Adsorption Techniques

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Disclosures

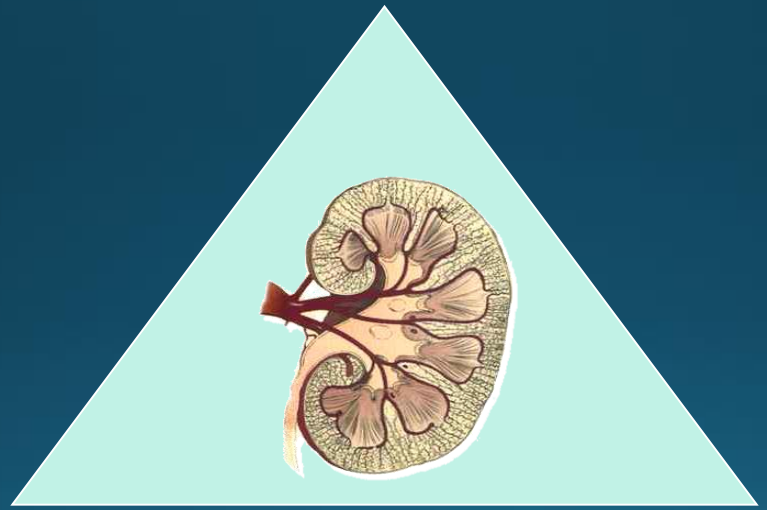
- None

Objectives

- Background
- Different applications
- **Lessons learnt from the published literature**
- Conclusions

Mechanisms of Solute Removal in Extracorporeal Blood Purification Techniques

Diffusion



Convection

Adsorption

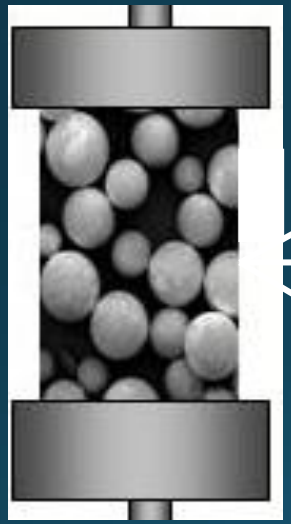
Mechanisms of Solute Removal in Extracorporeal Blood Purification Techniques

Diffusion **Convection**

Both molecule/membrane-related factors can limit clearance via these mechanisms

eg.
the sieving properties of the membrane, diffusion coefficients of the molecules, temperature, surface area.

Fibers, granules, spheres, flakes powder



High surface area 300 – 1200 m^2/g

Single particle diameter between 50 mm and 1.2 cm.

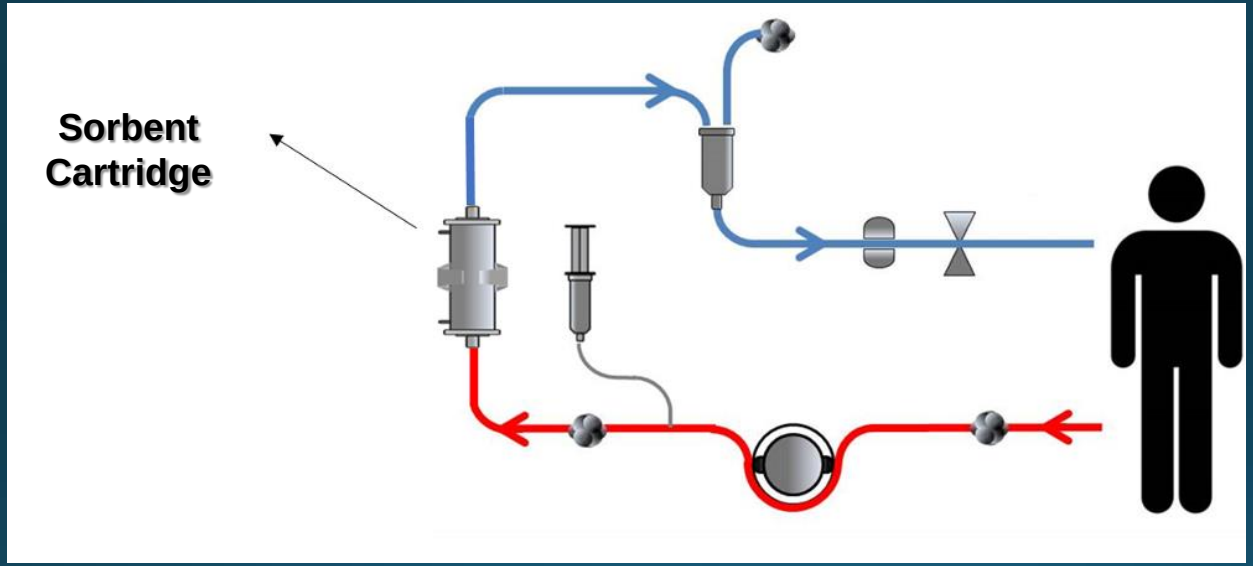
Macroporous = Pore size > 500 Å (50 nm)

