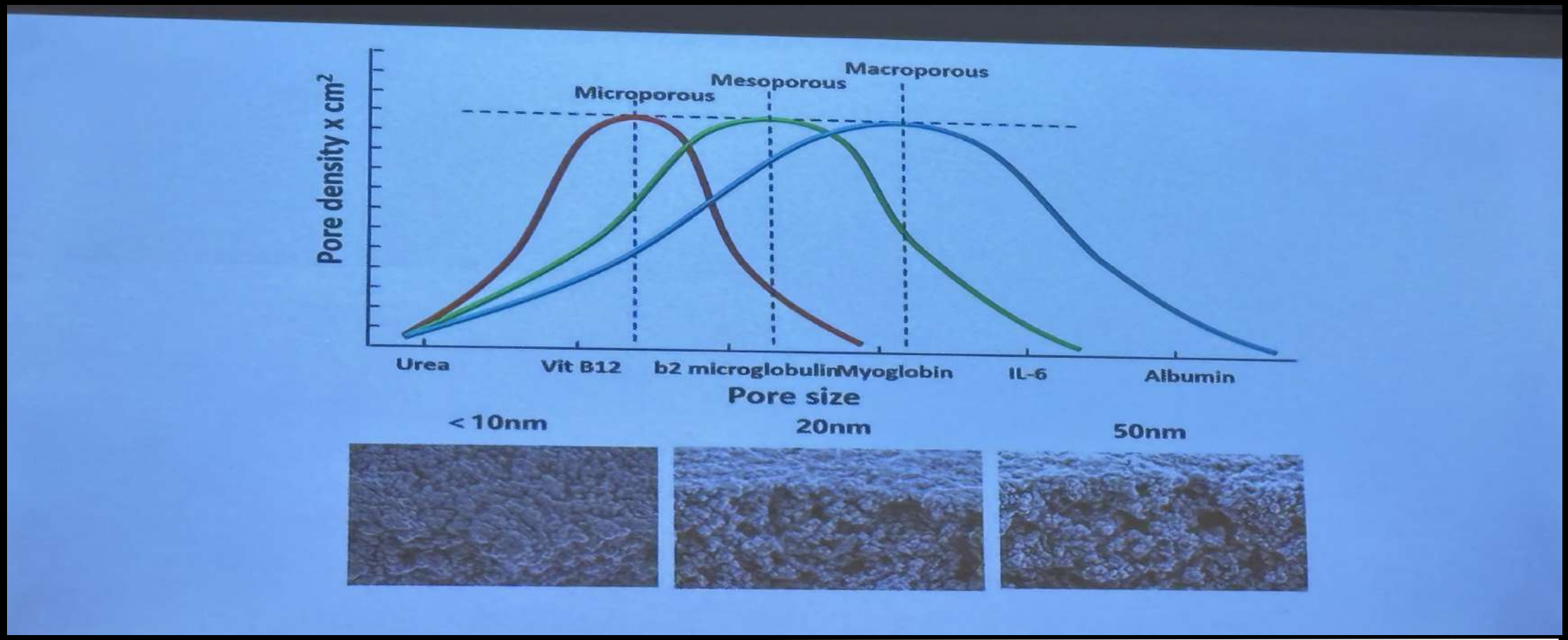
Modality



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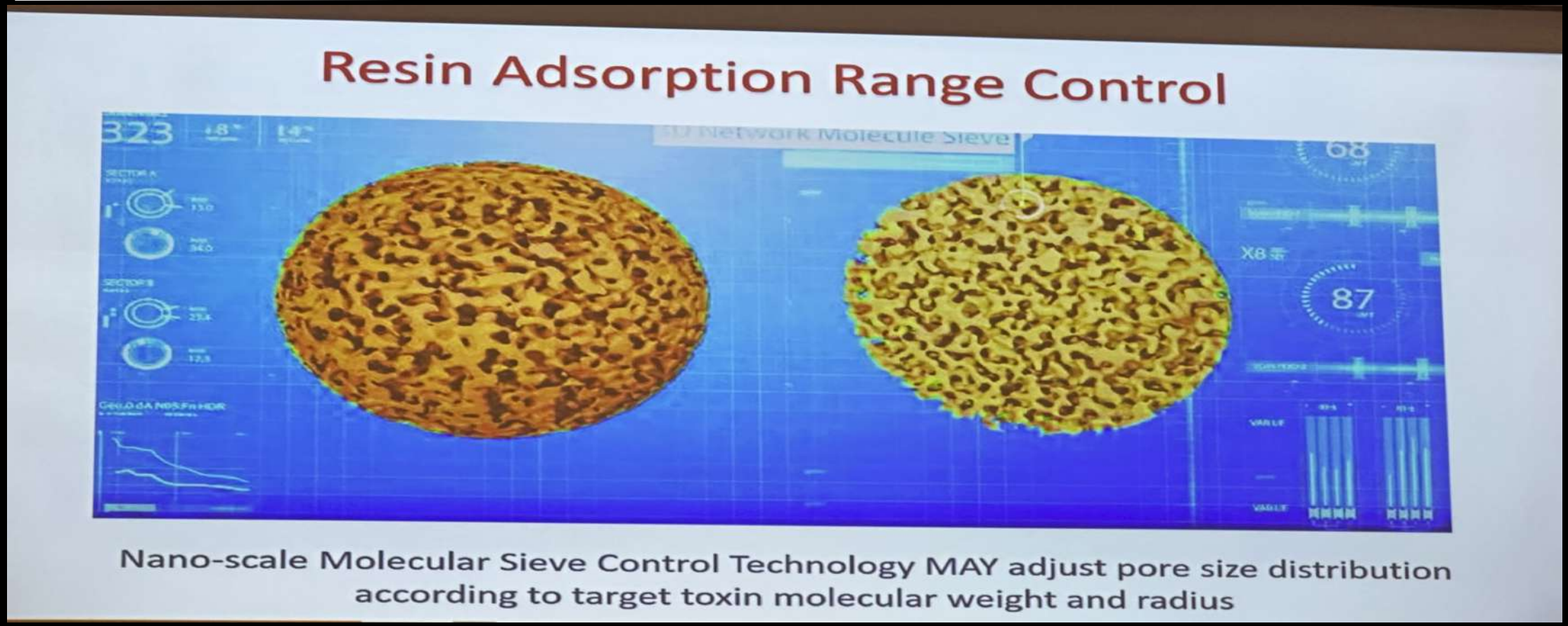
Modality



So Do We Need Pathogen Removal Techniques?

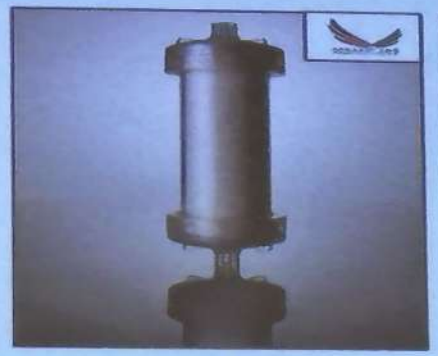
Menu

Modality

A Different Approach?

Pathogen Removal by Haemadsorption

4 ± 1 hr. Tx Time
5 min. Setup Time
100-350 ml/min Q_b
40 m^2 Surface Area
~300 µm Bead Dia.
160 ml Volume
Ø7.6 x 23 cm Size
3 yr. shelf life



