Hemoperfusion in critically ill patients with COVID-19

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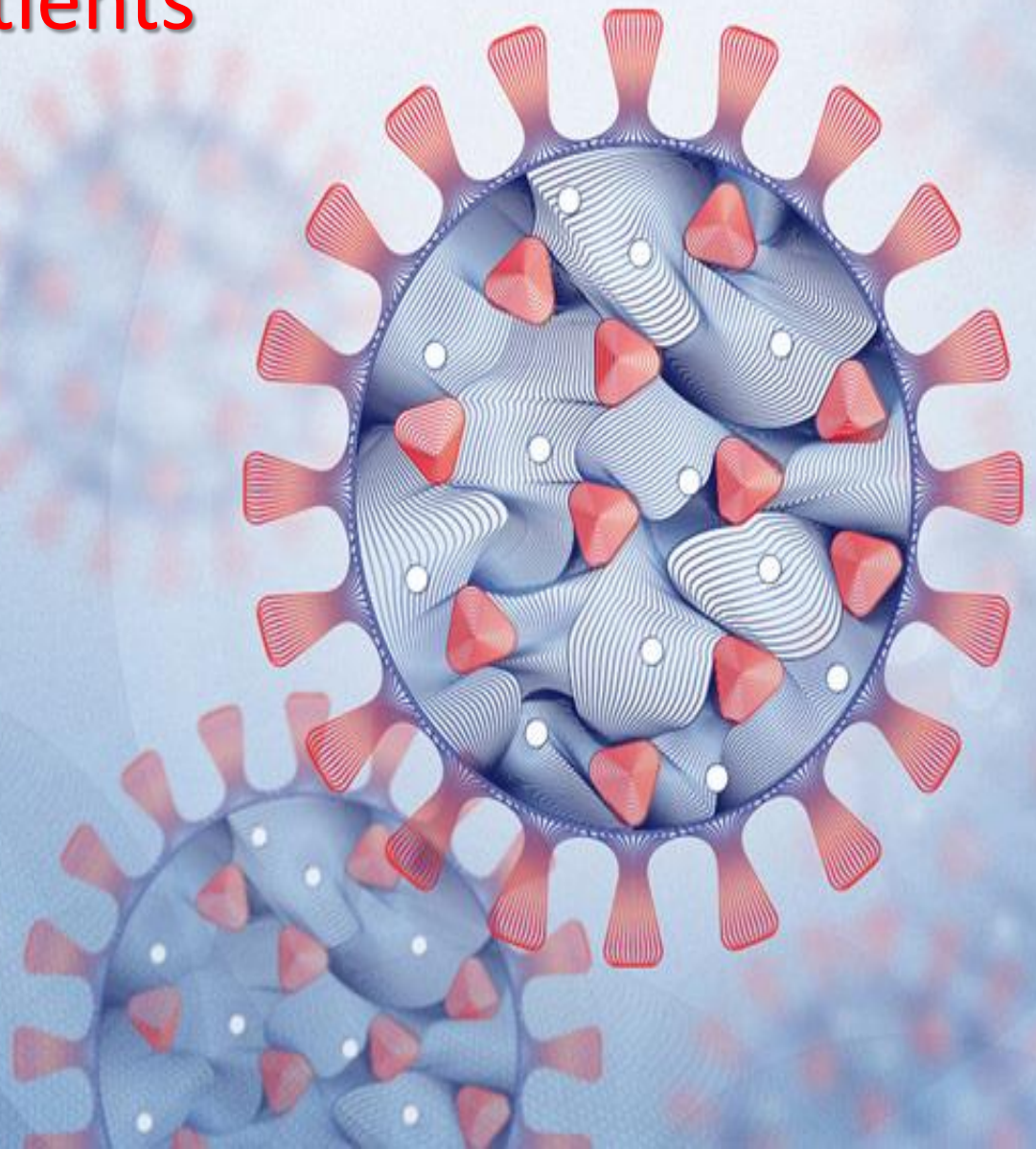
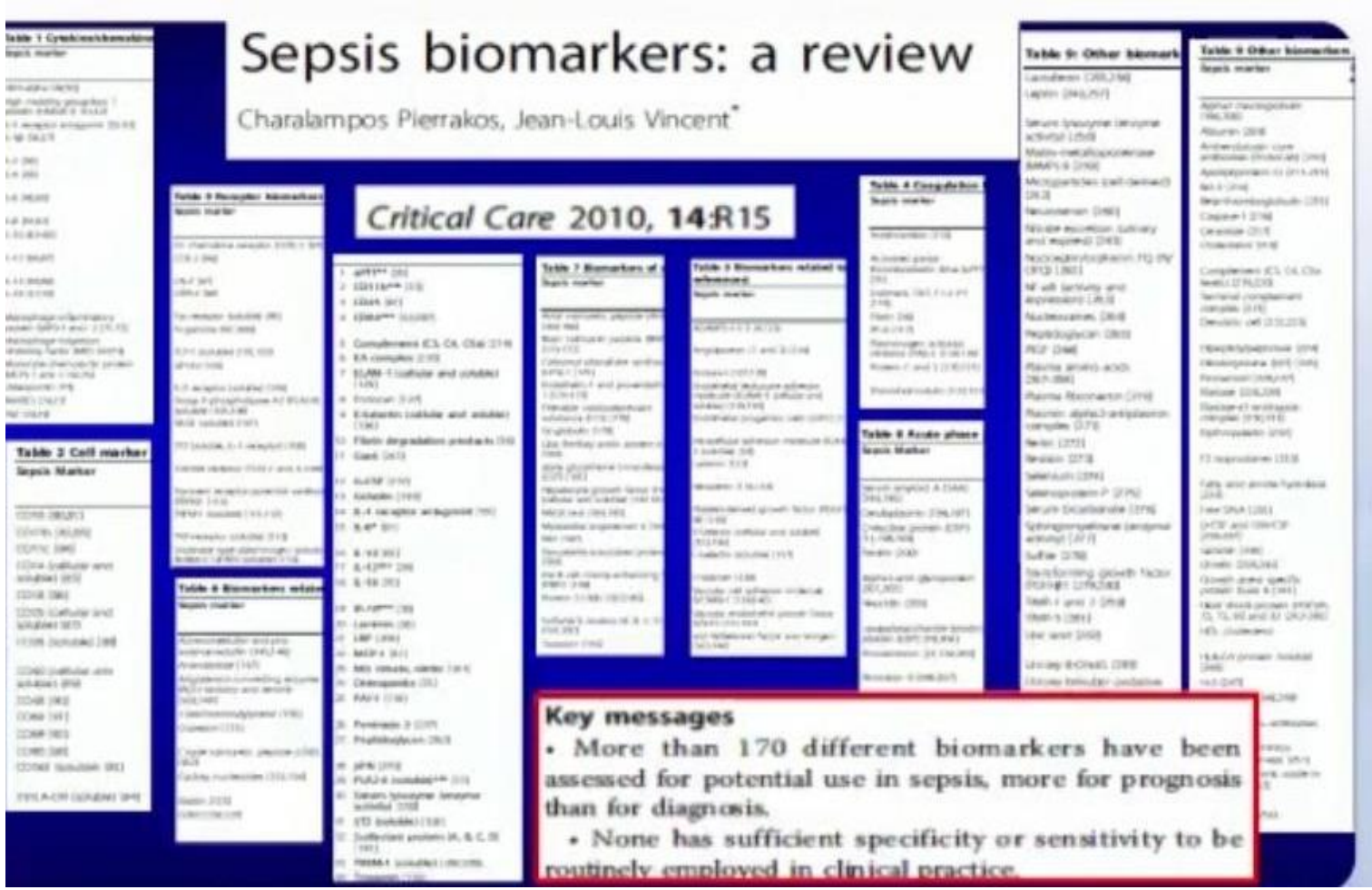
TBZMed, 2021