Mesoporous = Pore size 20-500 Å

Microporous = Pore size < 20 Å

MW removed 100-40,000 daltons

Hemoperfusion Extracorporeal Circuit

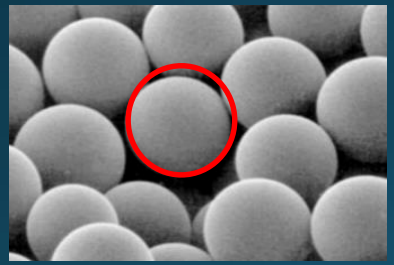


Chills, Fever, Cutaneous rush
Thrombocytopenia, Leucopenia
Aluminum Load

Ankawi et al. Critical Care, 2018

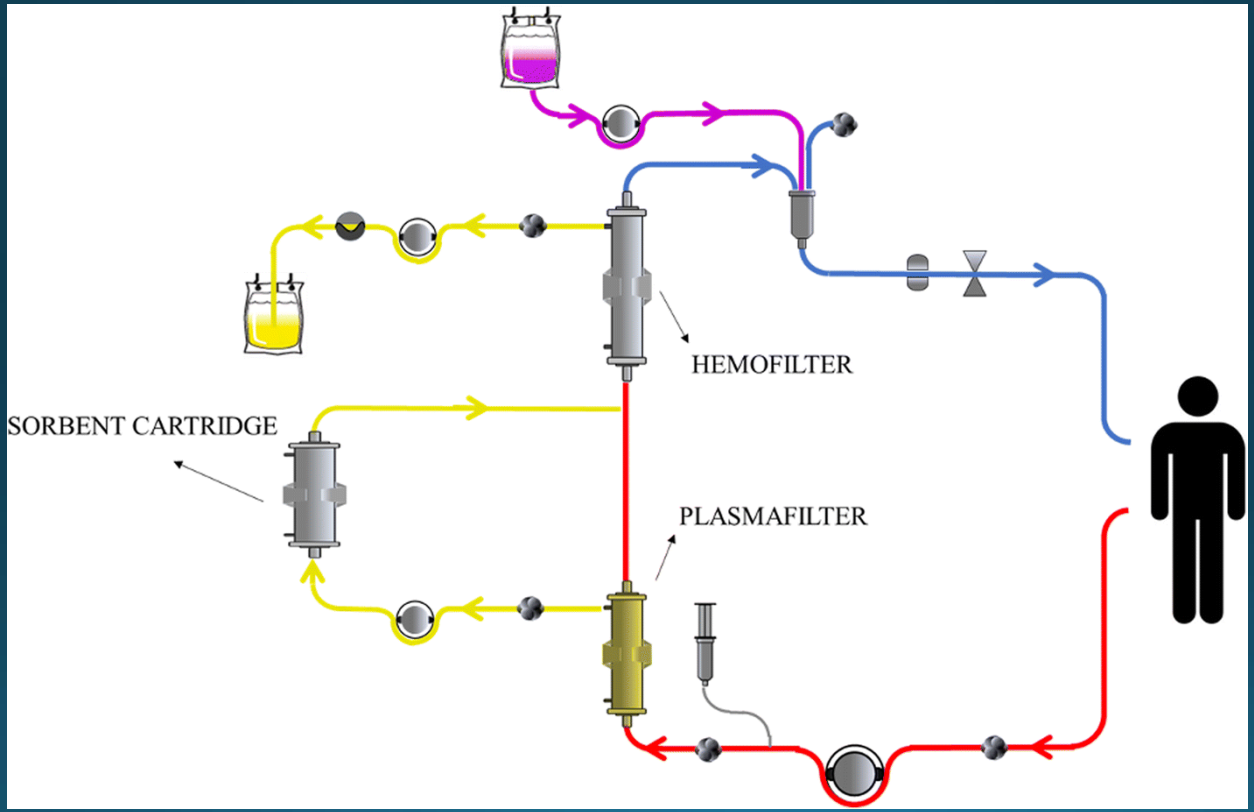
Methods to Overcome Incompatibility

- Coating the particles with specific biomaterials.