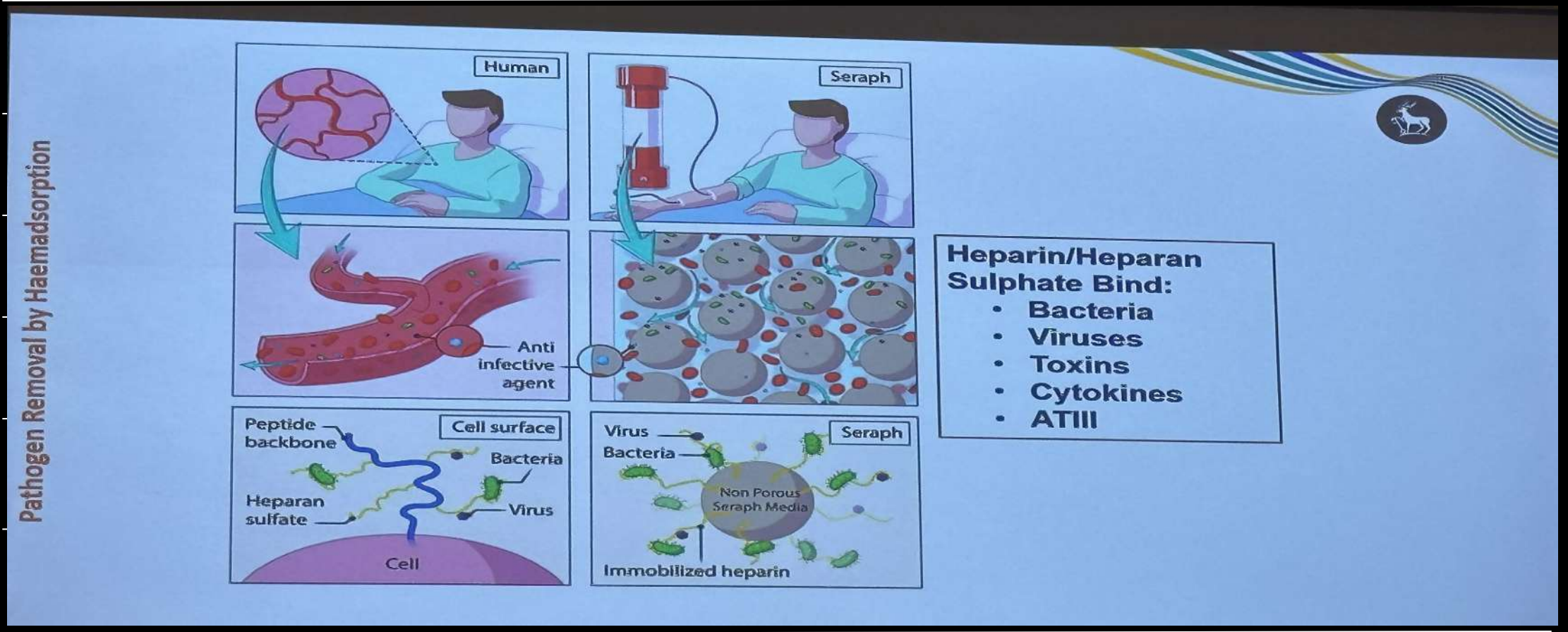
Hemopurification Differentiators

- Broad-spectrum pathogen binding capability of proprietary end-point attached heparin[7]
  - Gram-negative and gram-positive bacteria as well as viruses demonstrated in-vitro[7]
- Only product commercially available with the indication: *Bloodstream pathogen reduction*[6]
  - Early initiation feasible prior to pathogen identification
- Endpoint attached heparin is anti-thrombogenic and anti-inflammatory[8]
- Minimal adsorption of antibiotics[9]
- Compatible with most RRT/hemoperfusion machines
  - Used concurrently in RRT or stand-alone
- Safety profile consistent with standard extracorporeal labelling[6]

CE **EU Indication – "*Seraph 100 is indicated for the reduction of pathogens from the bloodstream in adjunction to antibiotic treatment during BSI (blood-stream infections).*[6]"**

Menu

Modality



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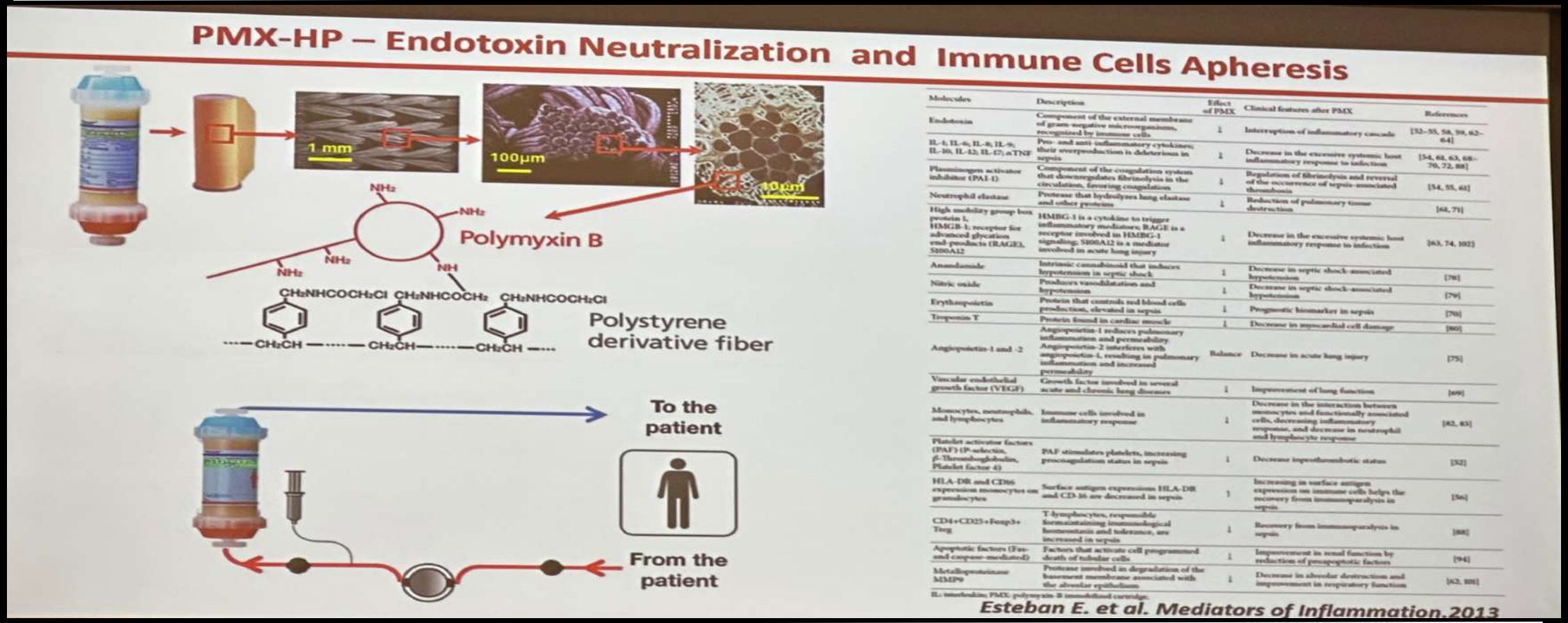
Modality



Modality

Pmx-HP: Extracorporeal removal of endotoxin

In Vitro

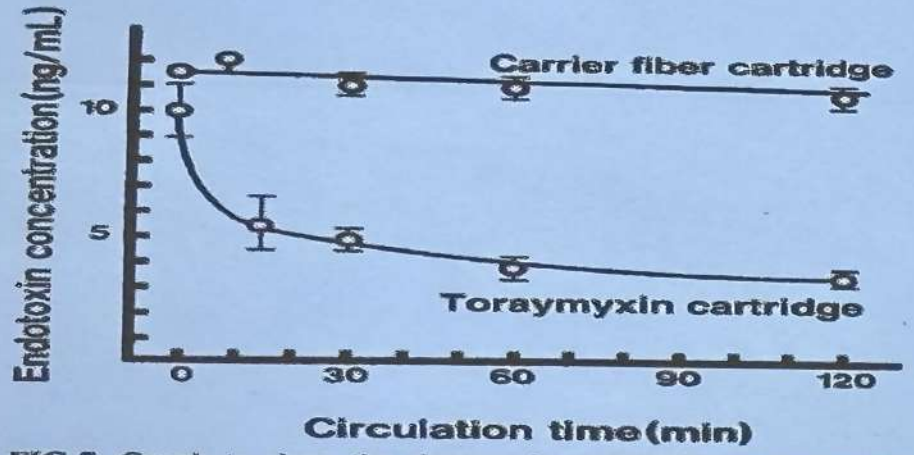
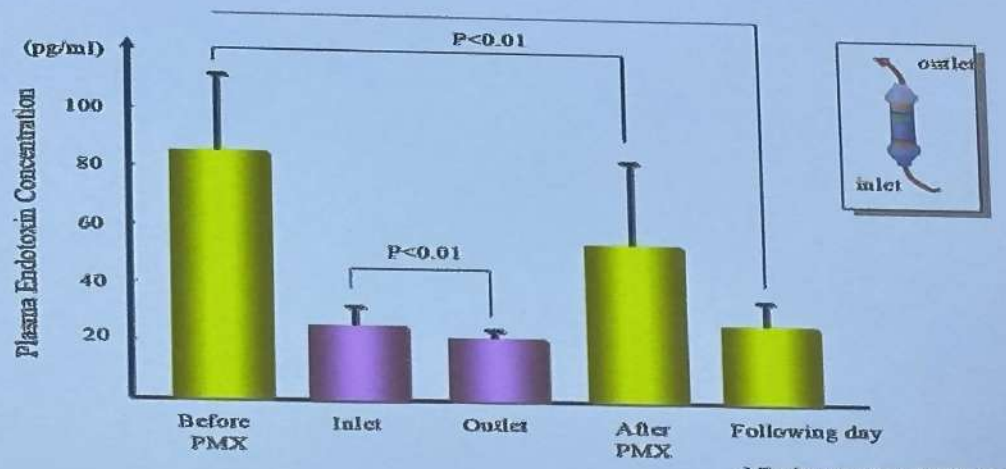


FIG. 7. Graph to show the changes in endotoxin concentration with a carrier fiber cartridge and a PMX cartridge over 2 h.