Crises in Intensive Care Medicine!

Reliance for evidence on RCT

- Mortality as primarily clinical end point?
- Propensity weighted trials


Sepsis biomarkers: a review
Charalampos Pierrakos, Jean-Louis Vincent*
Critical Care 2010, 14:R15
Key messages
• More than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis.
• None has sufficient specificity or sensitivity to be routinely employed in clinical practice

Innovative therapy needs innovation based on pathophysiology and the reality of ICU to demonstrate efficacy.

Conventional therapies:	drugs, magic bullets (e.g. APC)
Conventional measurements:	hemodynamics, biomarkers
Conventional study design:	Randomized Controled Trials (RCT)

nothing works!!

Innovative therapy:	Cytosorbents
Innovative measurements:	Microcirculatory imaging
Innovative study design:	sIPTW propensity scoring

stabilized Inverse Probability of Treatment Weights

- Cytokine leads to organ failure
- Blockade of 1 cytokine vs cytokines
- Controlling the inflammatory response may be as important as targeting the virus.

Attenuation of cytokine storm

- Disease complication
- Multi organ failure
- Duration of symptoms

- But what is the best tool and do we use it?
- Traditional therapies
- Like bringing knife to a gun fight
- Some times we need better, stronger and smarter therapies

Evolution of CRRT Technology

1980

CAVA-CAVHD

Focus on Rheology, Membrane and Filter Technology

CVVA-CVVHD

Focus on Mechanical Circulation and Adoptive Technology

1990

First generation CRRT machines
CVVH
CVVHD
CVVHDF

1995

Second generation CRRT machines
CVVH
CVVHD
CVVHDF
and studies on Dose and Adequacy
35 mL/Kg/h

2000

Third generation CRRT machines
HVHF and HCO Membr.

2005

Liver support
MOST, CPFA

2010

Lung support
ECCO2R
Cutrate
Endotoxin and Cytokine Removal.
Sorbent Hemoperfusion

Fourth generation CRRT machines

2020
ECOS

Blood purification techniques

Proof of concept	Clinical benefit	Potential complications
Removal of harmful substances WBC reprograming	Decreased need for vasopressors Less organ dysfunction (Survival ?)	Removal of other substances (nutrient, vitamins, trace elements, antibiotics...) Invasiveness Bleeding

- **Hemoperfusion** — use of a sorbent cartridge or column to remove certain agents from the blood. Examples of hemoperfusion devices include: PMX (also known as Toraymyxin), CytoSorb, Jafron HA380, and the D2000 Adsorption Cartridge.

- **Hemofiltration** — use of an adsorptive filtering membrane to remove inflammatory mediators. An example of a hemofiltration membrane device is oXiris (an AN69 membrane)

Brouwer *et al. Critical Care* (2019) 23:317
https://doi.org/10.1186/s13054-019-2588-1

Critical Care

RESEARCH Open Access

Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study

Willem Pieter Brouwer[1,2*], Servet Duran[3], Martijn Kuijper[4] and Can Ince[5]

