A.N.T.E.
Associazione Nazionale Tecnici Emodialisi

XXX Corso Nazionale ANTE - Dialisi e Tecnologia
"Presente e futuro della Nefrologia Italiana"

17-18-19 Aprile 2023 Sala Congressi Hotel Mediterraneo

Nuove possibilità tecnologiche per le CRRT cosa offre il mercato?

Francesco Garzotto

ASL VCO

Università di Padova- Dipartimento di Scienze Cardio-Toraco-Vascolari e Sanità pubblica

Unita di Biostatistica Epidemiologia e Sanita' Pubblica

Azienda Sanitaria Locale del Verbano Cusio Ossola

Università degli Studi di Padova

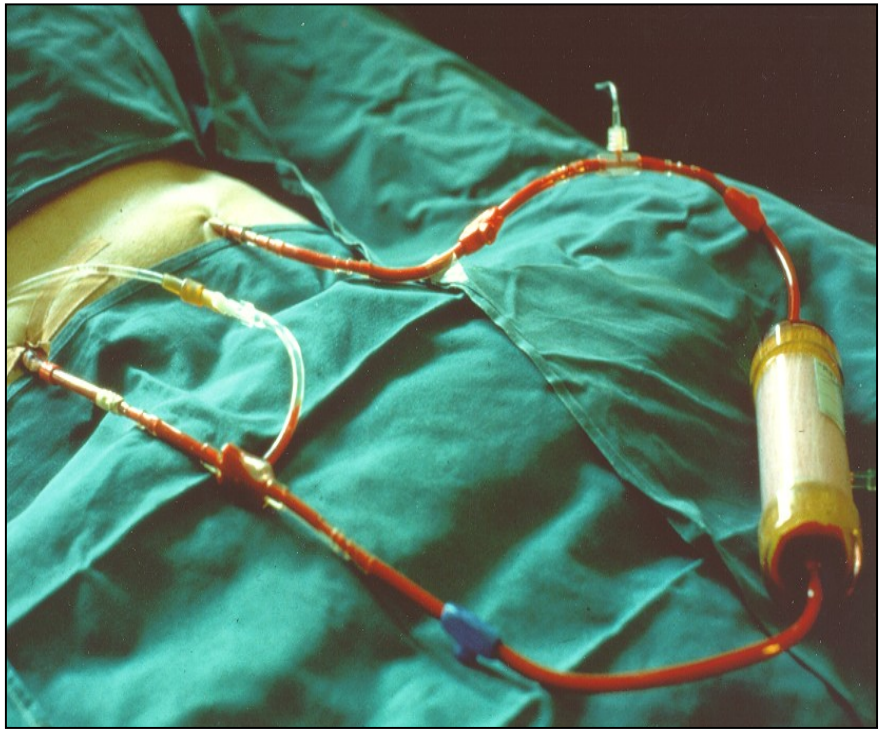
Dipartimento di Scienze Cardio-Toraco-Vascolari e Sanità pubblica

A Bit of History to Remember

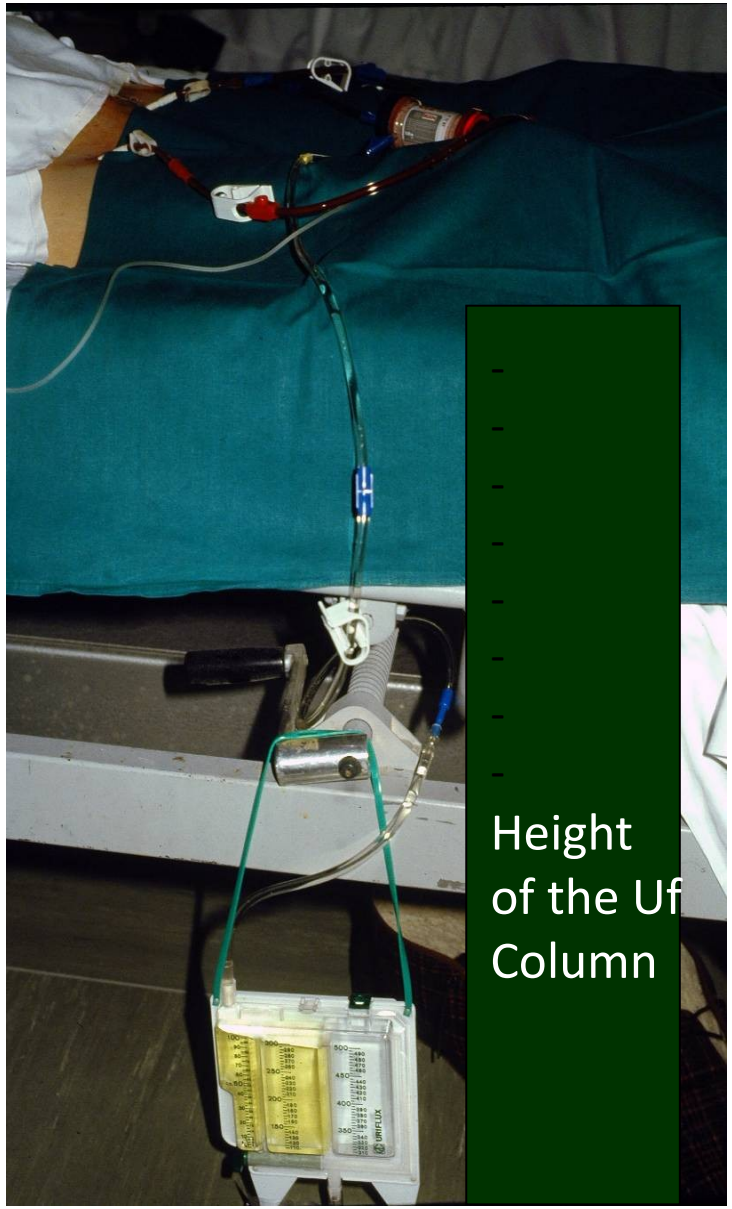
How did continuous renal replacement therapies start?

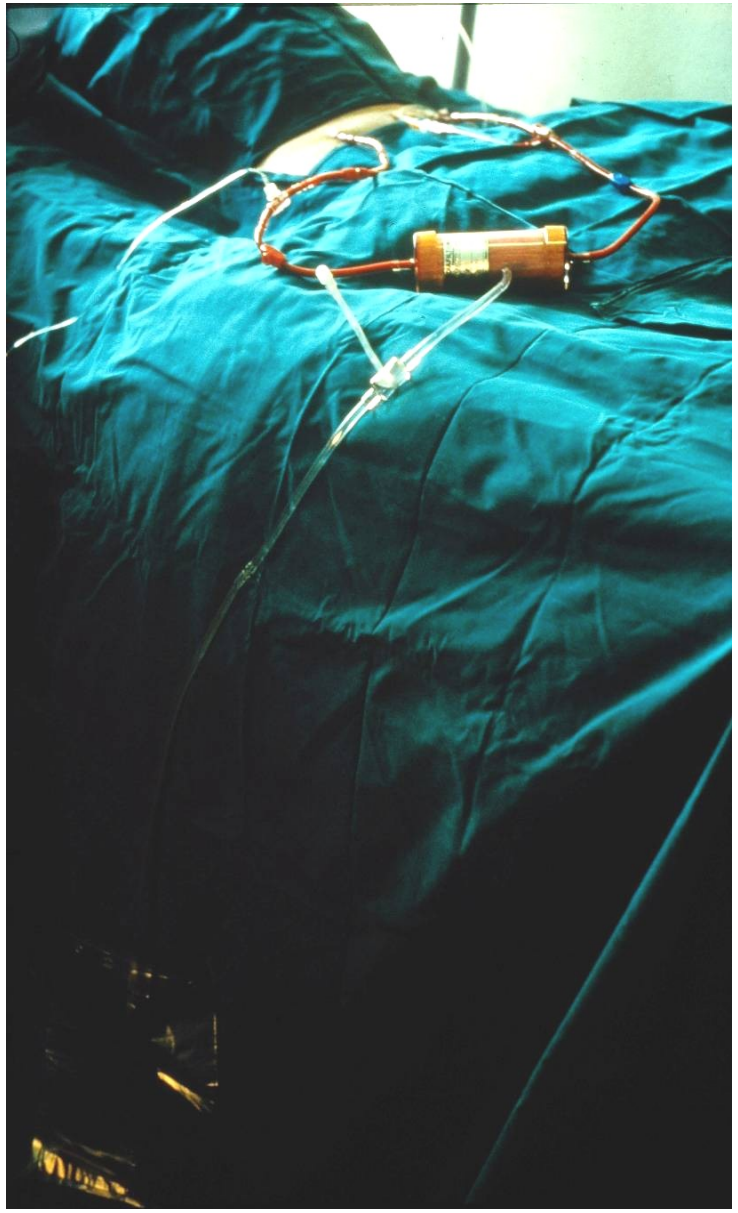
- In 1977 85% of acute renal failure were treated with peritoneal dialysis
- Critically unstable patients admitted to ICU with ARF often could not tolerate classic hemodialysis
- Hemodialysis was logistically difficult to perform in the ICU
- CAVH represented the beginning of CRRT as *"an alternative therapy for critically ill patients when hemo or peritoneal dialysis were precluded or contraindicated*".