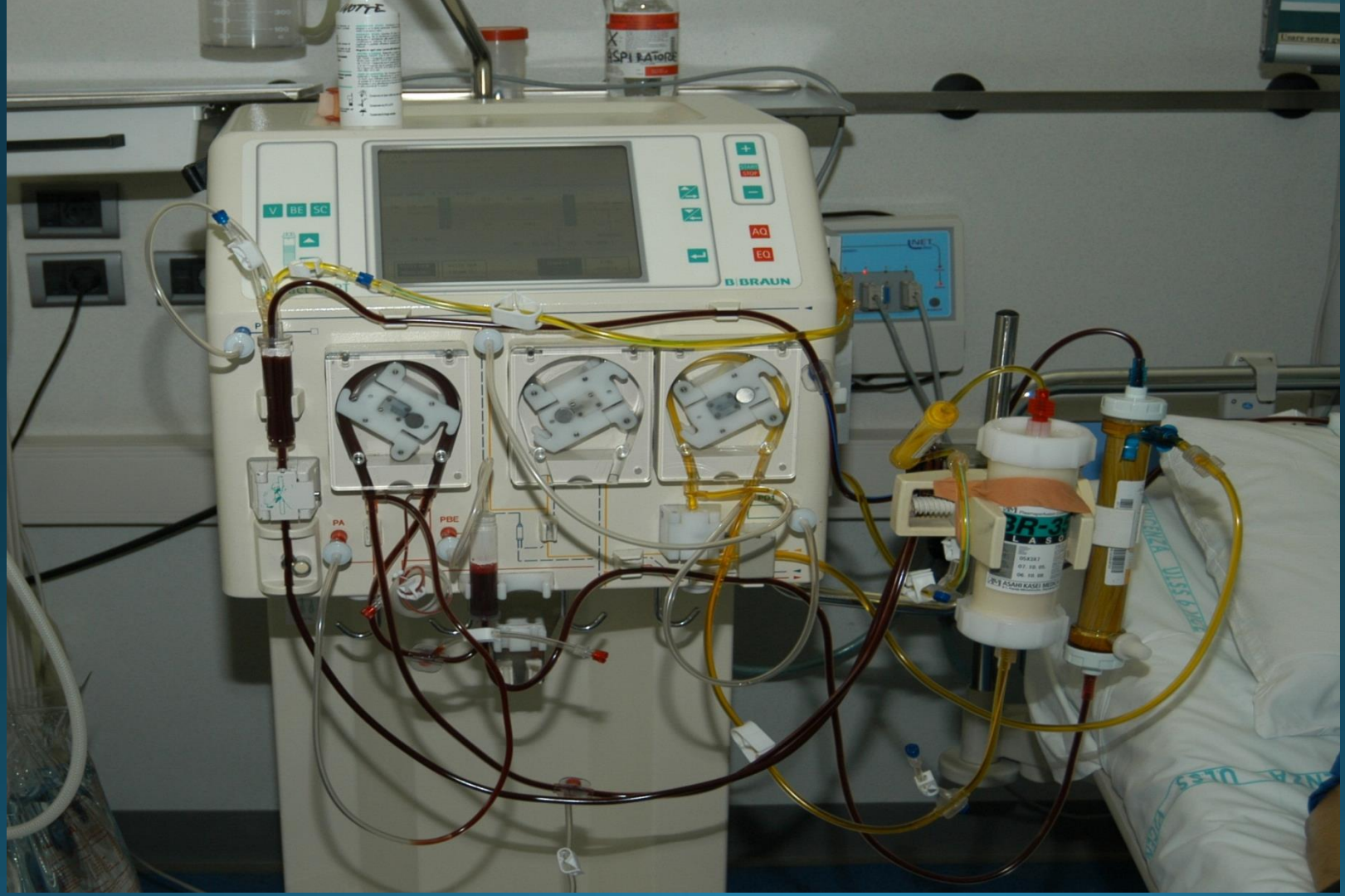


- Separating plasma from red cells and circulating only the separated plasma through the sorbent bed. **CPFA**