In Vivo

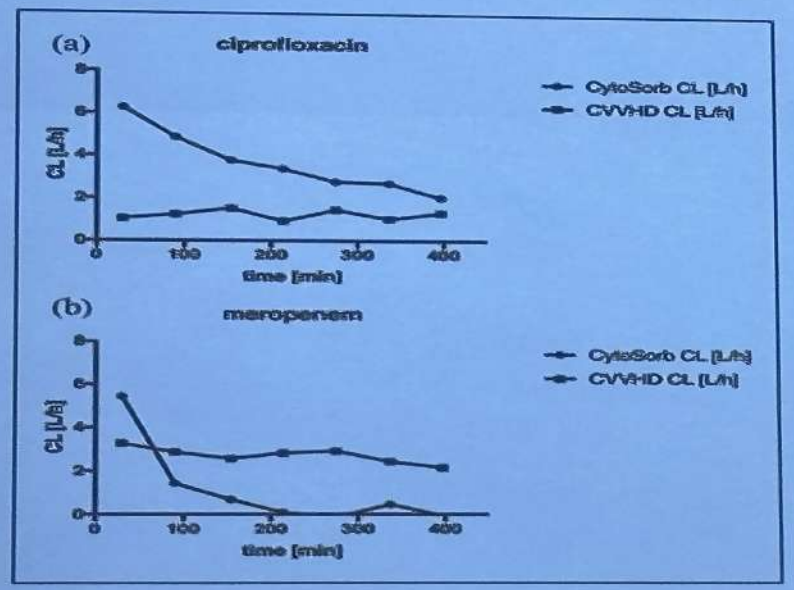


J Endotoxin Res 1997; 4: 293-30

Menu

Modality

Clearance in Reconstituted Blood



- High initial clearance
- Decrease over time

Authors concluded that:

- all study drugs were adsorbed by the cartridge in relevant amount
- Administration of additional doses should be considered

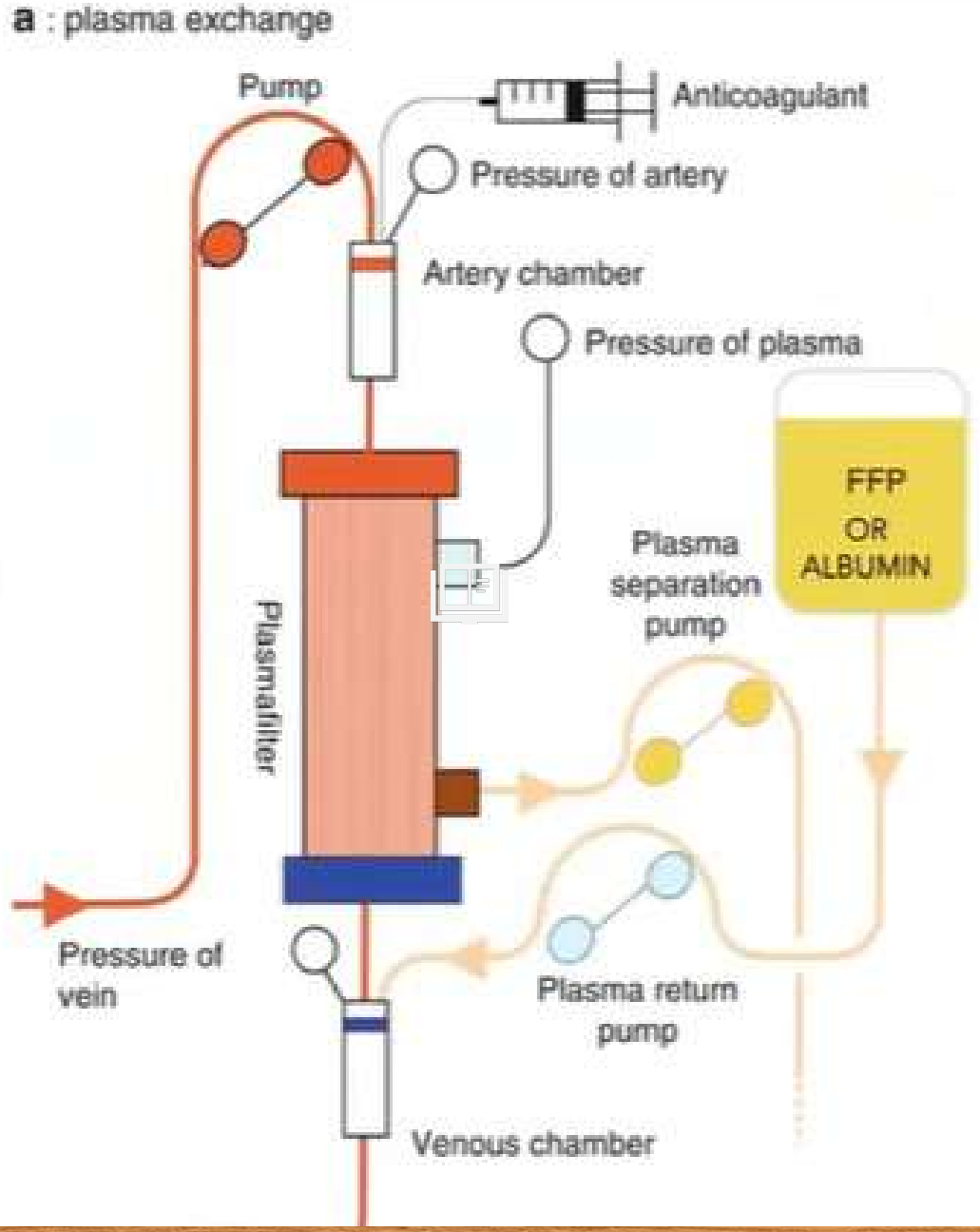
König et al IJAO 2019 Vol 42(2) 57-64

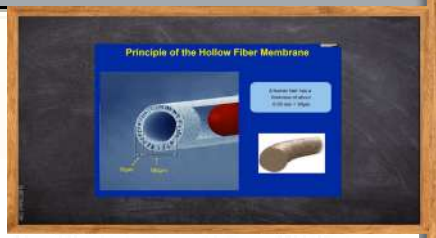
Modality

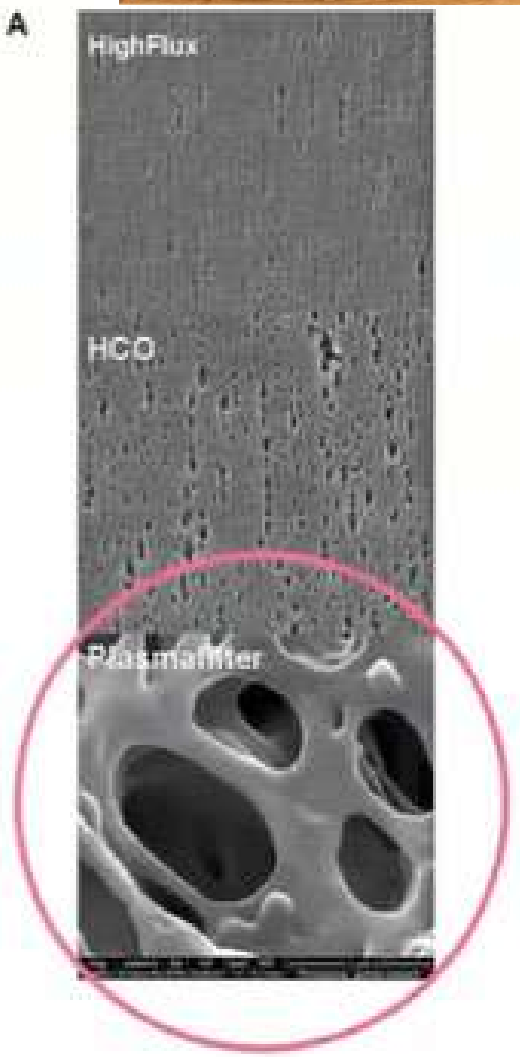
Anti-infectives Clearance by Hemoadsorption: In Vitro Data