Peter Kramer, 1977



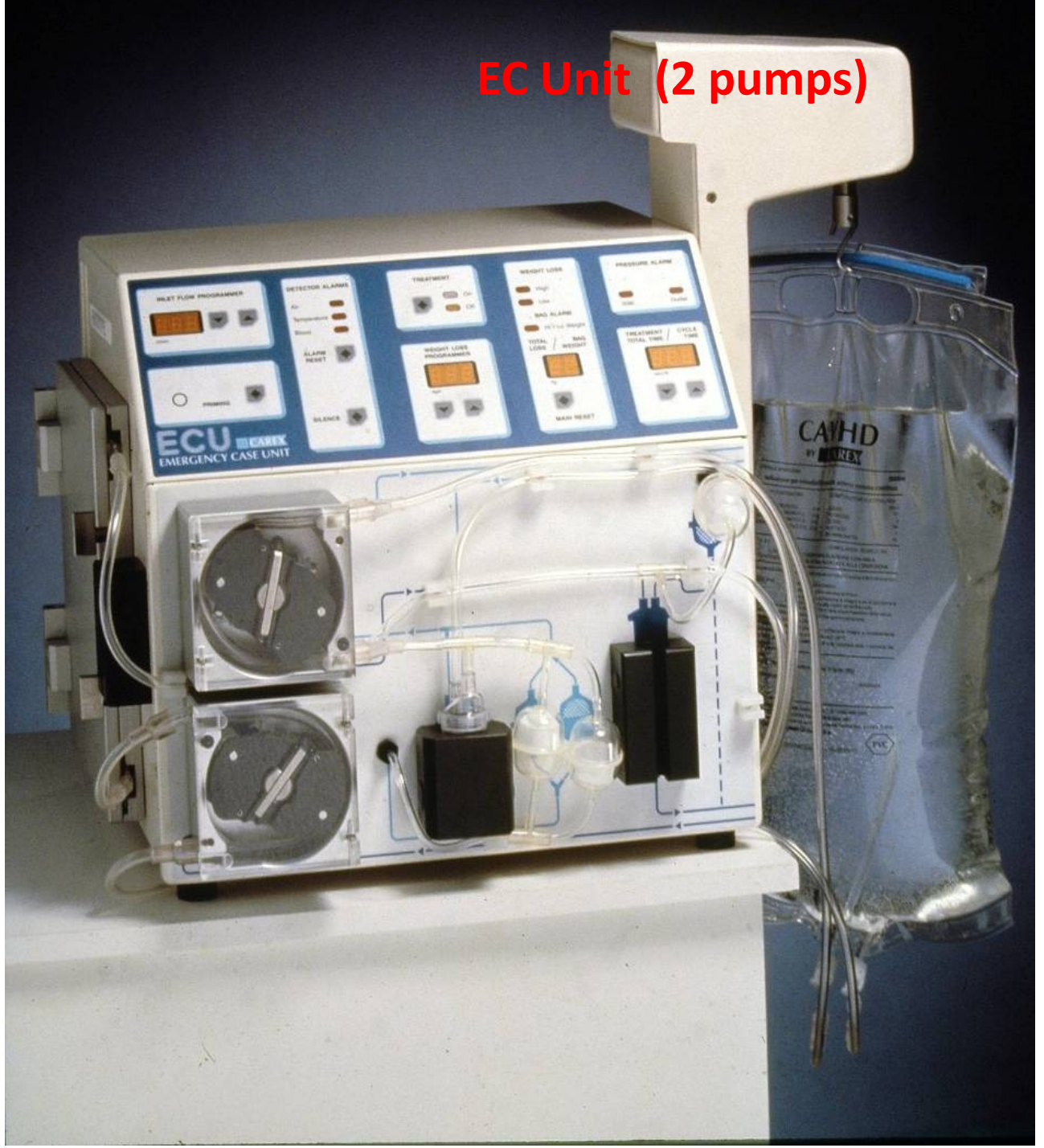
La posizione della sacca determinava la pressione negativa (Ultrafiltrazione)



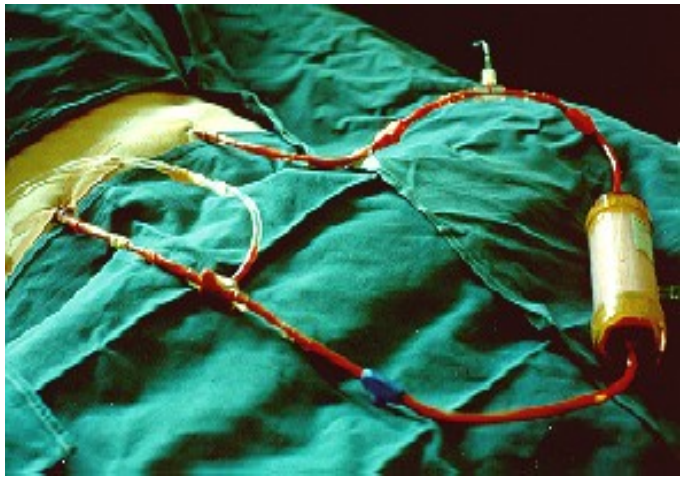


Equaline (no pumps)

EC Unit (2 pumps)