CPFA Circuit



Ankawi et al. Critical Care, 2018


V
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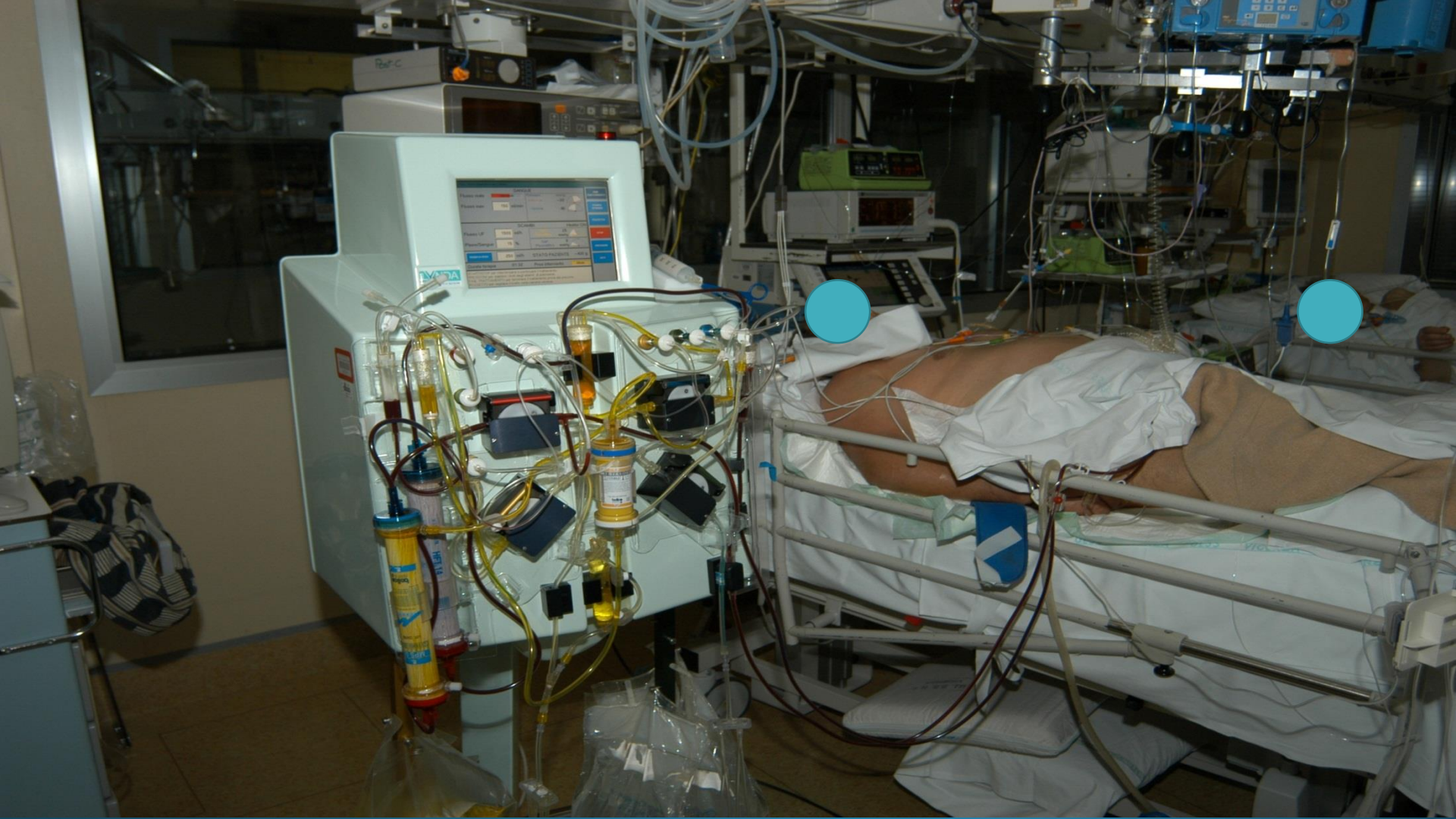
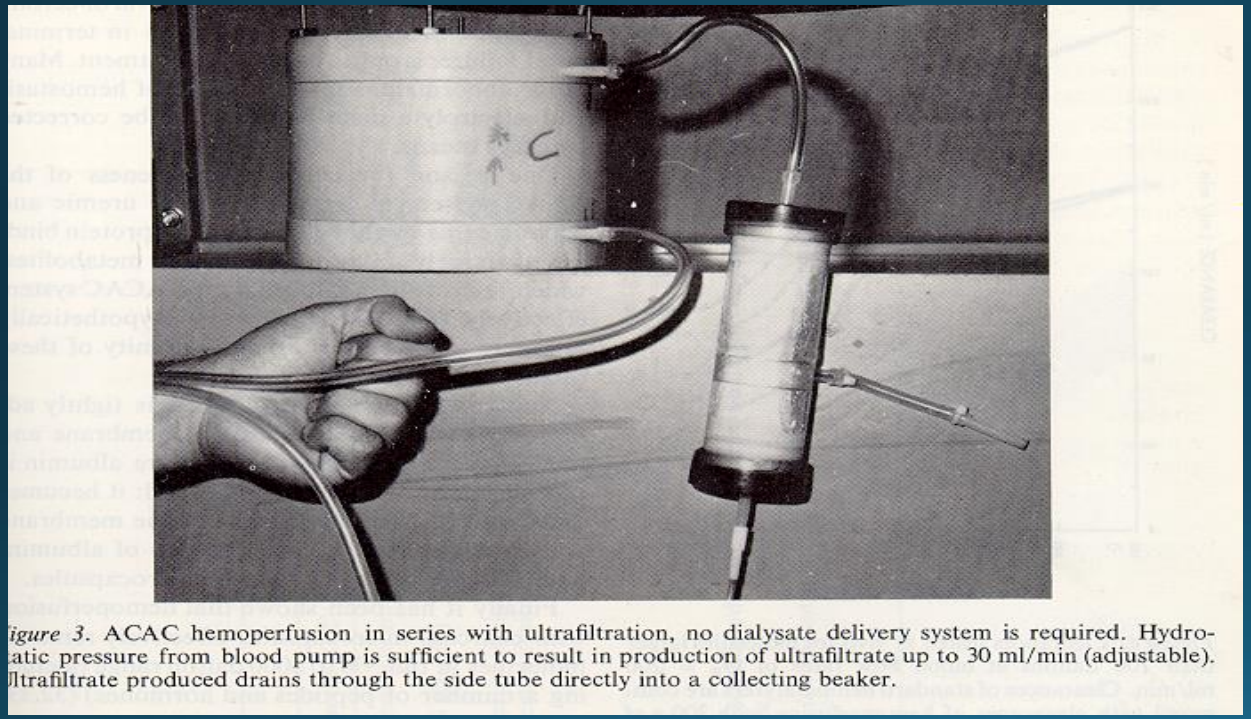


Early Hemoperfusion Treatments (Charcoal sorbent)



igure 3. ACAC hemoperfusion in series with ultrafiltration, no dialysate delivery system is required. Hydro-atic pressure from blood pump is sufficient to result in production of ultrafiltrate up to 30 ml/min (adjustable). ltrafiltrate produced drains through the side tube directly into a collecting beaker.