- In vitro data provide important insights into adsorption's ability to remove drugs
- However, it might not be directly translatable in vivo
  - Volume of distribution
  - Protein level / protein binding

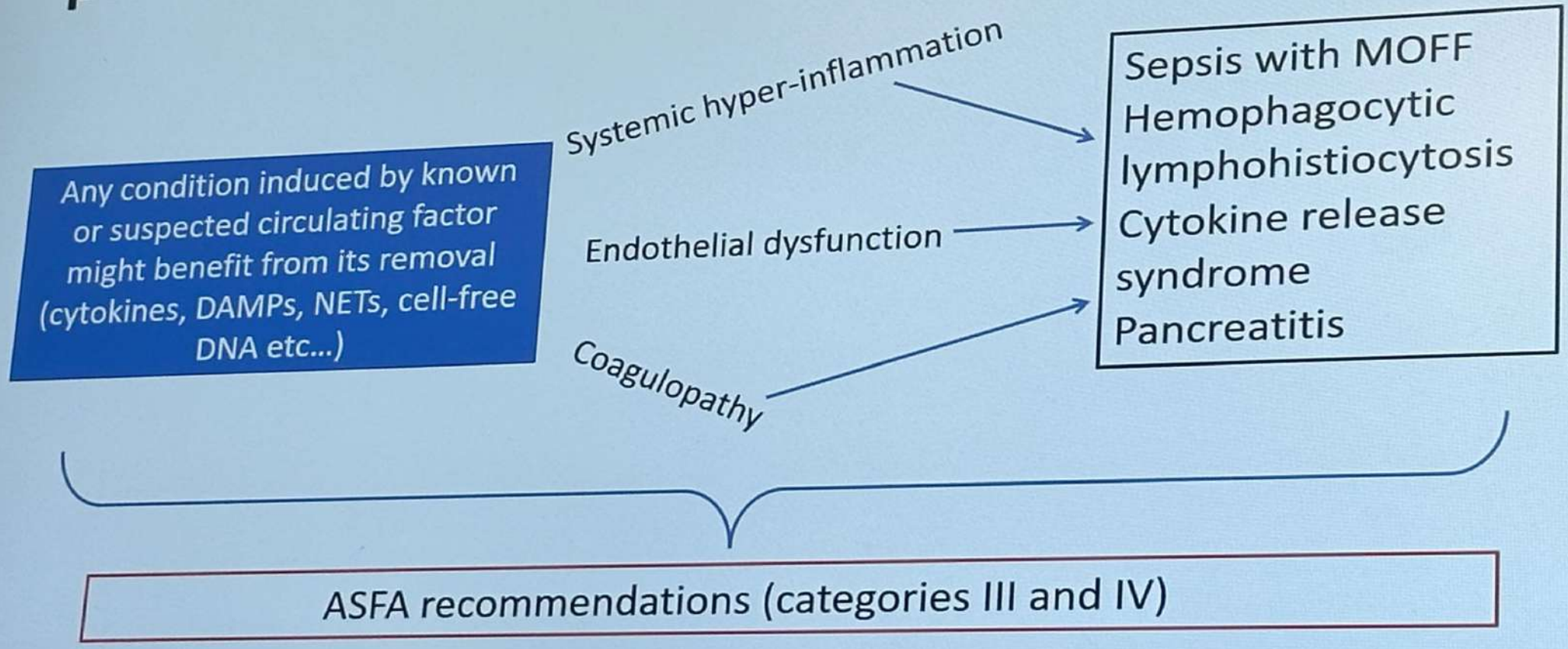
THERAPEUTIC PLASMA EXCHANGE







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



TPE in septic conditions

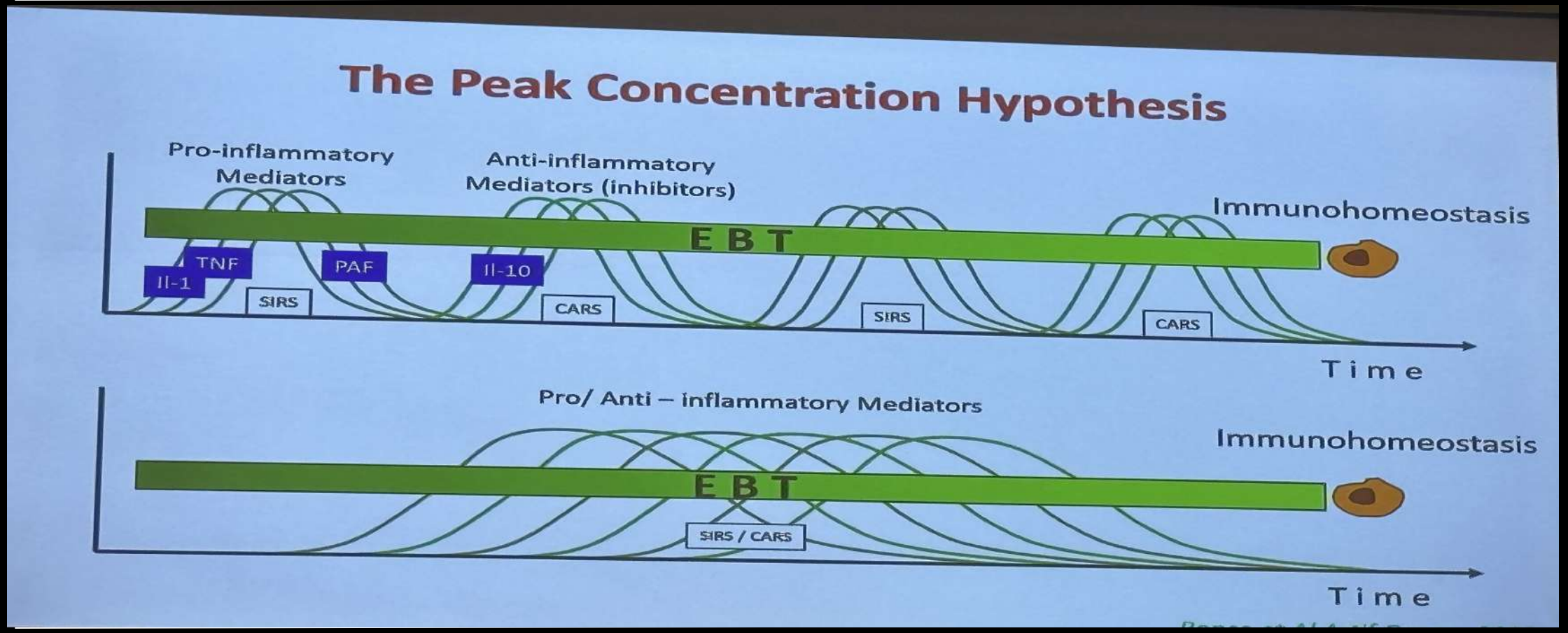
- The theoretical rationale for TPE goes beyond the simple elimination of circulating injurious molecules.

- 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).