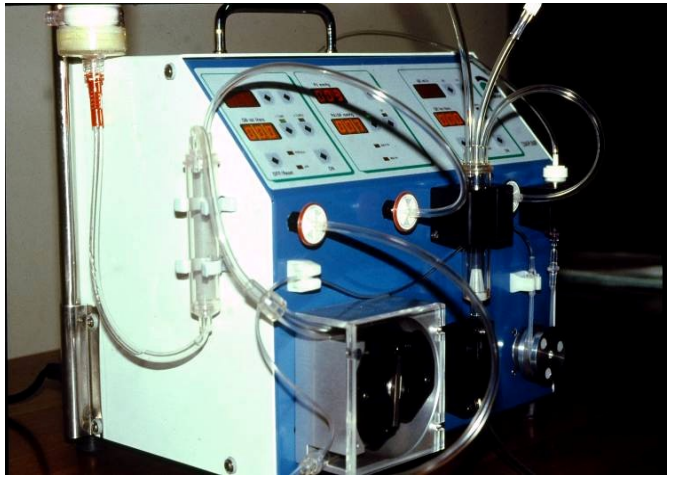


THE INTRODUCTION OF THE BLOOD PUMP



Continuous Arterio-Venous Hemofiltration

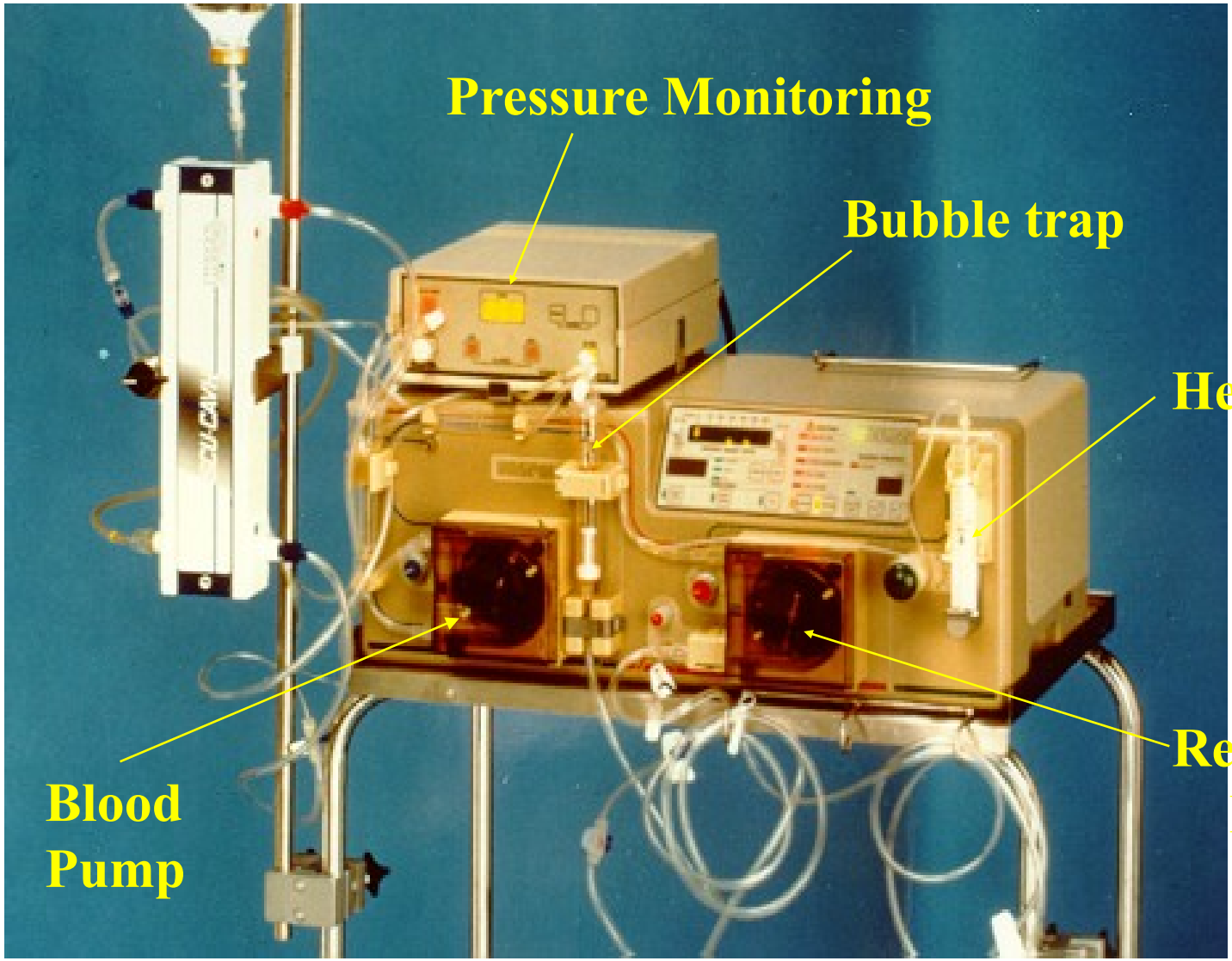
Femoral Artery and Femoral Vein
Brachial Artery and Jugular Vein



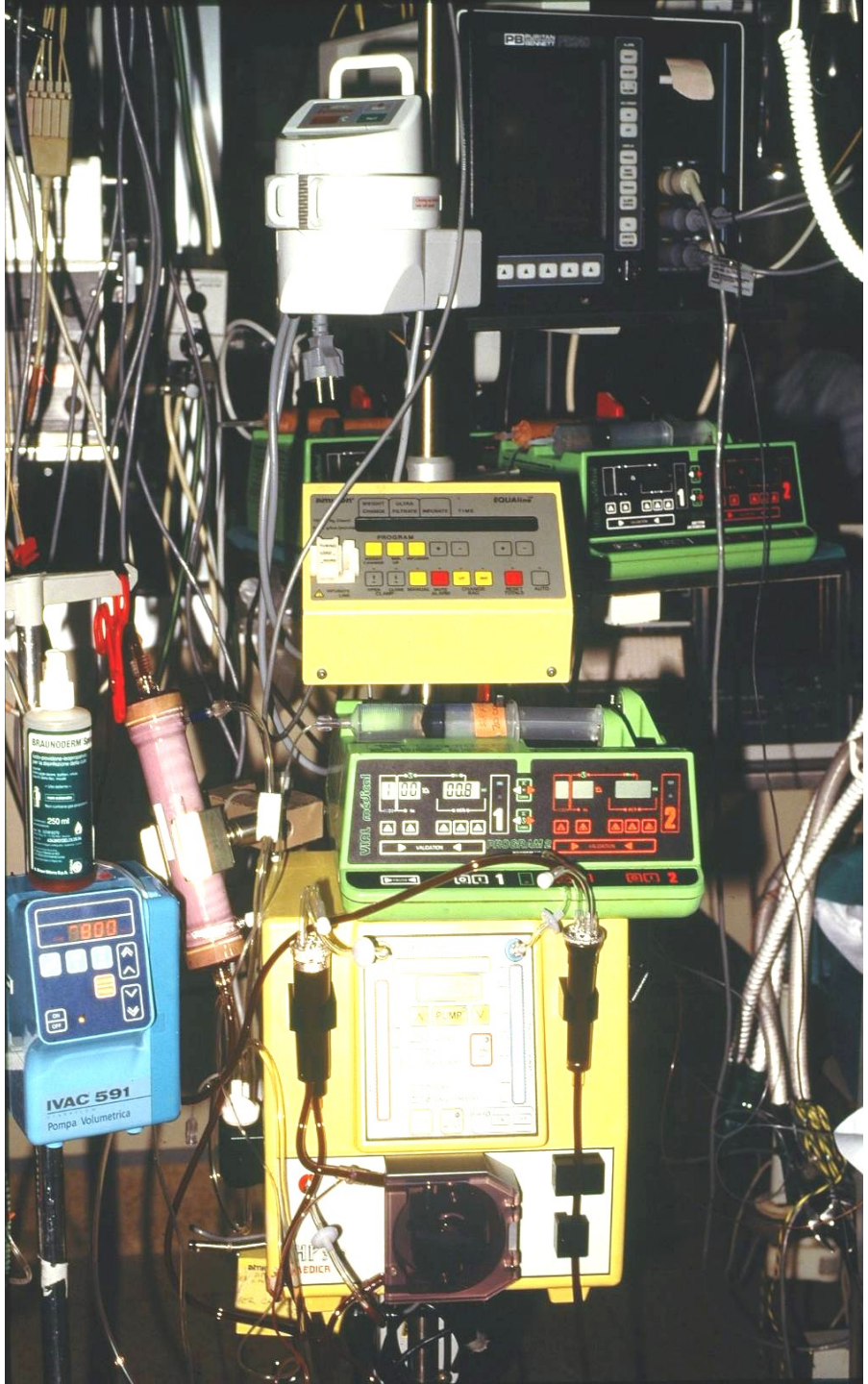
Continuous Veno-Venous Hemofiltration

Femoral Vein, Subclavian Vein
Jugular Vein (D.Lument Cath.)