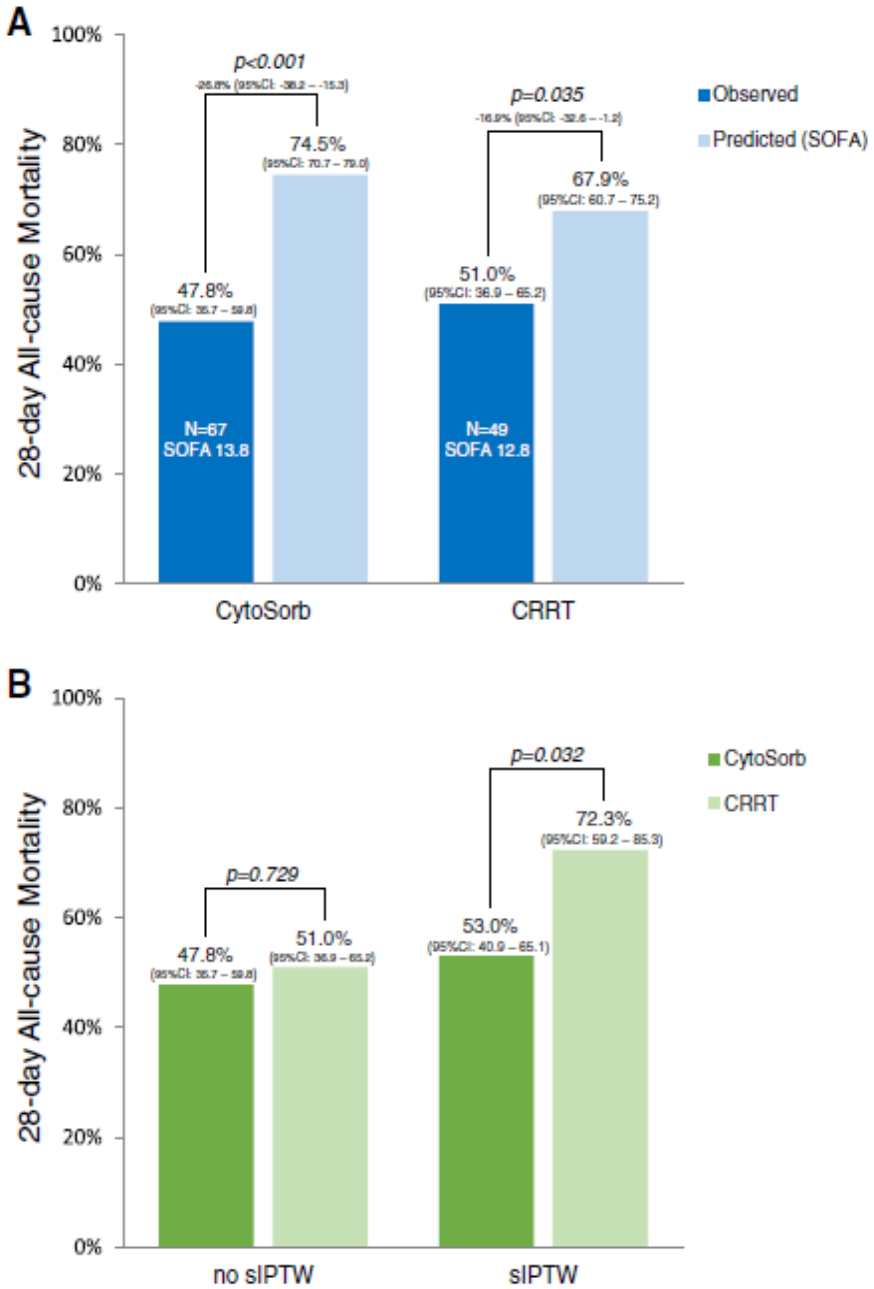


Fig. 2 a Observed versus predicted mortality rate according to the SOFA score for CytoSorb- and CRRT-treated patients. **b** CytoSorb is associated with a reduced 28-day mortality in sIPTW analysis

- The nonspecific or specific removal of some damage-associated molecular patterns and/or pathogen-associated molecular patterns most likely plays a key role in the modulation of the inflammatory response to sepsis.

- The removal result in a decrease of peaks of cytokine concentrations and/ or a modification of the cytokine/chemokine ratio from the tissues to the blood, positively impacting the leukocyte trafficking.

- The leading cause of these complications is usually cytokine storms, which contribute to a significant systemic inflammatory reaction, leading to damage in the organs including the lung, heart, and kidney.

Asgharpour *et al. BMC Nephrology* (2020) 21:356
https://doi.org/10.1186/s12882-020-02020-3

BMC Nephrology

RESEARCH ARTICLE Open Access

Effectiveness of extracorporeal blood purification (hemoadsorption) in patients with severe coronavirus disease 2019 (COVID-19)

Masoumeh Asgharpour[1], Hamed Mehdinezhad[1], Masoumeh Bayani[2], Mahmoud Sadeghi Haddad Zavareh[2], Seyed Hossein Hamidi[3], Roghayeh Akbari[4], Reza Ghadimi[5], Ali Bijani[5] and Simin Mouodi[5*]

Conclusions: Extracorporeal hemoadsorption could improve the general condition in most of recruited patients with severe coronavirus disease; however, large prospective multicenter trials in carefully selected patients are needed to definitely evaluate the efficacy of hemoperfusion in COVID-19 patients.