Since 1960, sorbents have been used for the removal of uremic toxins, hepatic toxins, drugs, and chemical poisons

Slide courtesy; Prof. Ronco

Yatzidis H. Proc Eur Dial Transplant Assoc 1964;1:83–85.
Chang TMS Can J Physiol Pharmacol 1969;47:1043–1045.

Clinical applications **beyond Poisoning**….

Acute conditions
Sepsis, pancreatitis, trauma, cardiac surgery

Chronic Conditions
(uremic complications)

Others
Liver diseases
Autoimmune diseases

PMX

Endotoxin

Polymyxin B-immobilized fiber

CytoSorb

Cytokines

Porous polymer beads

HA-330

Endotoxin/Cytokines

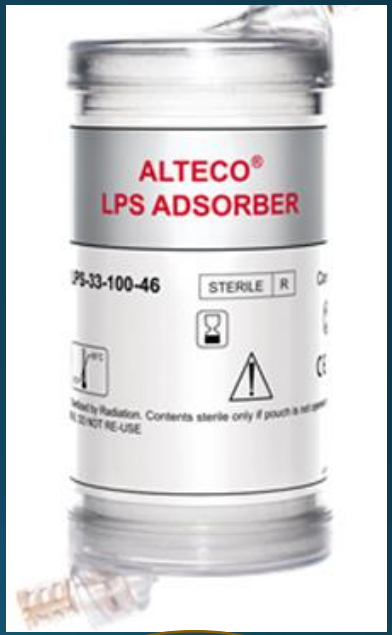
Styrene Divinylbenzene Copolymers

Oxiris

Endotoxin/Cytokines

AN69-based membrane, surface treated with PEI and grafted with heparin

LPS Adsorber



Endotoxin

Synthetic polypeptide bound to porous polyethylene discs

HA cartridges

Study	Patient Population	Mean Treatment Time	Intervention	Inflammatory Mediators	Hemodynamics	Mortality	Other Outcomes	Side Effects, Clotting Rate
Huang et al (2010)	N= 44, severe sepsis		ST+ HP vs ST (2hr session daily X3days).	Y (IL-6, IL-8)	Y	Y ICU (but not hospital 28-days mortality)	Y ICU LOS (but not hospital LOS)	1 patient with fever in the HP group
Liu et al (2012)	N=30 MODS	Only one session of HP	HP+CVVH (10h+2 h HP) vs CVVH (12h)	Y (IL-1β, IL-6 , TNF)	N	N	-	-
Huang et al (2013)	N=45 ALI/extrapulmonary sepsis		ST+ HP vs ST (2hr session daily X3days)	Y (IL-1, TNFα)	Y	Y ICU 28-days	Y PaO2/FiO2 Lung injury score CXR score ICU LOS CRRT duration	-

PMX

Study	Patient Population	Intervention	Inflammatory Mediators	Hemodynamics	Mortality	Other Outcomes	Side Effects, Clotting rate
European Pilot Study (2005)	N=36 intra-abdominal sepsis	PMX vs ST (2-hr session)	(IL)-6 N	Y	N		Clotting (24%)
EUPHAS (2009)	N=64 intra-abdominal sepsis	PMX+ST vs ST (2-hr session X2)	-	Y	Y		Hypotension (1.5%) Tacycardia (3%)
Japan Registry (2014) Propensity-matched analysis	N=590 in each group, Lower GI tract perforation	1-2 sessions	-	-	N		-
ABDO-MIX (2015)	N=232 intra-abdominal septic shock/peritonitis	1-2 2-hr sessions 2 sessions in only 69.5 %	-	N	N		Hemorrhagic episodes 6 (PMX) vs 3 (controls)
Japan Registry (2016) propensity-matched analysis	N=975 in each group, Septic shock+ CRRT-requiring AKI	1-2 sessions	-	N	Y		
EUPHRATES Trial	N=450 septic shock & SAA+0.6	-	-	Y	Y (with SAA 0.6-0.9)		Clotting rate of only 5 %.
JSEPTIC DIC study Database (2017)	N=262 in each group septic shock	PMX-HP vs non-PMX-HP	-	-	Y		-