Menu

Clinical Approach



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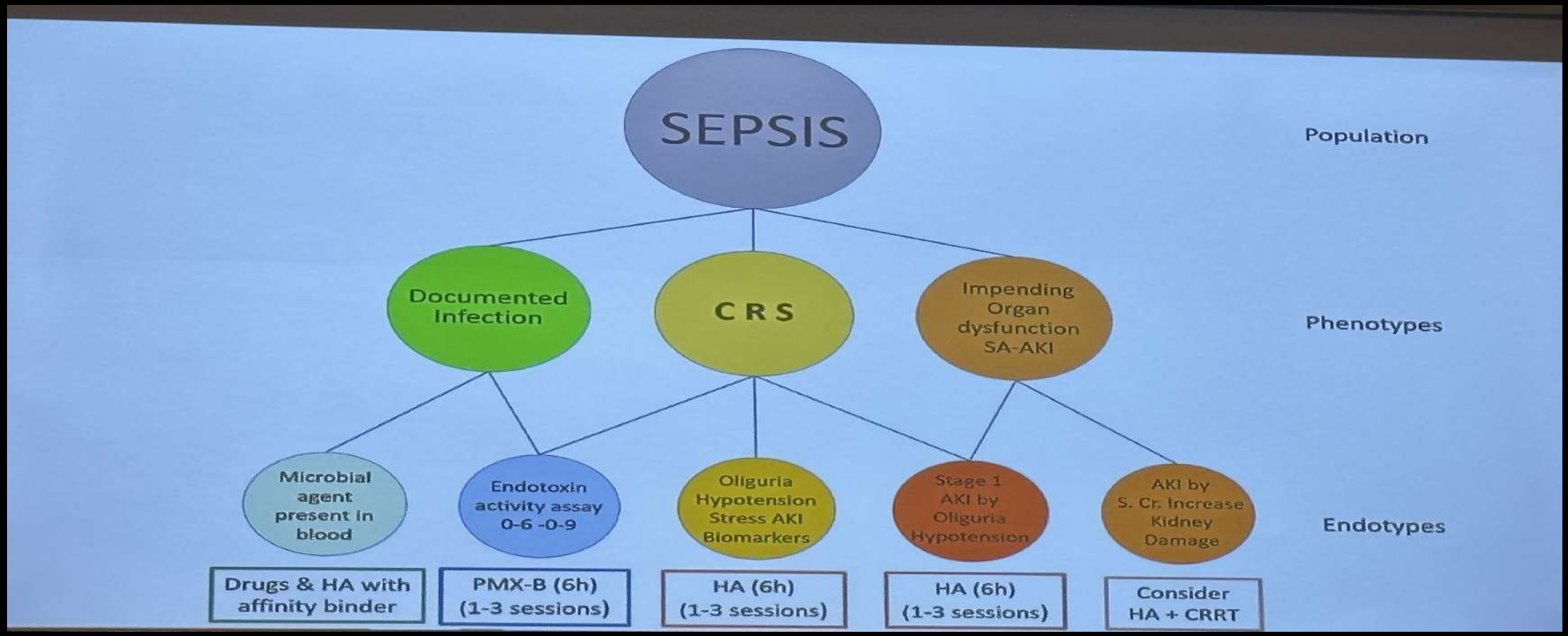
Clinical Approach



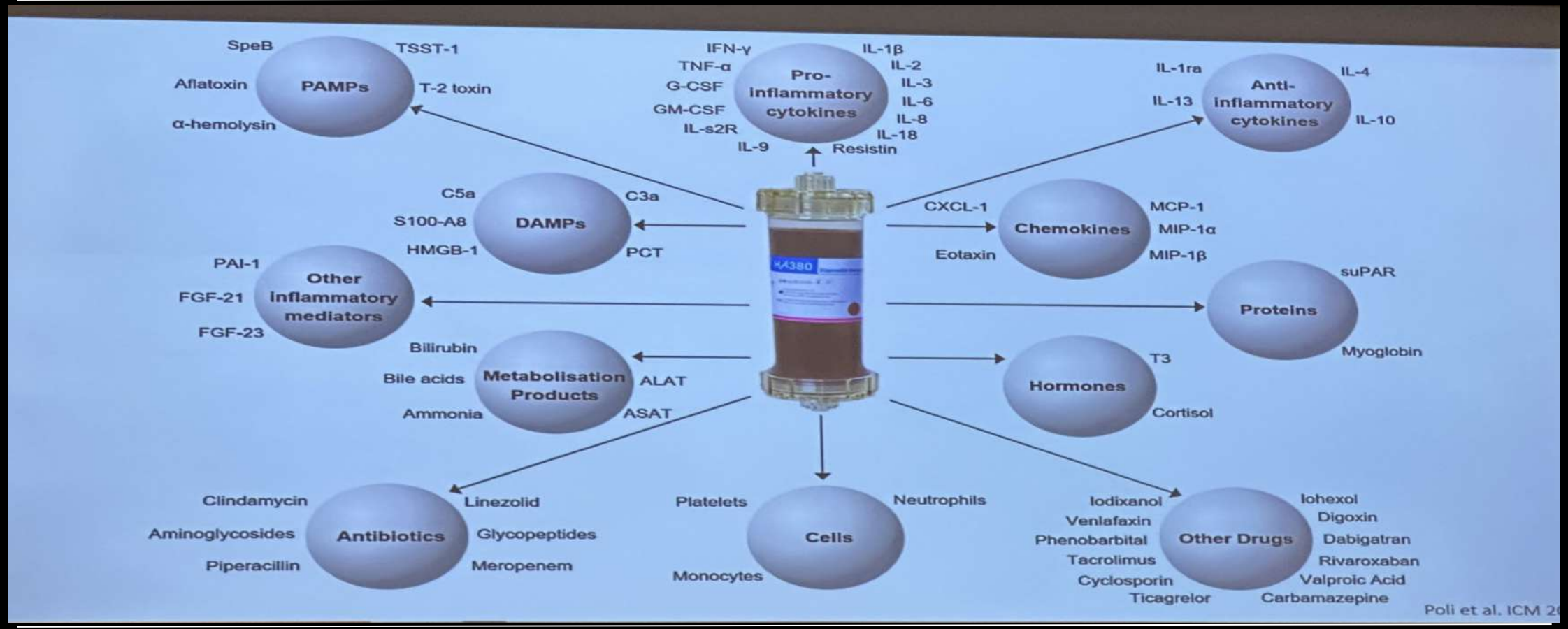
Clinical Approach

Conclusions

- Sepsis requires a time-sensitive approach
- Endotoxin and Cytokines represent possible target molecules for preventive and protective treatment
- Studies should evaluate criteria for indication and initiation, duration of treatment, clinical and biological endpoints for efficacy measurement.
- We need tp identify patients who possibly benefit from the treatment and prescription must be made in specific patients, early, monitoring inflammation parameters and organ function.

Menu

Clinical Approach



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Clinical Approach

The next pandemic: not if, but when

Illustration: Julian Rentzsch / DER SPIEGEL

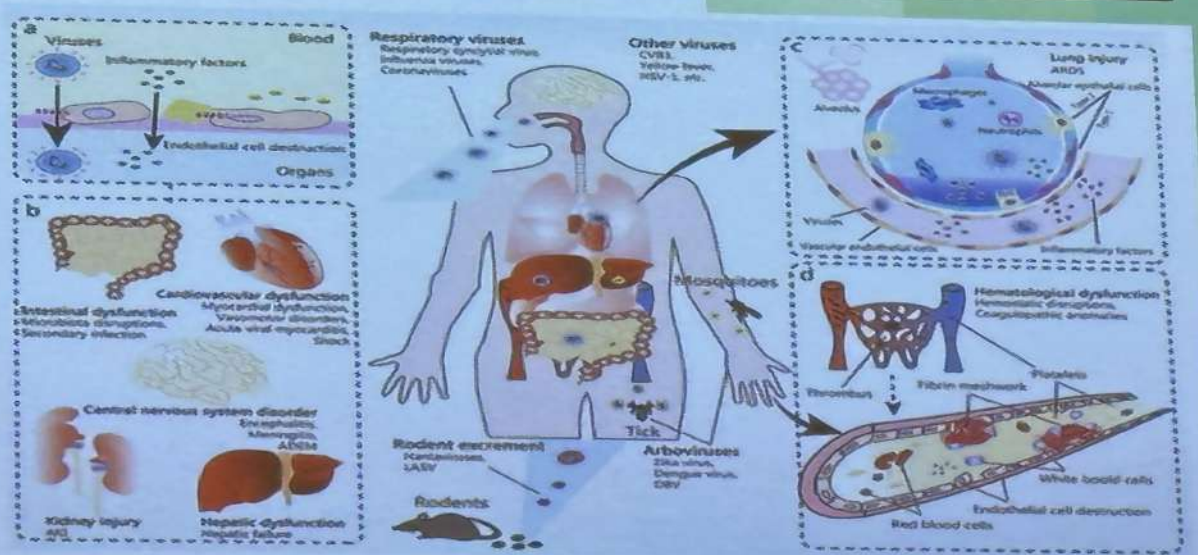
www.pbs.org/newshour/health/analysis-monitoring-disease-hot-spots-could-prevent-the-next-pandemic