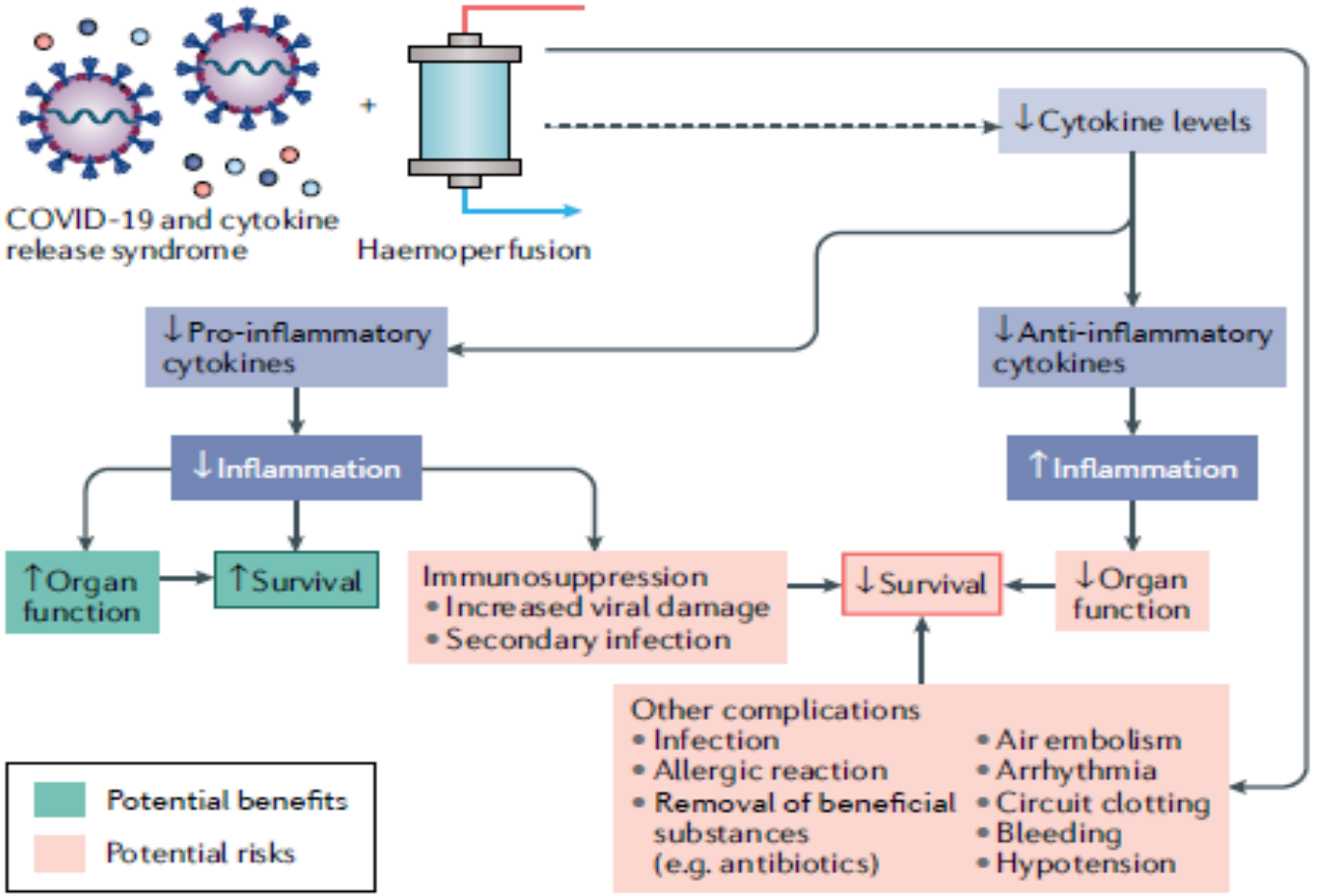


Fig. 1 | **Potential risks and benefits of haemoperfusion for cytokine removal in severe COVID-19.** Although haemoperfusion can remove cytokines from the blood, evidence suggests that this intervention might not substantially reduce circulating cytokine levels[6]. Moreover, in addition to potential benefits, a non-selective reduction in pro-inflammatory and anti-inflammatory cytokines carries potential risks. Haemoperfusion can also potentially lead to complications that are not directly related to cytokine removal, including hypotension and arrhythmias.

- The **CytoSorb** cartridge is filled with biocompatible polymer beads about the size of grains of salt. The pores in each bead are sized to allow larger components, such as blood cells, to pass around the beads and smaller components, such as electrolytes, to pass through.
- However, hydrophobic substances, such as cytokines, are rapped inside the beads and removed from the bloodstream.
- An initial three-day-course of therapy for patients with severe COVID-19, with a cartridge change every 12 hours on day one and every 24 hours on days two and three.
- After the third day of treatment, patients should be assessed to determine whether there are signs of benefit, in which case CytoSorb treatment can continue until their conditions are stable.

- The **Jafron** adsorption cartridge consists of a “neutral, macroporous resin,” with a large surface area that adsorbs inflammatory agents, including cytokines.

- The Jafron hemoperfusion cartridges recommend a three-day-course of therapy, with two treatments (cartridges) in the first 24 hours and one treatment on days two and three