CONTINUOUS VENO-VENOUS HEMOFILTRATION



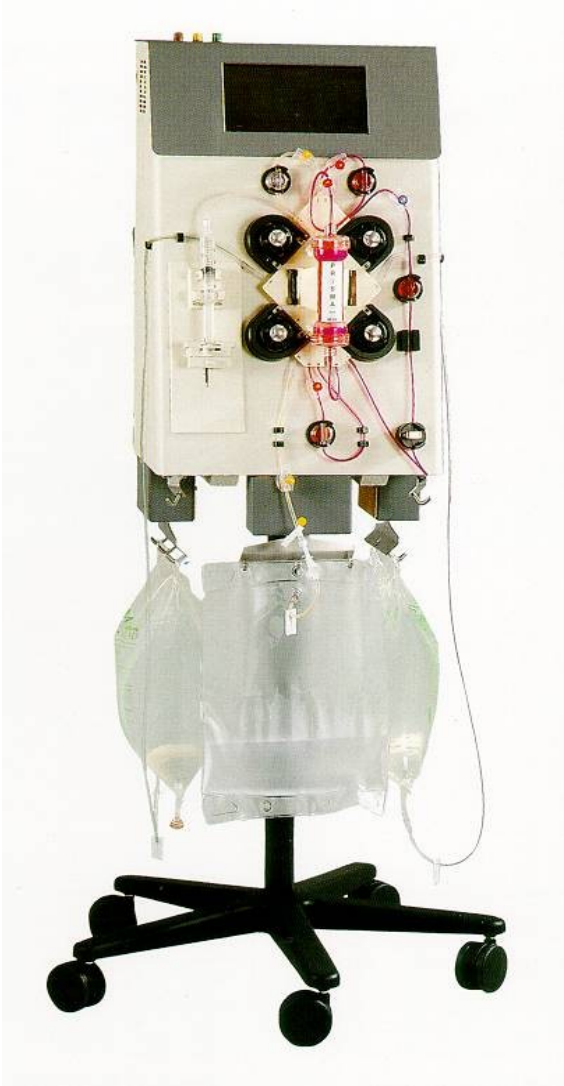
The Christmas Tree Syndrome

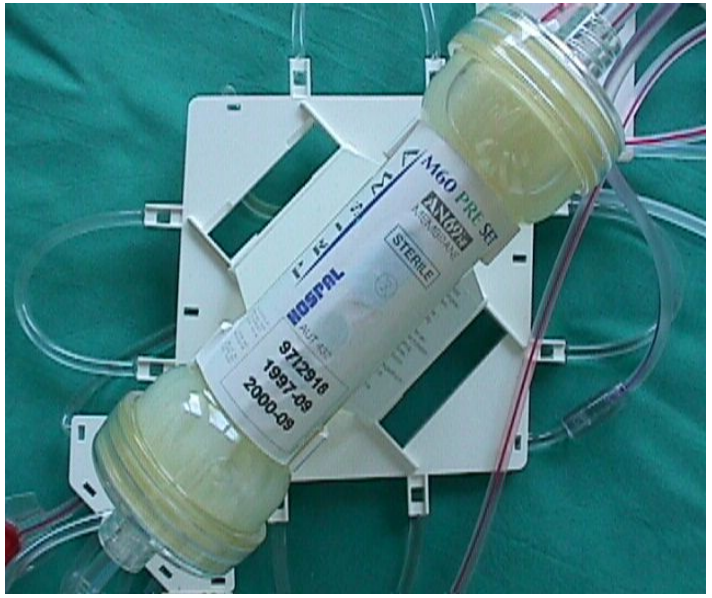


A quantum Leap in CRRT

Cobe Renal intensive

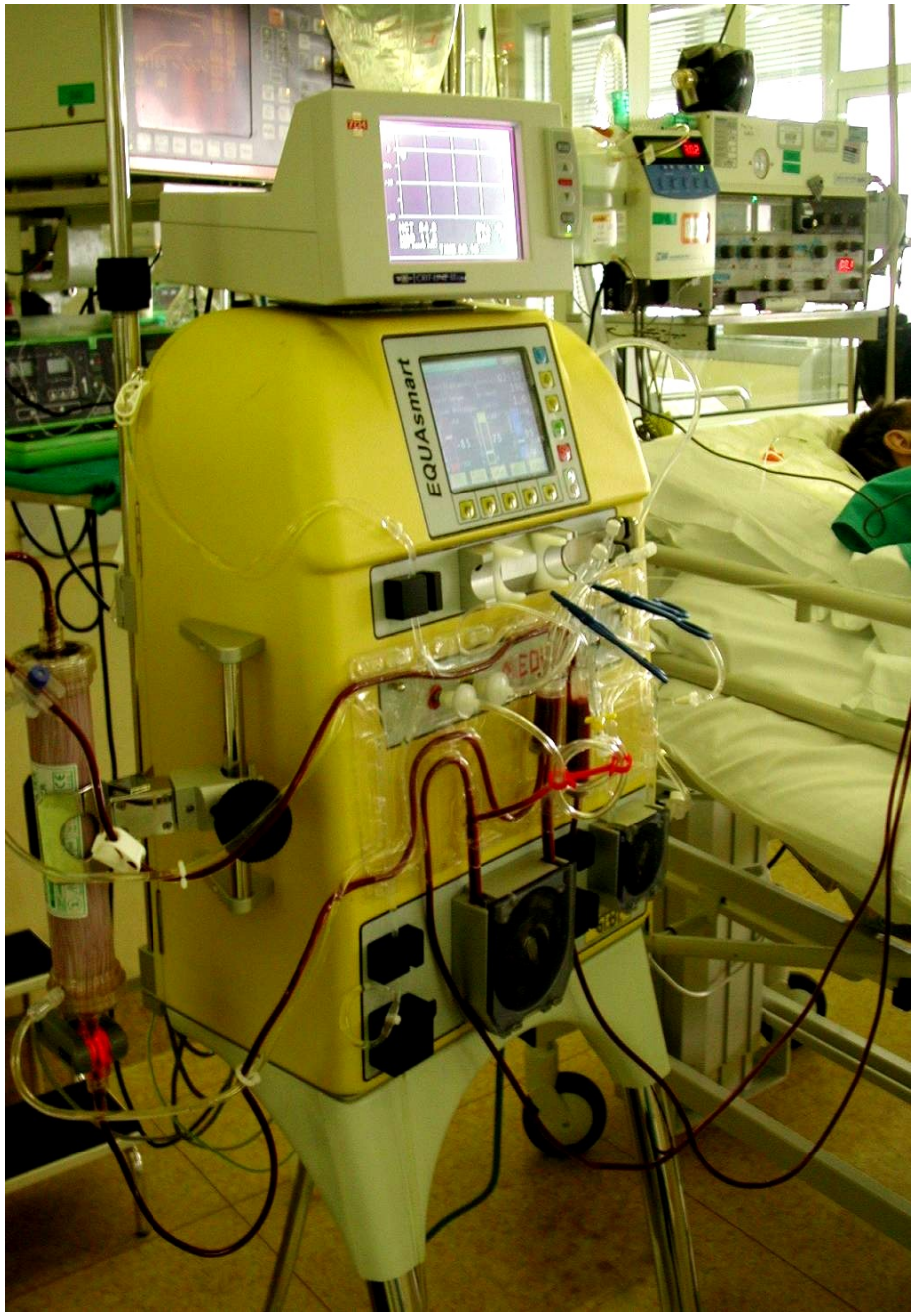
PRISMA

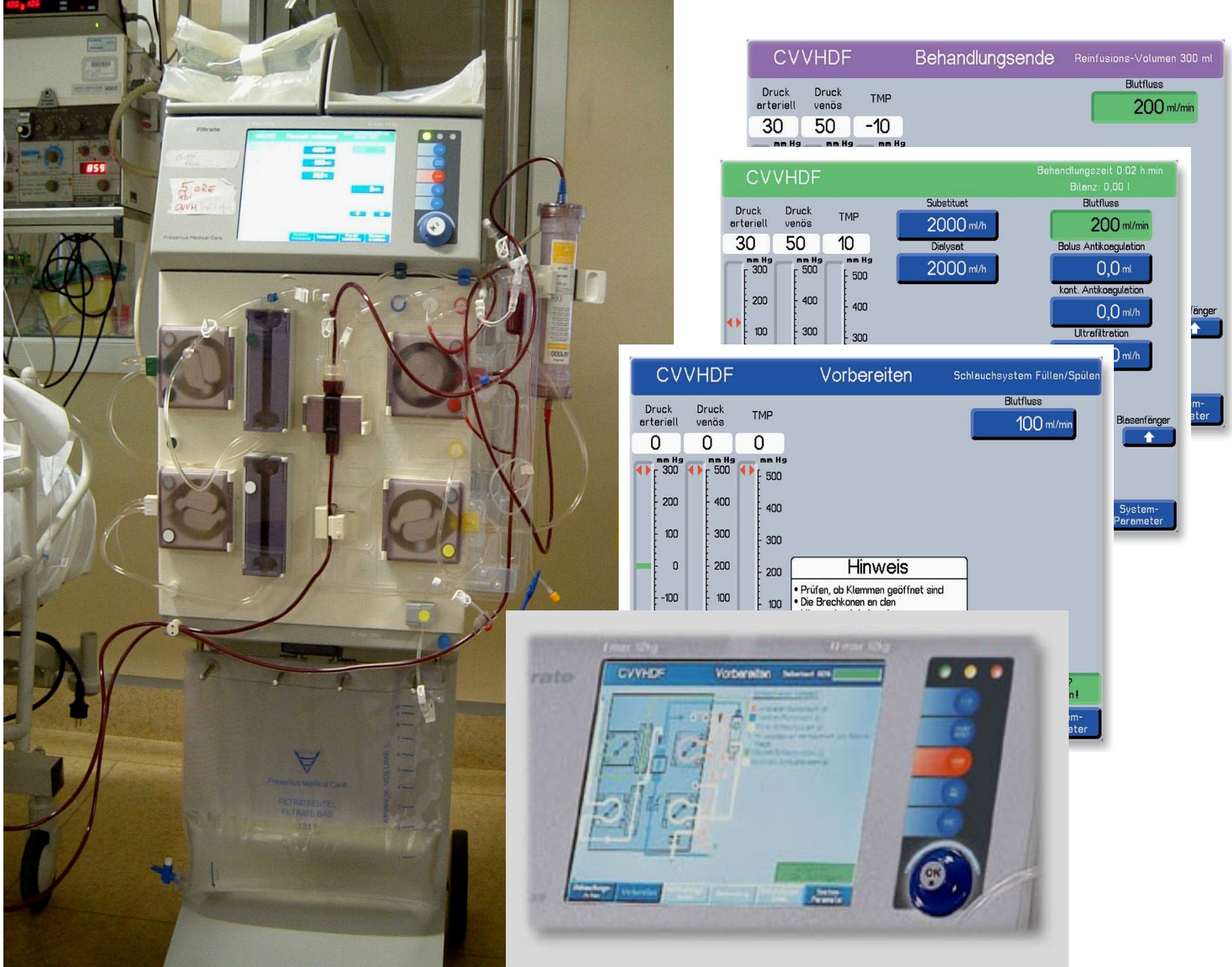




Features:

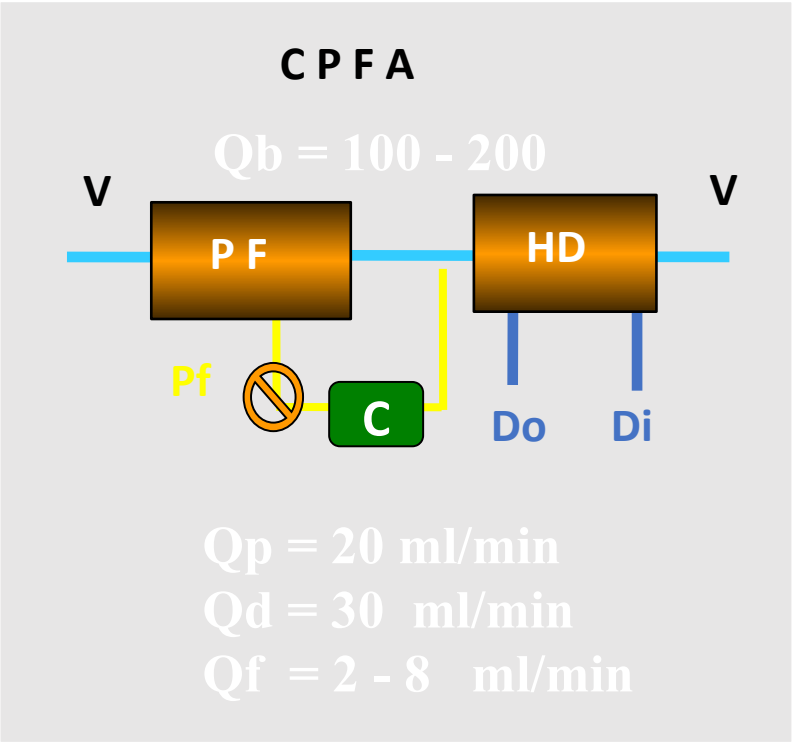
Self loading of lines and autopriming of the circuit. Treatments performed: CVVH-CVVHD - CVVHDF with large capacity of fluid handling. Large display for operations.

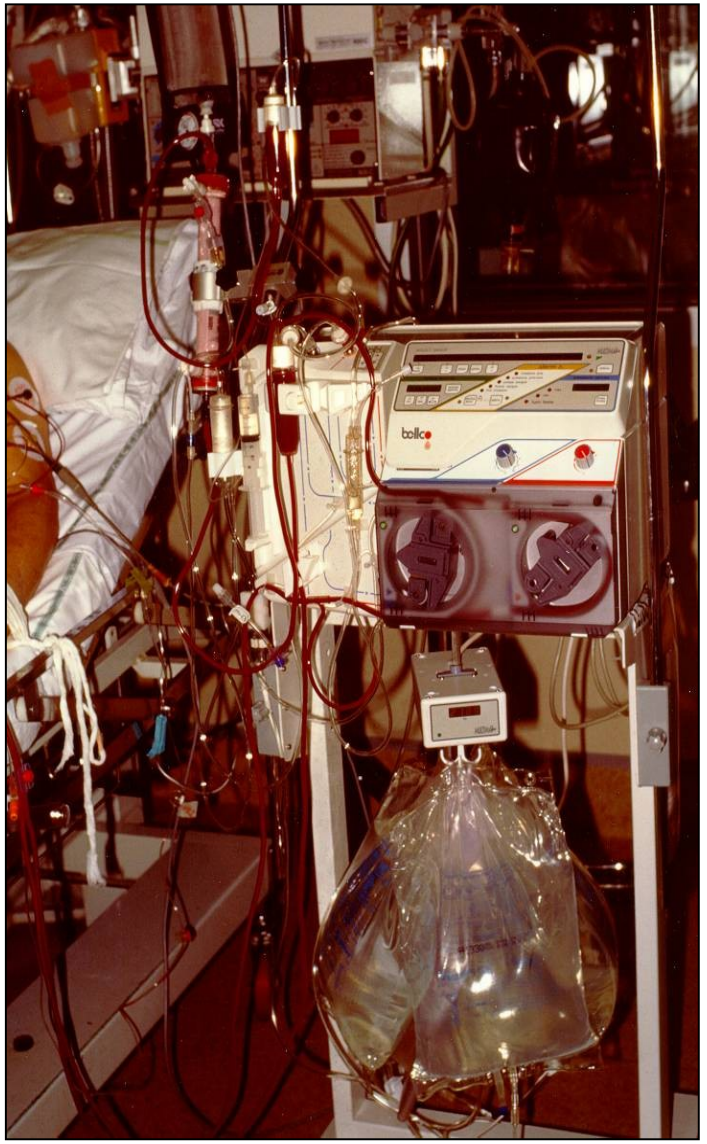

EQUAsmart


CVVHDF
Behandlungsende
Reinfusions-Volumen 300 ml
Druck arteriell
Druck venös
TMP
30
50
-10
mm Hg
Blutfluss
200 ml/min
CVVHDF
Behandlungszeit 0:02 h:min
Bilanz: 0,00 l
Druck arteriell
Druck venös
TMP
30
50
10
Substituat
2000 ml/h
Dialysat
2000 ml/h
Blutfluss
200 ml/min
Bolus Antikoagulation
0,0 ml
kont. Antikoagulation
0,0 ml/h
Ultrafiltration
Blasenfänger
System-Parameter
CVVHDF
Vorbereiten
Schlauchsystem Füllen/Spülen
Druck arteriell
Druck venös
TMP
0
0
0
mm Hg
Blutfluss
100 ml/min
Hinweis
• Prüfen, ob Klemmen geöffnet sind
• Die Brechkonen an den
Blasenfänger
System-Parameter