Cytosorb

Study	Patient Population	Mean Treatment Time	Intervention	Inflammatory Mediators	Hemodynamics	Mortality	Other Outcomes	Side Effects, Clotting Rate
Schädler et al (2013)	N=43 septic patients with ALI		ST+HP vs ST	Y (IL-6, MCP-1, IL-1ra, IL-8)	-	N		Drop in PLT(+10%), sb(+5%)
Bernard et al (2016)	N=37 elective CPB	191 ± 56 minutes	ST+HP vs ST	N	N	N		-
Friesecke et al (2017)	N=25 septic shock patients		ST + HA	Y (IL-6)	Y	-		N
Schädler et al (2017)	N=97 severe sepsis & ALI or ARDS		ST+HP vs ST	Y (IL-6)	-	N		Drop in PLT (1 patient in HP)
Kogelmann et al (2017)	N=16 septic shock		HA in addition to CRRT	-	Y	Y Compared to predicted mortality by APACHE II		N
Nemeh et al (2018)	N=54 CHT	203 ± 22 minutes	Adsorption vs controls	N (CRP, PCT)	Y	Y	Lower IRAI 12.5% vs 23% P=0.03	N

LPS Absorber

Study	Patient Population	Intervention	Inflammatory Mediators	Hemodynamics	Mortality	Side Effects, Clotting rate
Yaroustovsky et al (2009)	13 Gram-negative sepsis patients	Alteco adsorber procedures (n=6) Toraymyxin (n=7)	Y	Y	-	-
Ala-Kokko et al (2011)	24 septic shock patients with and endotoxemia	2-hour venovenous LPS	Y	Y	-	Low platelets , 2 patients requiring pli tx but no bleeding
Adamik (2015)	62 septic shock patients and suspected Gram-negative infection	1-2 sessions	Y	Y	N	Low platelets

Lessons learnt

The right window of opportunity

Biomarker-driven therapy

EUPHAS

Early post-OP PMX-B HP (2 treatments) vs standard care
among 64 patients
Increase in MAP, a decrease in VP requirements.
Improved survival at 28 days

ABDOMIX

PMX-B HP (2 treatments) vs standard care among 243 patients
No significant difference in:
28 or 90-day mortality
Organ dysfunction

EUPHRATES

PMX-B HP (2 treatments in addition to standard of care) vs sham HP among 450 patients
No significant difference in 28-day mortality
(37.7% in the PMX group vs 34.5% in the controls (P= 0.92))

EUPHRATES

Post hoc analysis *(D. J. Klein et al, Intensive care medicine)* → patients with endotoxin activity of 0.6–0.89

10.7% risk reduction in mortality [OR 0.52, 95% CI (0.27, 0.99), P=0.047]

Longer 28-day survival time
Greater change in MAP

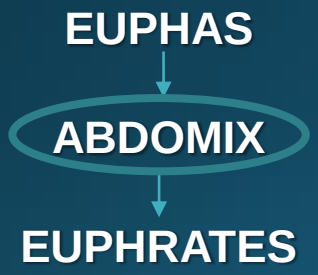
Catching up the patient early on (as guided by endotoxin assays) before endotoxin-mediated damage may improve the effectiveness of sorbent therapy

Its impact on efficiency of sorbent therapy

Technical aspects

Alteration of the anticoagulation requirement in the circuit

Polymyxin B immobilized fibers column



- High rate of cartridge clotting treatment failure
- Incomplete treatment in 38 % of patients.
- Two sessions in only 8/119 (69.8 %) patients

Alteration of the anticoagulation requirement in the circuit

CPFA

The **COMPACT** trial

192 patients CPFA plus standard of care vs standard of care

No difference in hospital mortality (controls

(47.3%) vs CPFA (45.1%); p = 0.76)

Nearly half of the patients in the CPFA arm did not reach the planned dose.