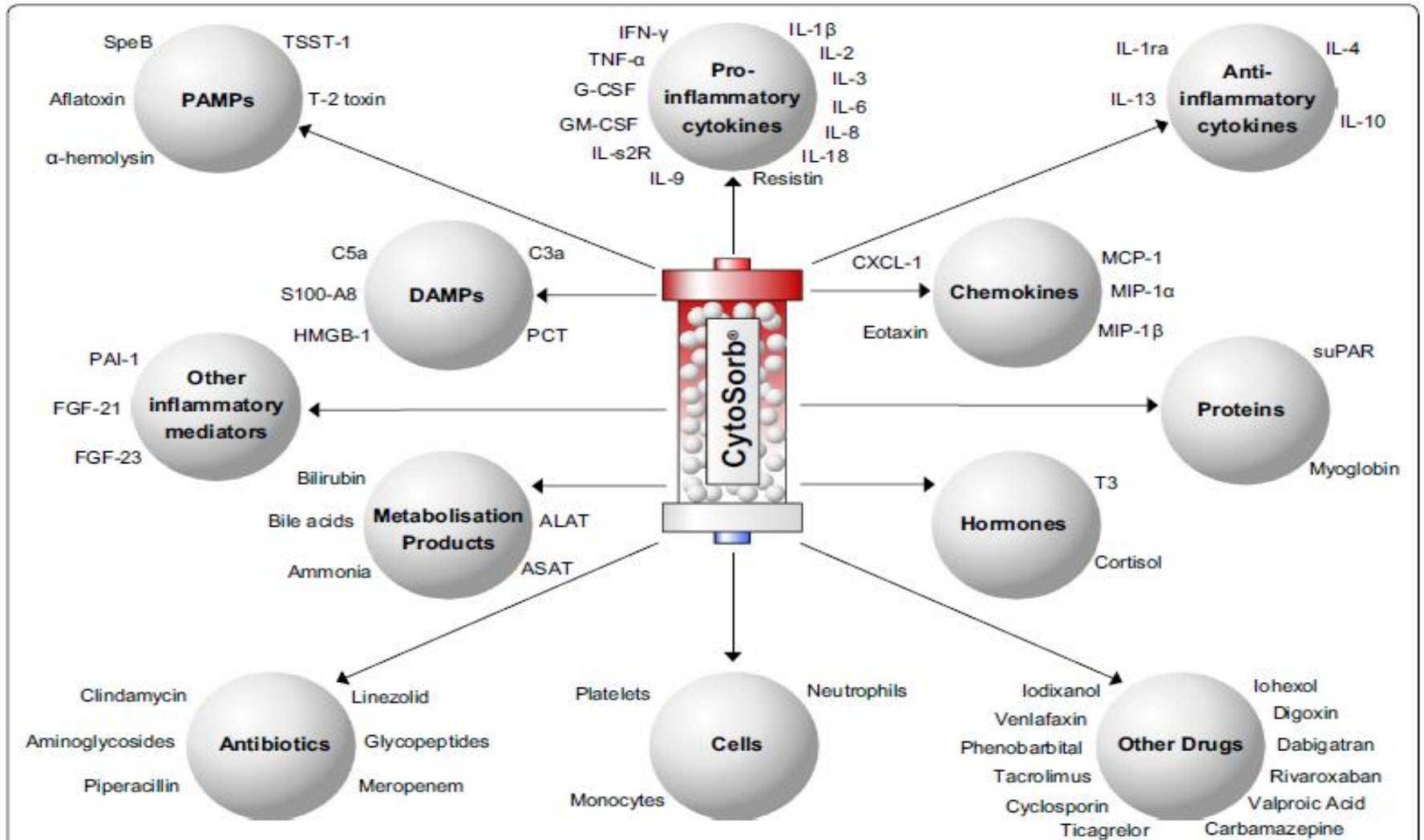


Fig. 1 Scope of adsorption by CytoSorb®. Figure mostly based on in vitro data. The clinical relevance of CytoSorb® hemoadsorption for the majority of those molecules remains to be evaluated. DAMPs damage-associated molecular patterns, FGF fibroblast growth factor, HMGB-1 high-mobility group box 1, MCP-1 monocyte chemoattractant protein 1, MIP macrophage inflammatory protein, PAI-1 plasminogen activator-inhibitor 1, PAMPs pathogen-associated molecular patterns, PCT procalcitonin, SpeB streptococcal pyrogenic exotoxin B, S100-A8 S100 calcium-binding protein A8, suPAR soluble urokinase-type plasminogen activator receptor, T3 triiodothyronine, TSST-1 toxic shock syndrome toxin 1

Indications

- IL6> 400-1000 pg/ml
- Ferritin>1000-1500
- Lactate >4 (better response in lact>6)
- CRP>125
- CPK> 2 times NL value
- Vasoplegic shock with NE>0.3 micr/kg/min
- MOF