4

Clinical Approach

Viral sepsis pathogenesis and targeted organ vulnerability

- predominantly respiratory and vector-borne viruses
- targeted cellular infection and waekening of endothelial barrier
- migration to bloodstream
- Induction of
  - coagulation disorders
  - hemorrhagic fever
  - extensive organ damage
- *Cytotoxic effects and host immune defense increase the for MOD*



Xu JQ et al. Military Medical Research (2024)11:78

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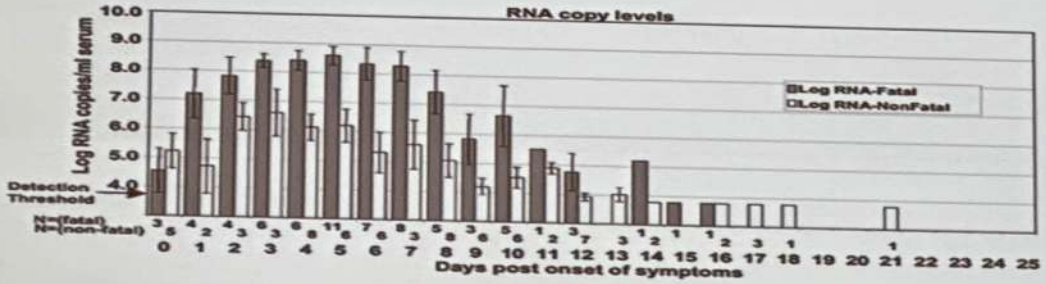
Clinical Approach

Viral Load - *predictor of outcome*



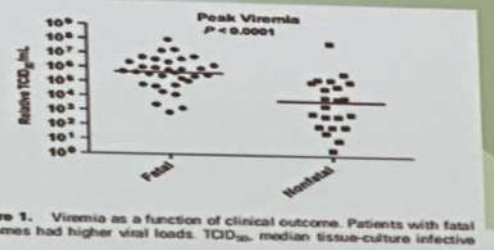


Figure 1. Viremia as a function of clinical outcome. Patients with fatal outcomes had higher viral loads. $TCID_{50}$, median tissue-culture infective dose.

Table 2. Correlation of viral load with disease severity and outcomes

Virus	Viral load correlation	Clinical benefit/ market clearance
Dengue	lethality correlates with high viral load	yes
Ebola	lethality correlates with high viral load	yes
Hepatitis C	pegylated IFN + ribavirin treatment	yes/yes
	disease severity and treatment response correlates with viral load	yes
Herpes	antiherpetic drugs	yes/yes
HIV	drug cocktails	yes/yes
	long-term nonresponders (<1,000 cpm) and 'elite controllers'	yes
Influenza A	Tamiflu	yes/yes
Marburg	plasmapheresis	yes (1 patient)
Sin Nombre	lethality correlates with high viral load	yes

Towner et al. J. Virol. 2004;78:4330-4341; McElroy; J Infect Dis. 2014; Tullis RH et al. Blood Purif 2009;27(1):64-9

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Menu

Clinical Approach

Extracorporeal Virus Elimination – *Technique*

Seraph® 100

Hemopurifier®

Garnet™

11

Clinical Approach

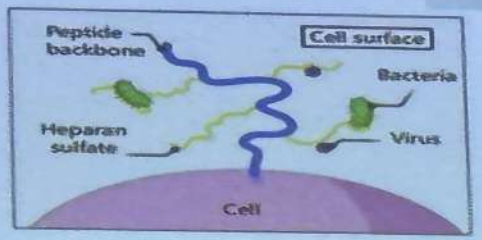
SERAPH® 100 Microbind® Affinity Blood Filter

Ultra-high molecular weight polyethylen beads containing end-point attached heparin on the surface

- mimics heparan sulfate receptors

Captures both bacteria and viruses

First licensed device in the EU



Seffer MT et al. PLOS One, 2023;18(3):1-14; Seffer MT et al. Blood Purif. 2021;50(1):28-34

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Clinical Approach

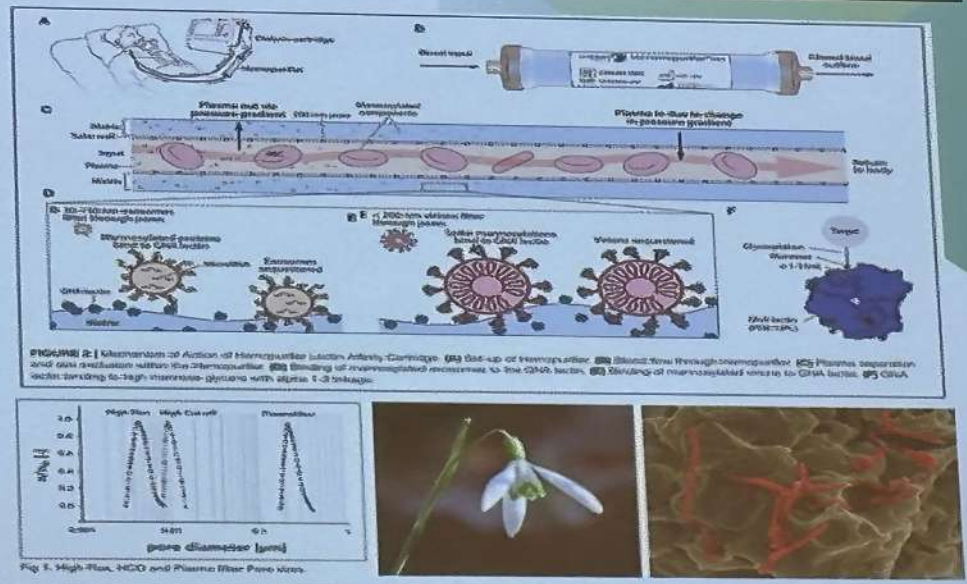
Hemopurifier®

fundamentally a plasmafilter

- Plasma seperation with virus and glycoprotein capture by Galantus nivalis agglutinin (lectin, GNA) in the extracapillary space

Lectin protein derived from the common snowdrop

Enveloped viruses and soluble gylocoproteins



Amundson DE et al. Front Med (Lausanne). 2021 Oct 8;8:744141

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Clinical Approach

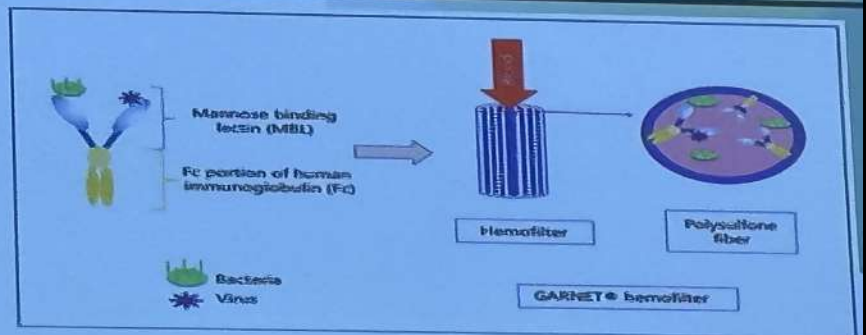
Garnet™

Inner surface of polysulfon fibres coated with engineered Mannose-binding lectin (MBL) fused with the Fc protion of a human immunglobulin