Clotting of the circuit was the cause in 48% of cases

Treatment duration as an example

Variability in prescription

Cytosorb in the context of cardiac surgery

Träger et al. Int J Artif Organs, 2016
16 patients with severe post-CPB SIRS/AKI → Reduction in IL-6/IL-8
Improvement of hemodynamics

Bernardi et al. Critical Care, 2016
Elective CPB surgery → No differences in:
IL-6 level, VP requirement
30-day mortality

Träger et al. Int J Artif Organs, 2016
39 patients with IE
undergoing CS with HP vs.
28 historical patients with
IE undergoing CPB with no HP → Reduction in cytokines
Improvement of hemodynamics

Cytosorb in the context of cardiac surgery

Träger et al. Int J Artif Organs, 2016
16 patients with severe post-CPB SIRS/AKI

Bernardi et al. Critical Care, 2016
Elective CPB surgery

→ Treatment duration, (average 191 +/- 56 min, compared to treatment lasting for up to 7 days in other studies)

Träger et al. Int J Artif Organs, 2016
39 patients with IE undergoing CS with HP vs.
28 historical patients with IE undergoing CPB with no HP

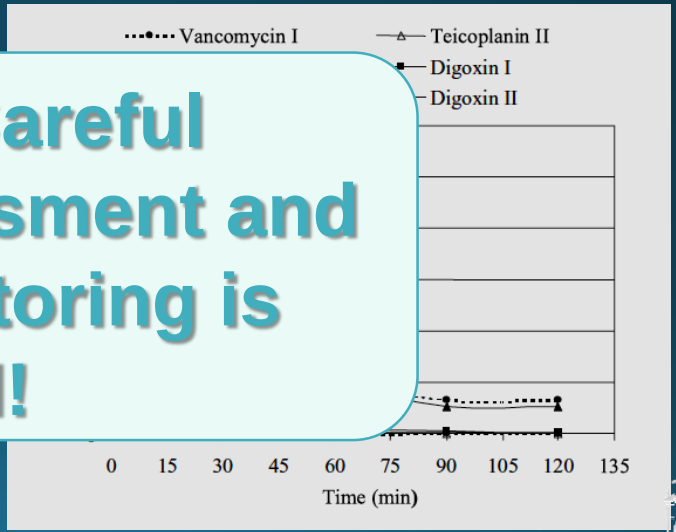
Drugs (specifically antibiotics) !

Undesired losses

Drug Removal

In vitro Removal of Therapeutic Drugs with a Novel Adsorbent System *(Ronco et al, Blood Purification, 2002)*

- ✓ Betasorb for ß2- microglobulin (11.8 kD) removal.
- ✓ Uremic bloo
  concentrate
  patient with
  healthy volu
- ✓ 14 commonly
  protein binding 0–95%, and different solubility).



Bottomline- Careful risk/benefit assessment and drug level monitoring is essential!

Novel uses

SAVE UK Trial M-2016-313

Research type

Research Study

Full title

Proof-of-Concept Trial on Selective Removal of the Antiangiogenic Factor Soluble Fms-like Tyrosine Kinase-1 (sFlt-1) in Pregnant Women with Preeclampsia via Apheresis Utilizing the Flt-1 Adsorption Column (SAVE UK Trial)

Conclusions

- ✓Adsorption represents an interesting technique for blood purification.
- ✓Overall, it's considered safe with no significant side effects.
- ✓It's associated with reduction in inflammatory mediators, improvement in hemodynamics, but not mortality.
- ✓Technical aspects, and variability of prescription may have an impact on its effectiveness.
- ✓Undesired losses remains a concern and should be accounted for.
- ✓ Biomarker-driven therapy, may be an attractive approach to help identify which patients would benefit the most.
- ✓Novel uses continue to evolve and may be promising.

Questions ?

Thank you