Contraindication

Absolute

- Thrombocytopenia<20000
- Pregnancy
- Allergy
- SCA
- Skill

Relative

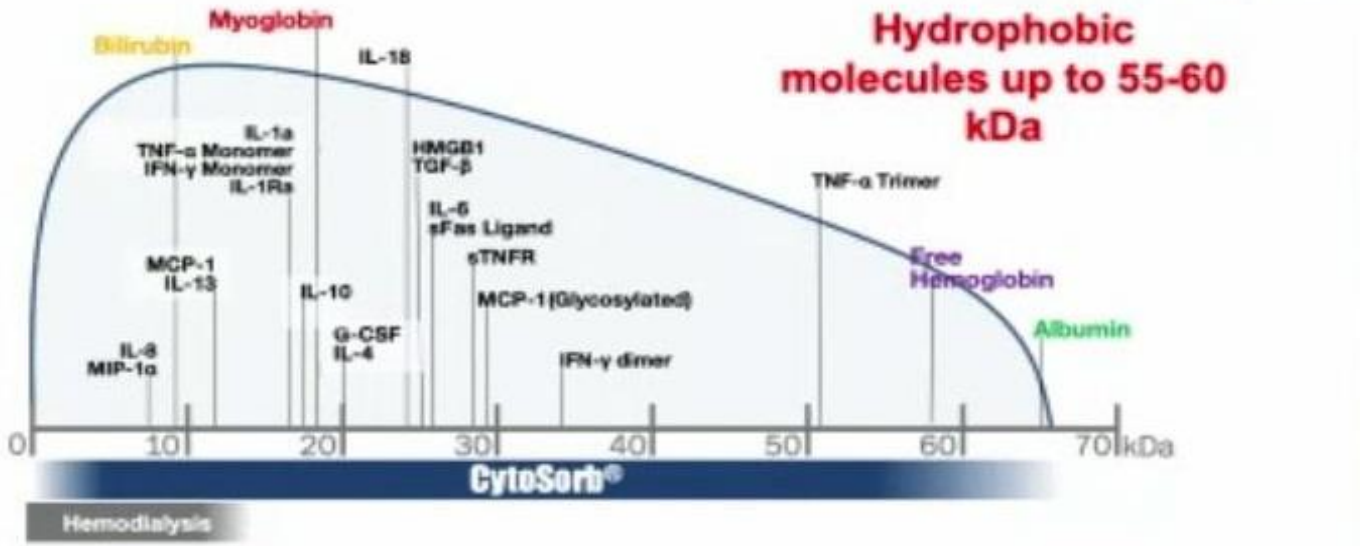
- BMI>40
- HIT
- Age<12

Key points

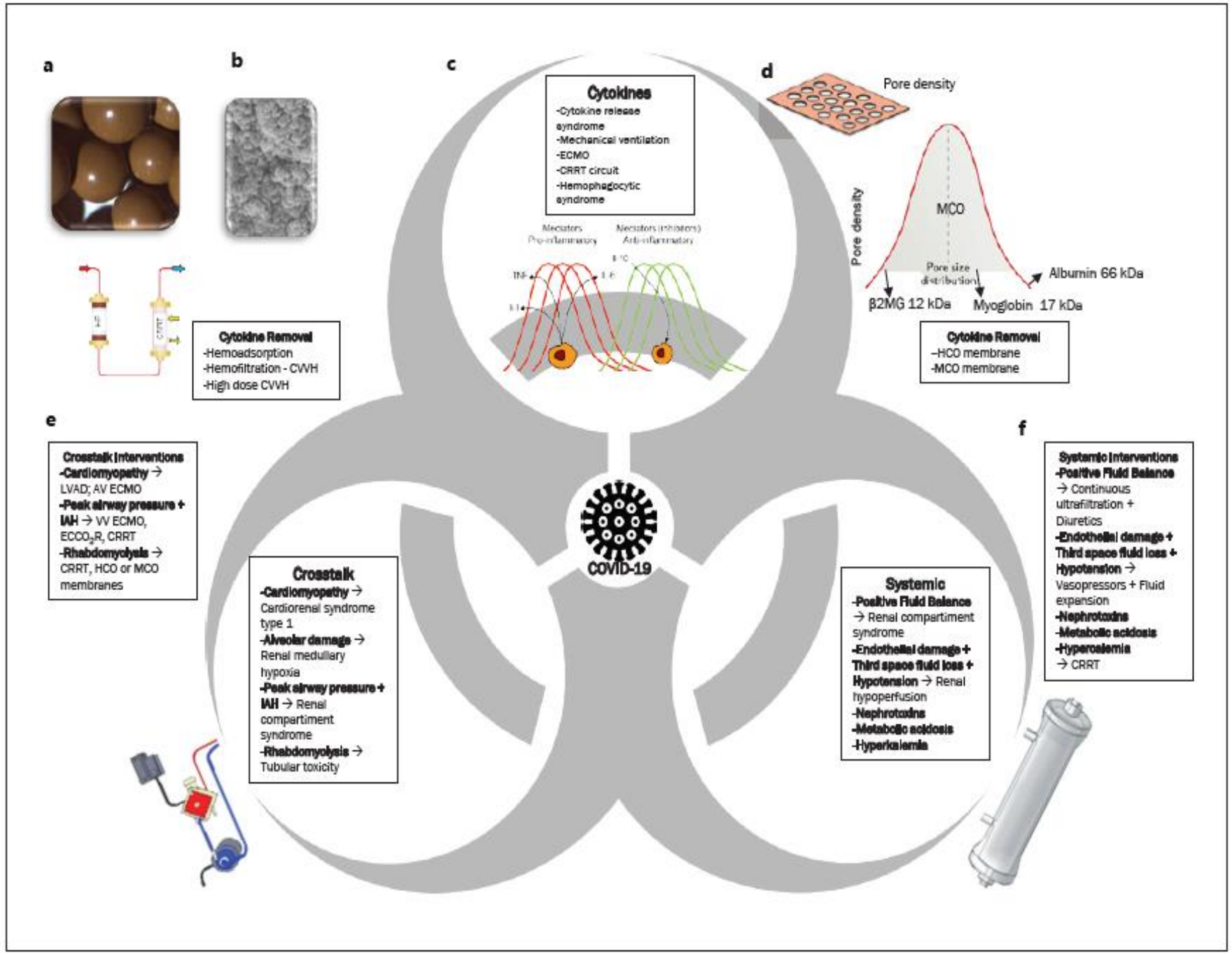
- Time(onset: ASAP, duration: 3-7 d, exchange filter /24h)
- Phenotype(polymorphism)
- Severity(Ref Septic shock, SOFA)
- Biomarkers: bed side(CRP,IL6)

- 1980s: Kt/v
- 2000s: adequacy of dialysis
- 2020: adequacy of adsorbtion(sufficient, appropriate, high)

Removal selectivity: Role of size exclusion



Hydrophobic molecules up to 55-60 kDa


a
b
c
d
e
f
Cytokines
-Cytokine release syndrome
-Mechanical ventilation
-ECMO
-CRRT circuit
-Hemophagocytic syndrome
Mediators Pro-inflammatory
Mediators (inhibitors) Anti-inflammatory
Cytokine Removal
-Hemoadsorption
-Hemofiltration - CVVH
-High dose CVVH
Pore density
MCO
Pore density
Pore size distribution
Albumin 66 kDa
β2MG 12 kDa
Myoglobin 17 kDa
Cytokine Removal
-HCO membrane
-MCO membrane
Crosstalk Interventions
-Cardiomyopathy → LVAD; AV ECMO
-Peak airway pressure + IAH → VV ECMO, ECCO2R, CRRT
-Rhabdomyolysis → CRRT, HCO or MCO membranes
COVID-19
Crosstalk
-Cardiomyopathy → Cardiorenal syndrome type 1
-Alveolar damage → Renal medullary hypoxia
-Peak airway pressure + IAH → Renal compartiment syndrome
-Rhabdomyolysis → Tubular toxicity
Systemic
-Positive Fluid Balance → Renal compartiment syndrome
-Endothelial damage + Third space fluid loss + Hypotension → Renal hypoperfusion
-Nephrotoxins
-Metabolic acidosis
-Hyperkalemia
Systemic Interventions
-Positive Fluid Balance → Continuous ultrafiltration + Diuretics
-Endothelial damage + Third space fluid loss + Hypotension → Vasopressors + Fluid expansion
-Nephrotoxins
-Metabolic acidosis
-Hyperkalemia → CRRT

- Blood flows above 150 mL/min and the use of diffusive techniques (CVVHD) with minimal FF(25%) further help avoiding circuit clotting.