C P F A

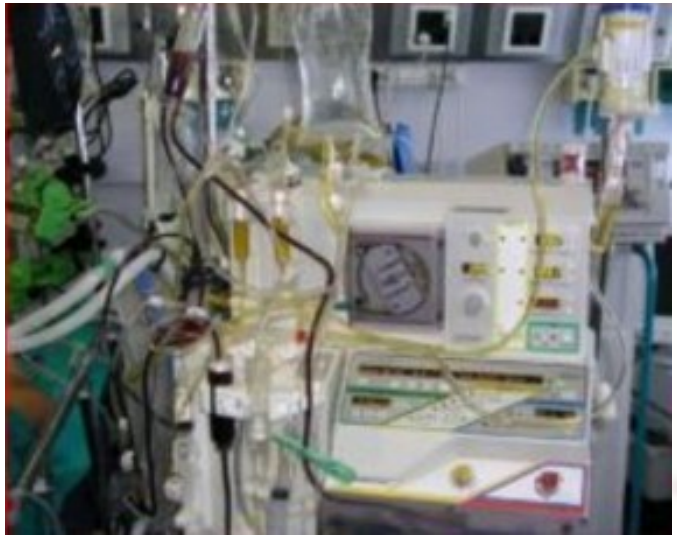
Coupling Plasmafiltration and adsorption with continuous hemodialysis for the treatment of sepsis