- FcMBL allows direct binidng of pathogens and PAMP

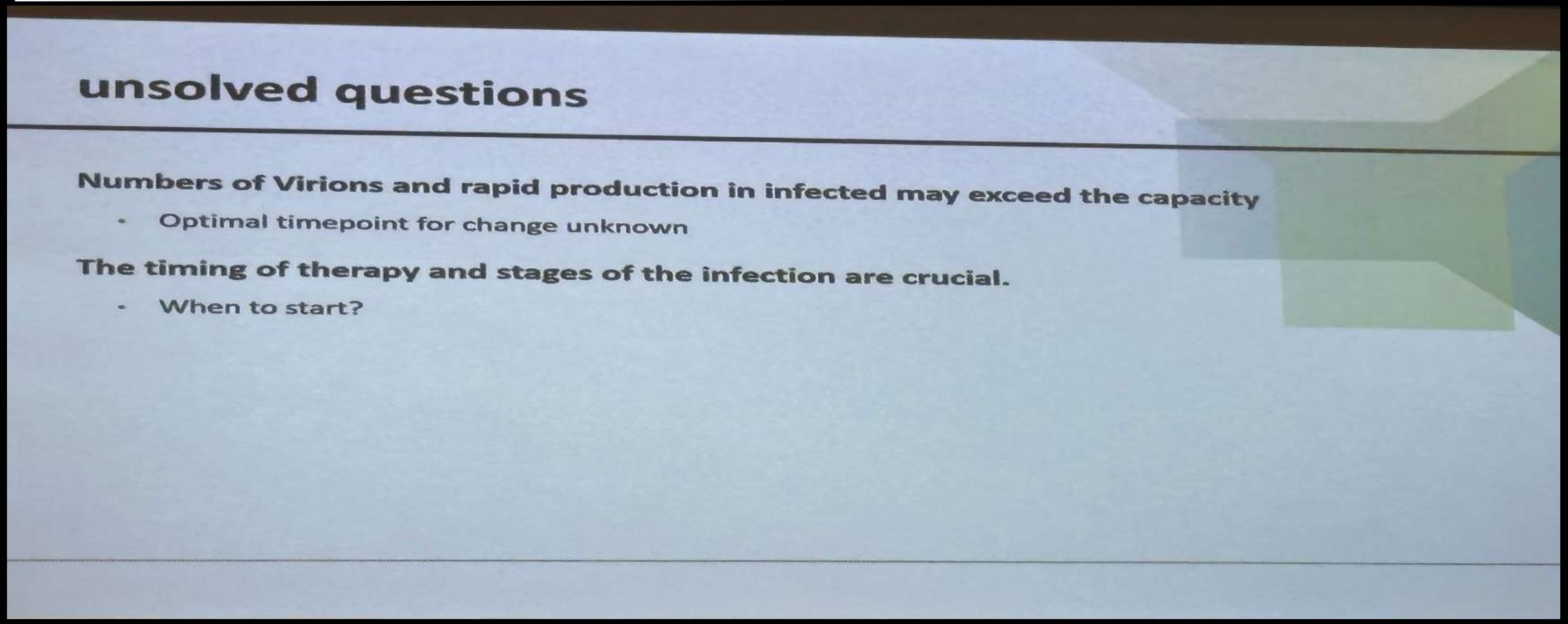
Specifically targets mannose

Under evaluation



Monard C et Blood Purif 2023;52:1-7; aL wyss.harvard.edu/technology/fcmbl-broad-spectrum-pathogen-capture-for-infectious-diseases/

Clinical Approach

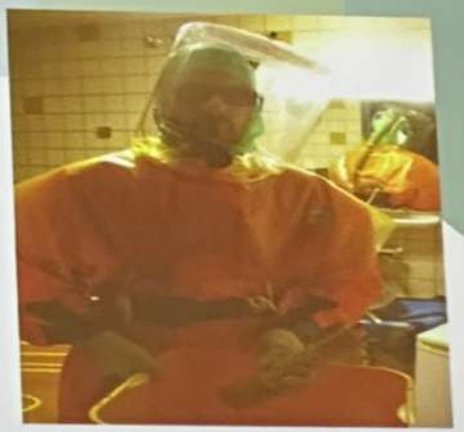


Menu

Clinical Approach

Conclusion

- In the absence of proven therapies, extracorporeal virus elimination holds promise as a potential option for managing deadly viral diseases.
- Treatment is well tolerated and feasable,
- The complexity of viral multiplication highlights the need for further exploration to thus enhance the effectiveness of these techniques




OUR GOAL
ZERO
DEFECTS

Quality

- Smart Goals
  - Specific
  - Measurable
  - Attainable
  - Relevant
  - Time based

Thank you!

Do you have any questions?

giannisgriv@hotmail.com
www.athens-nephrology.gr

Menu

Menu

This is the title for section A

The next pandemic: not if, but when

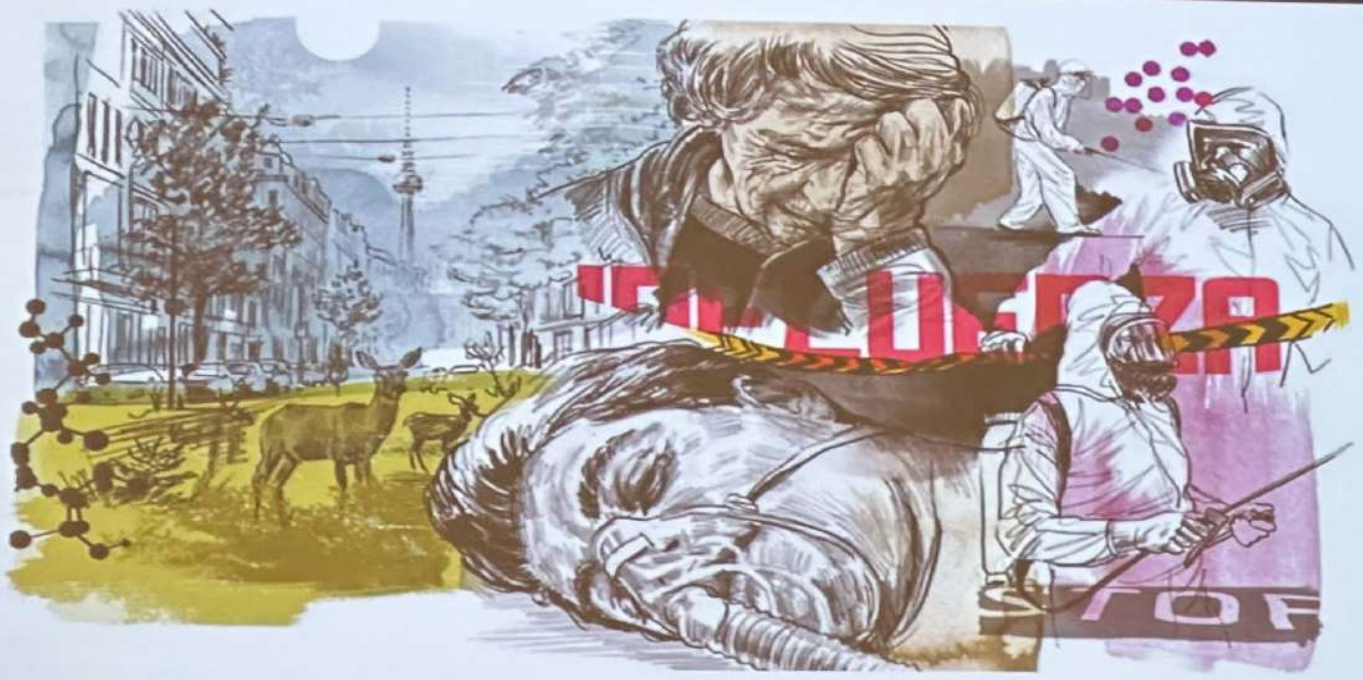
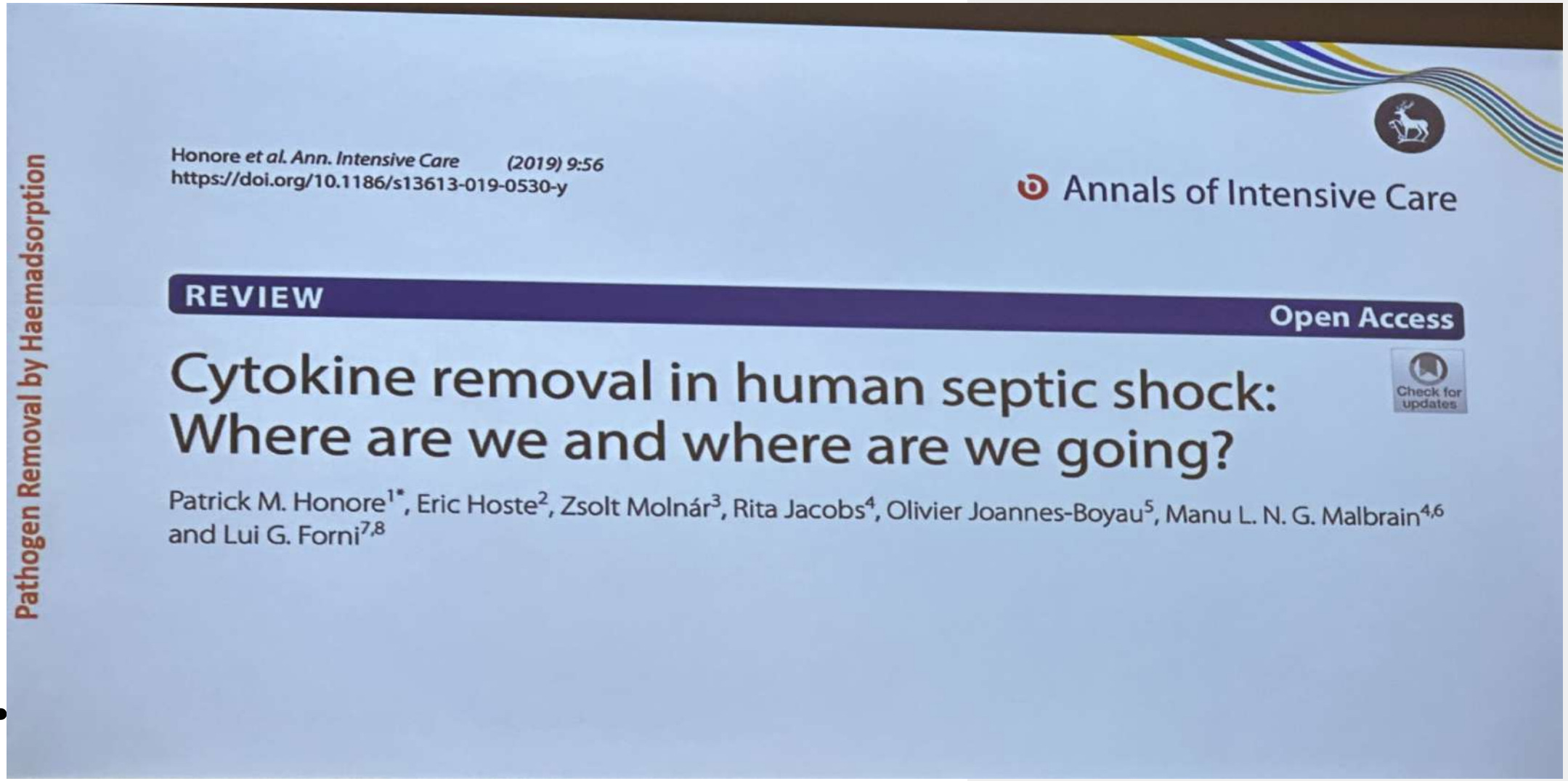