- In long-term treatment, regional citrate anticoagulation, (although no evidence of superior outcomes has been provided).

- Hemoadsorption would essentially reduce high levels of several mediators and by this ‘limit the storm’ in cytokine storm syndrome, rather than actively targeting individual pathways during inflammation.

Villa et al. Critical Care (2020) 24:605
https://doi.org/10.1186/s13054-020-03322-6

Critical Care

RESEARCH Open Access

Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study

Gianluca Villa[1,2*], Stefano Romagnoli[1,2], Silvia De Rosa[3,4], Massimiliano Greco[5,6], Marco Resta[7], Diego Pomarè Montin[1,4], Federico Prato[8], Francesco Patera[9], Fiorenza Ferrari[4,10], Giuseppe Rotondo[11] and Claudio Ronco[4,12,13]

Compared to the expected mortality rates, the mean observed rates were 8.3% lower after treatment.

The best improvement in mortality rate was observed in patients receiving EBP early on during the ICU stay.

an observational study

37 patients with AKI

oXiris membrane

Measures to improve circuit life

Anticoagulants

Maintain patency of extracorporeal circuit	• Avoid minor clotting in the capillary fibers and reduced solute clearances • Avoid major clotting leading to loss of the filter, tubing, and blood in the circuit
Avoid bleeding	• Avoid patient's complications
Provide an inert surface-blood interaction	• Minimize activation of complement and cytokine cascade • Reduce cellular activation

Maintaining the extracorporeal circuit is crucial for delivering the treatment effectively

Measures to improve circuit life

Non-anticoagulant

Reducing stasis of flow	▪ Vascular access (dimensions, material, tip position, vein choice) ▪ Training (reaction time to alarm, recognition of kinking catheter, etc)
Optimizing setting	• Filtration fraction • Predilution vs postdilution • Clogging • Membranes • Filter size

Maintaining the extracorporeal circuit is crucial for delivering the treatment effectively