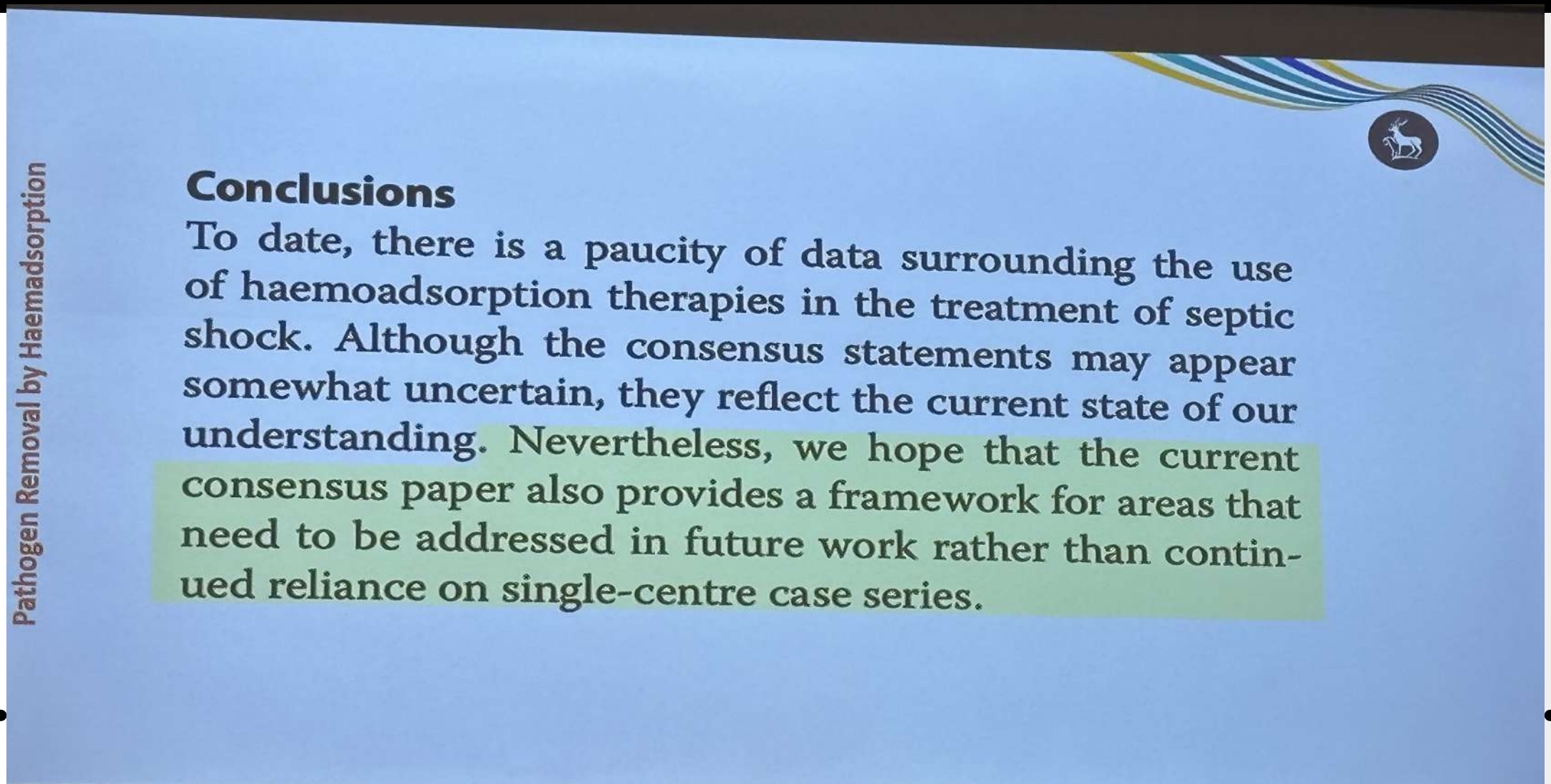
Illustration: Julian Rentzsch / DER SPIEGEL

www.pbs.org/newshour/health/analysis-monitoring-disease-hot-spots-could-prevent-the-next-pandemic

This is the title for section A



This is the title for section A



Conclusions

To date, there is a paucity of data surrounding the use of haemoadsorption therapies in the treatment of septic shock. Although the consensus statements may appear somewhat uncertain, they reflect the current state of our understanding. Nevertheless, we hope that the current consensus paper also provides a framework for areas that need to be addressed in future work rather than continued reliance on single-centre case series.

Now what...

Conclusions

- While the evidence on mortality remains inconclusive, EBP remains a promising tool to support organ function and interact with the pathophysiologic mechanisms underlying multiple organ dysfunction in critically ill patients.
- Although the pathophysiologic rationale for EBP remains strong, we need to refine our tools and strategies for future research, moving from broad mortality endpoints to more refined morbidity-focused outcomes and tailored patient selection.
- Although the effect on organ dysfunction appears consistent across multiple meta-analyses, understanding which patients truly benefit from EBP is key - precision and personalization will drive its future success; we urge manufacturers and researchers to prioritize bedside applicability over mere technical innovation.
- Extracorporeal blood purification has potential, but its impact depends on targeted use, smarter trials, and integration of real-world evidence.

This is the title for section A

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.

This is the title for section A

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.

This is the title for section A

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.

This is the title for section B

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.

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.

This is the title for section C

01

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!

02

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.

03

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!

This is the title for section D

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

— Irene M. Pepperberg

This is the title for section E

Carlos V.

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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.

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Thank you!

Do you have any questions?

hello@mail.com

555-111-222

mydomain.com

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Google Slides or **PowerPoint**