Anticoagulation free

- High risk of bleeding
- Liver dysfunction
- Coagulation disorders

- Sites of clot formation

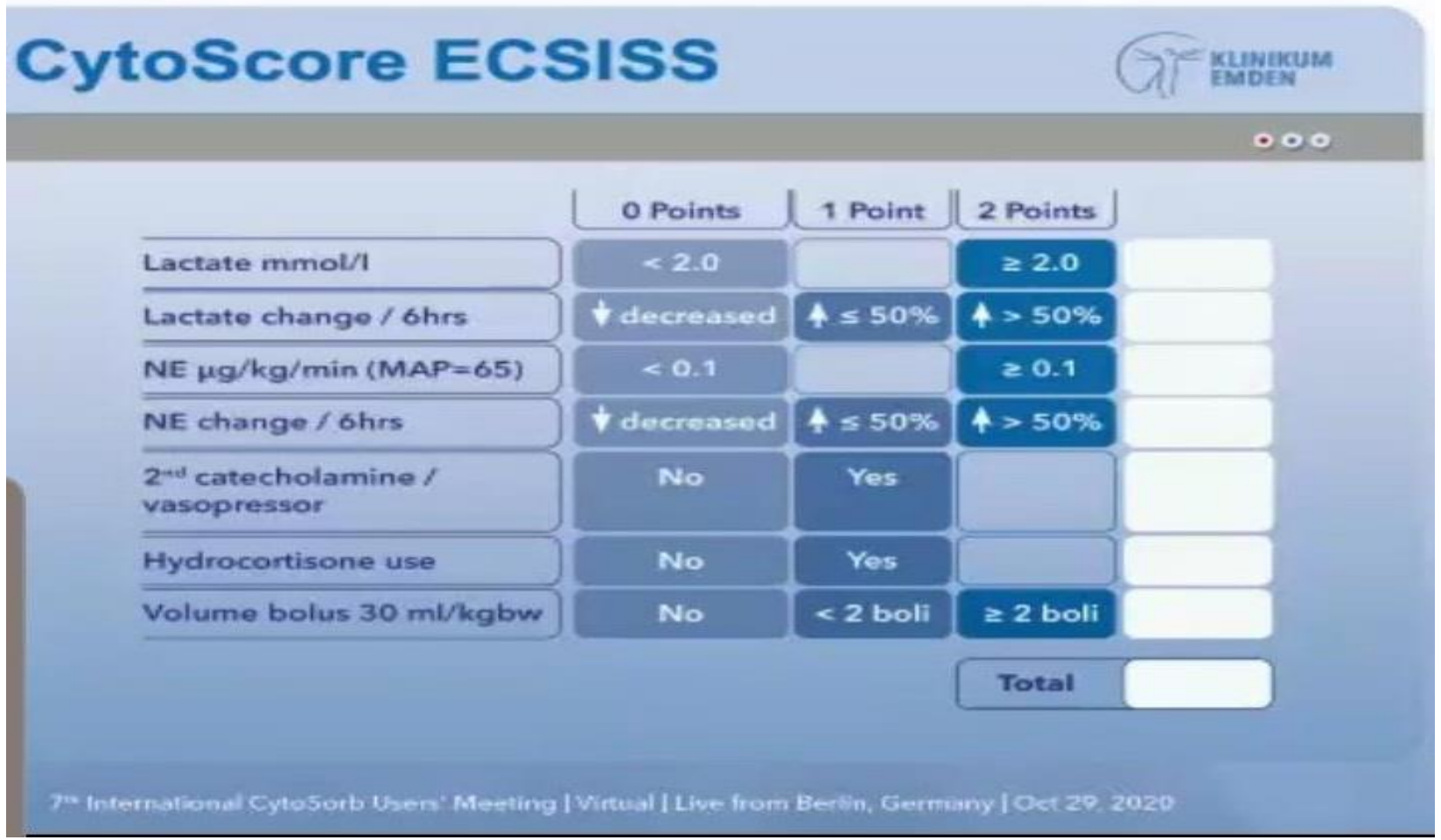
Hemofilter

Bubble trap, dearation chamber

Catheter

Leurlock and 3 way stopcock connections

Cytoscore: >8
a new tool to optimize the starting point



- Clinical data suggest high degree of patient safety
- No relevant removal of coagulation factors
- Relevant removal of various drugs
- Removal primarily in early phase of HP(15-60min)
- Sufficiently high dosage and TDM advisable.

Blood
Purification

Letter to the Editor

Blood Purif
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Hemoperfusion as a Potential Treatment for Critically Ill COVID-19 Patients with Cytokine Storm

Kamran Shadvar[a] Ali Tagizadiyeh[b] Ali Akbar Gamari[a] Hassan Soleimanpour[c] Ata Mahmoodpoor[a]

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- Finally, our results showed that hemoperfusion can decrease the level of inflammation and organ dysfunction in critically ill patients with COVID-19. We need more studies to show the best time for implementation of hemoperfusion and number of its sessions in outcome of these patients.
- Moreover, all ICU staff and physicians should be familiar with the concept of hemoperfusion in management of critically ill patients.
- So, hemoperfusion (early application) combined with appropriate antiviral therapies and supportive therapy may be considered as an adjunctive treatment for critically ill COVID-19 patients.
- For the moment, the pathophysiological rationale is the only reason to recommend that application of hemoperfusion, and a personalized evaluation is advised. In addition, if such intervention is being considered, it seems logical to apply it as soon as possible.

- According to current experience and in the absence of any specific therapy besides supportive measures, cytokine removal strategies should be reserved for COVID-19 patients with evidence of high circulating cytokines such as IL-6 and IL-8, a biochemically determined inflammatory status, high SOFA score, clinical symptoms of hemodynamic instability requiring vasopressors, and initial signs of immune dysregulation or disorders of coagulation cascade.
- Markers such as plasma ferritin or urinary biomarkers of kidney stress may also be useful to identify cases of hyper-inflammation.
- Clinical criteria alone may be surrogates of hyper-inflammation, but they should be evaluated case by case.

- In the future, genetic profiling may guide the initiation of this therapeutic strategy for specific patients.

- Due to frequent mobilization and pronation, patients may be treated with prolonged intermitted sessions (PIRRT) to allow nursing maneuvers.

- Because of severe hemodynamic instability and the need to control the patients' fluid balance, fluid removal should be carefully scheduled to avoid hypotension that could worsen kidney injury or delay recovery.

- These therapies, although considered as “under scientific investigation,” “salvage,” or “compassionate use” interventions, still represent an option for severe CRS and, in particular, for COVID-19 patients where pharmacological alternatives are lacking.

- For the moment, the pathophysiological rationale is the only reason to suggest the application of these methods, and a case-by-case evaluation is advised, although if such treatments are being considered, it seems logical to apply them early.

Stockmann *et al. Trials* (2020) 21:577
https://doi.org/10.1186/s13063-020-04501-0

Trials

LETTER Open Access

CytoResc – "CytoSorb" Rescue for critically ill patients undergoing the COVID-19 Cytokine Storm: A structured summary of a study protocol for a randomized controlled trial

Study protocol

- CRP>100 mg/l
- PCT<0.2 ng/l
- Cytokine storm(vasoplegic shock: NE>0.2 micro/kg/min

- 3-7 days
- Catheter exchange every 24 hours

- P.outcome: resolution of vasoplegic shock
- S.outcome: mortality at 7 and 28 day, IL6, MV, ICU stay, catecholamine dose, AKI

UKE Dep. of Intensive Care Medicine

CYTOCOV-19

CytoSorb® in COVID-19-sCAP
- single-centre RCT -

Question:
Does the reduction of elevated cytokine levels by hemadsorption have a positive effect on the disease severity of sCAP patients with COVID-19 and shock in terms of sustained hemodynamic stabilization?

Inclusion criteria:
- Confirmed COVID 19
- Refractory shock: MAD ≤ 65 mmHg with vasopressor therapy and adequate fluid substitution
- Noradrenaline dose ≥ 0.2 µg/kg/min
- IL-6 ≥ 500 ng/l
- Indication for extracorporeal therapy (e.g.: CRRT or ECMO, $ECCO_2R$)
- Age ≥ 18 and ≤ 90 y

Exclusion criteria:
- Liver cirrhosis Child-Pugh C
- Standing DNR-order, moribund patient
- Expected survival due to comorbidities ≤ 14 d
- Pregnancy oder lactation
- Participation in interventional trial

Primary endpoint:
- Significant stabilisation of hemodynamics („shock reversal"), defined as reduction of noradrenaline requirements (≤ 0.05 µg/kg/min) to maintain MAP ≥ 65 mmHg for at least 24 h compared to controls

Ethik: Zustimmung der EK Hamburg vom 31.3.2020 (PV7314)

Cytosorb registry

- Data from interim analysis:
- Severe sepsis/MOF

Haemoperfusion should only be used for COVID-19 in the context of randomized trials


DANGER
OUTBREAK ALERT
CORONA VIRUS
#COVID19