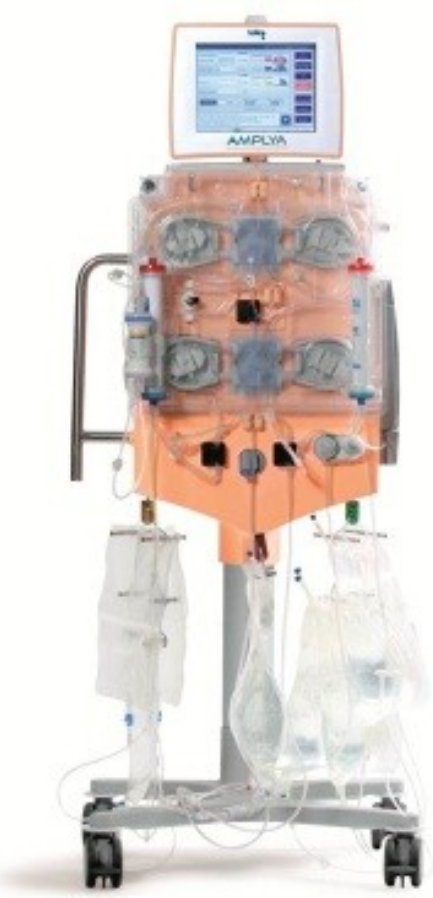




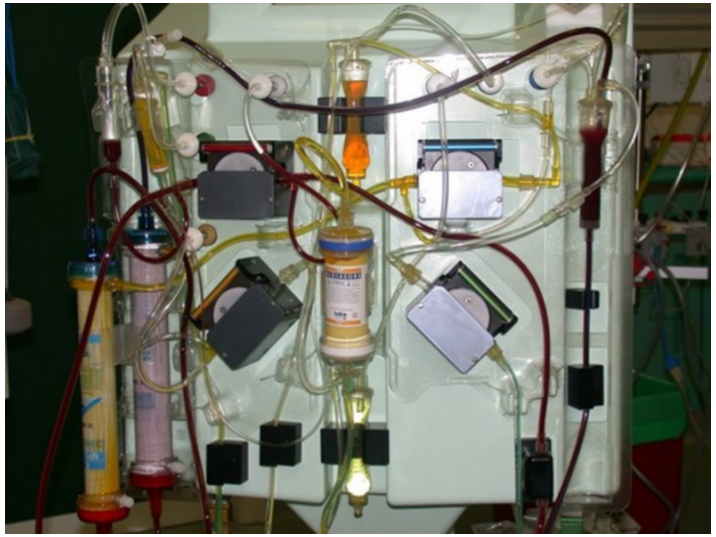
Semplificazione Tecnologica

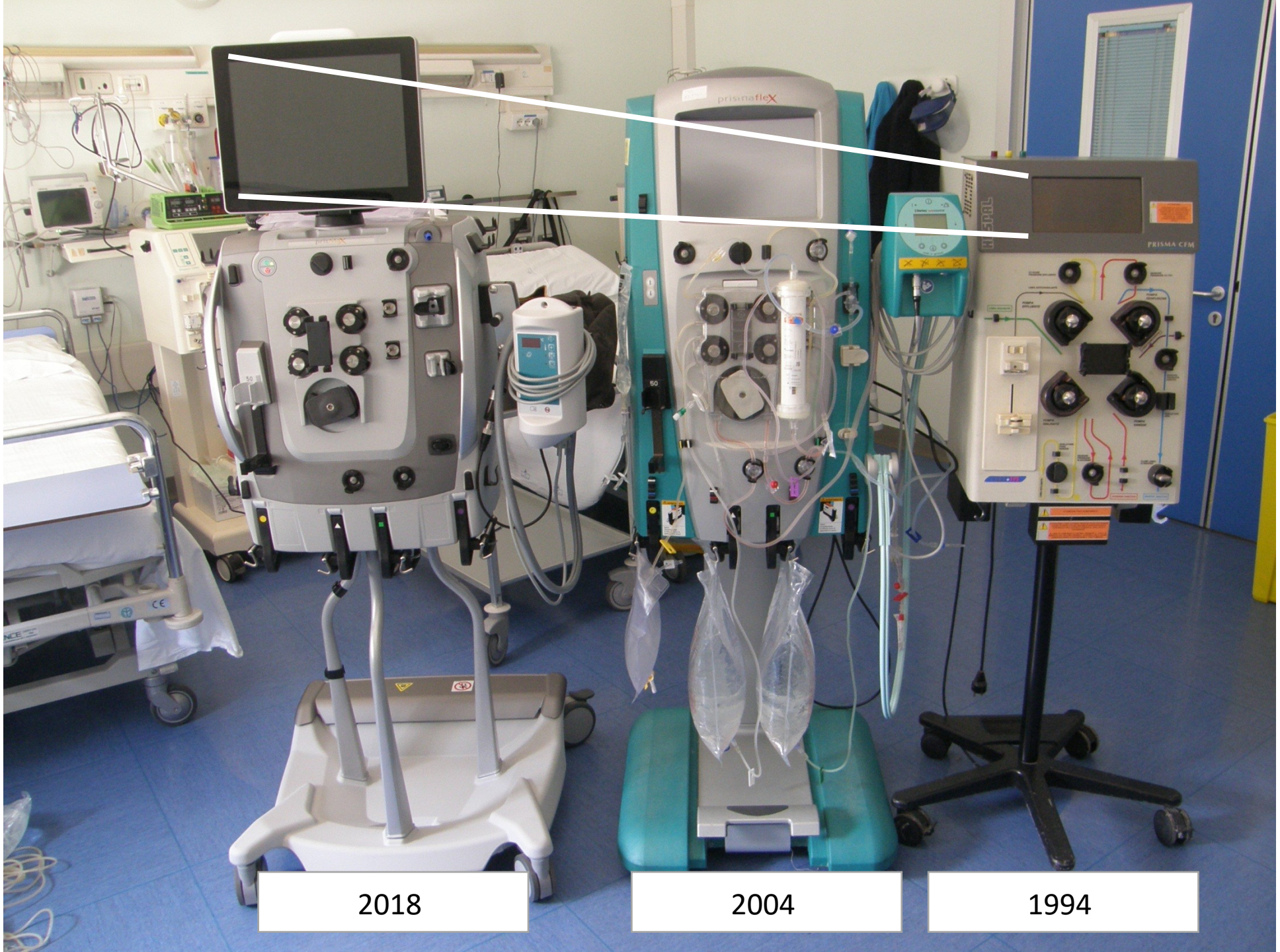
CPFA

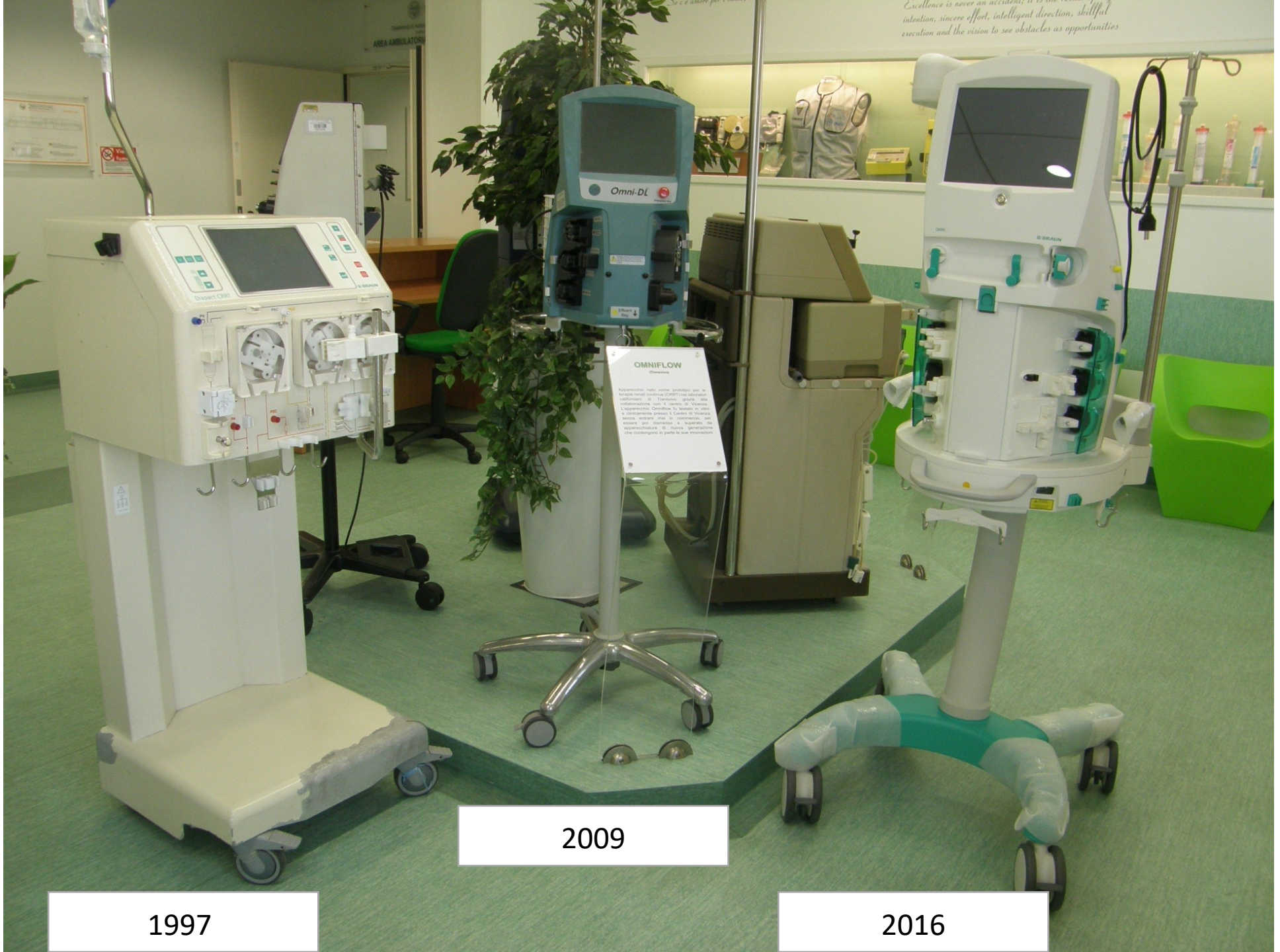




CPFA




prisma flex
PRISMA CFM
2018
2004
1994

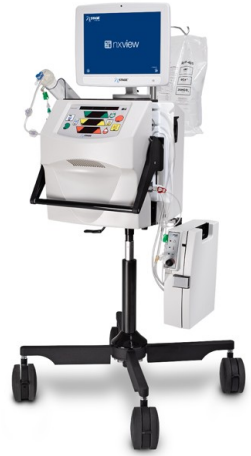

Omni-DL
OMNIFLOW
2009
1997
2016

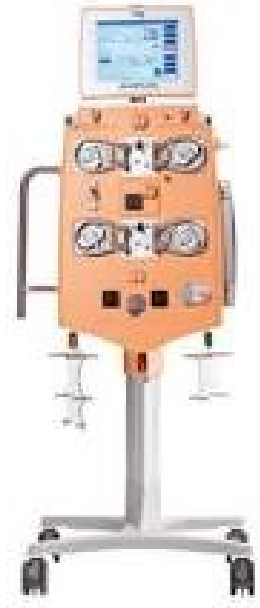
The cockpit Evolution

1993

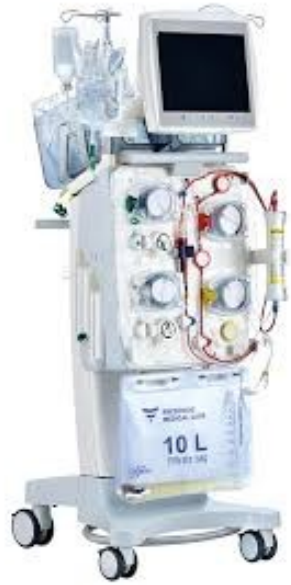
2008

2022


nxview



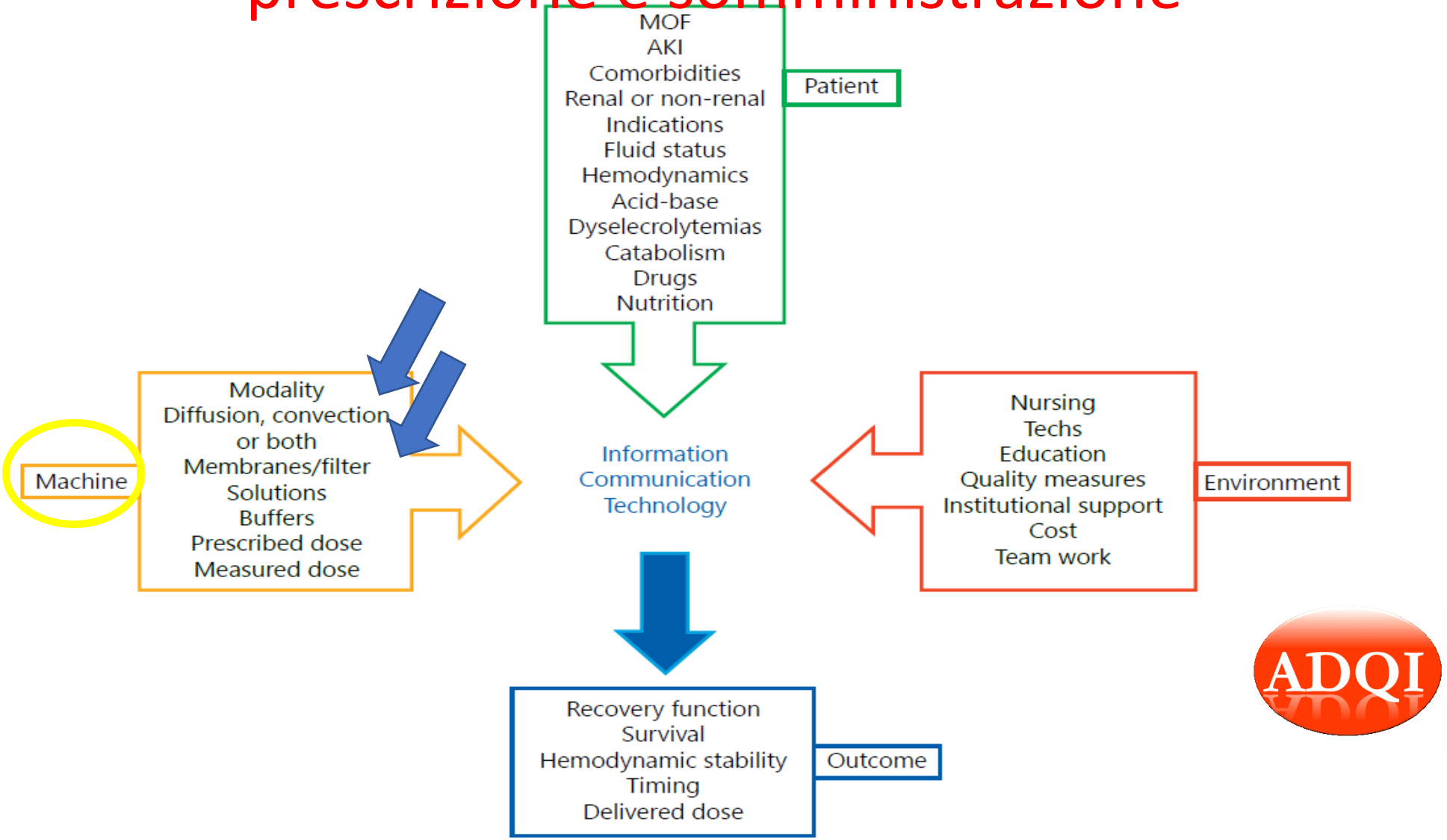

10 L


10 L

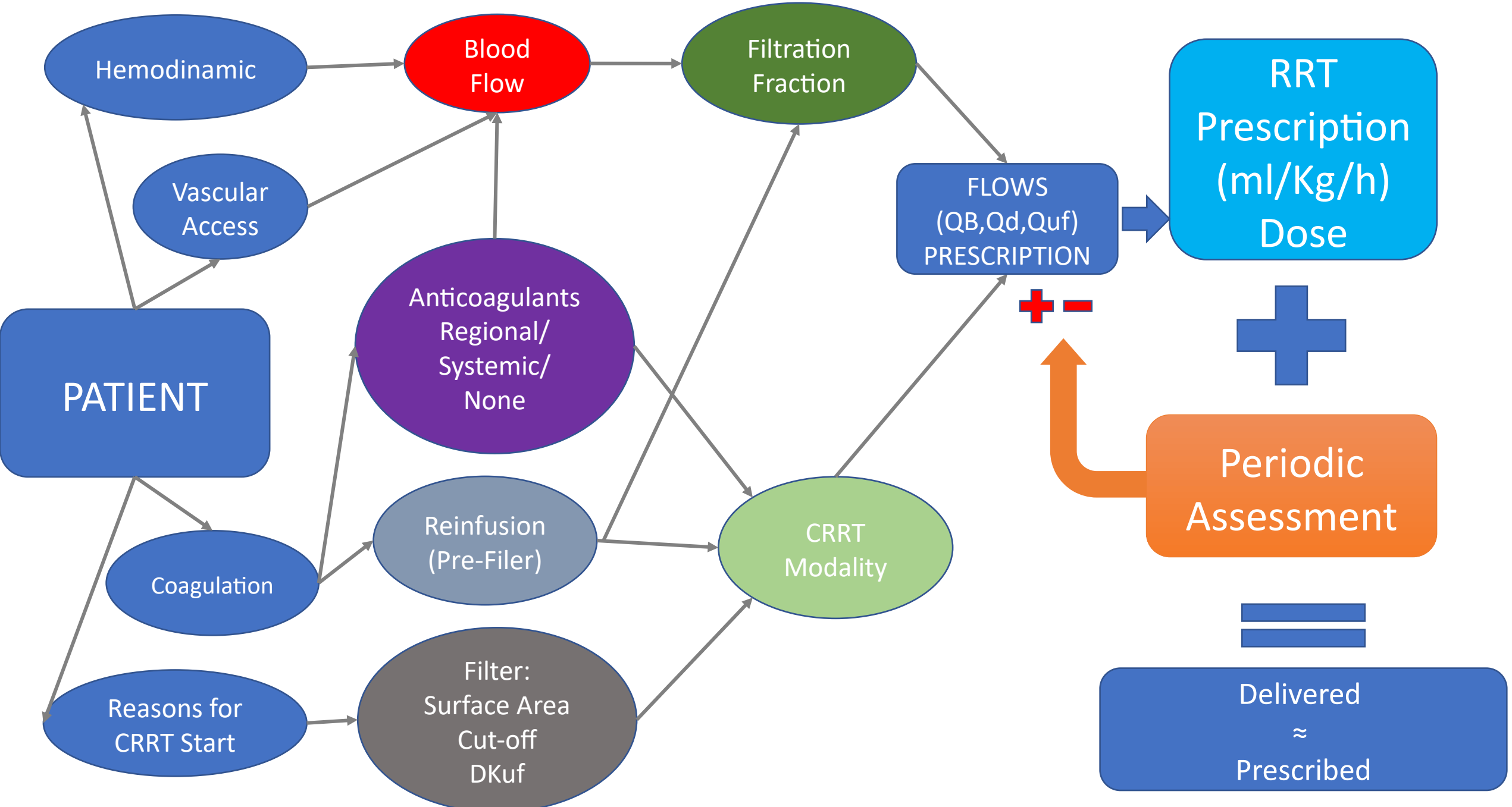

intensa

Role of Technology for the Management of AKI in Critically Ill Patients: From Adoptive Technology to Precision Continuous Renal Replacement Therapy J. Cerdá

Fattori che favoriscono una adeguata prescrizione e somministrazione



The complexity of a CRRT



...how to reach the goal?

Dose e nuove tecnologie

The Novel PrisMax Continuous Renal Replacement Therapy System in a Multinational, Multicentre Pilot Setting

– Adequate dose delivery with minimal deviations from prescribed values. This can be achieved in different ways depending on hardware and software integration.

A First Evaluation of OMNI®, A New Device for Continuous Renal Replacement Therapy

AcuSmart™

Development of the New Kibou® Equipment for Continuous Renal Replacement Therapy from Scratch to the Final Configuration

Delivered renal dose was 96.6% of prescribed

the landmark report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD)

<u>Only 50% of hospitalized patients dying with AKI received ‘good’ care, and fewer than a third with hospital-acquired AKI received adequate care</u>

develop new standards
for high-quality care for AKI and acute RRT patients

National Confidential Enquiry into Patient Outcome and Death. Adding insult to injury. http://www.ncepod.org.uk/2009aki.html; 2009, Accessed date: 31 May 2022.

Evaluating the quality of medical care - 50 Years Later

Avedis Donabedian and The Birth of Healthcare Quality Evalu...

Evaluating the Quality of Medical Care

AVEDIS DONABEDIAN

THIS PAPER IS AN ATTEMPT TO DESCRIBE AND evaluate current methods for assessing the quality of medical care and to suggest some directions for further study. It is con-

A triad of: structure, process, and outcome to evaluate the quality of health care

earch for the most used Quality Indicators (Qis) in literature

SYSTEMATIC REVIEW

Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review

Oleksa G. Rewa[1*], Pierre-Marc Villeneuve[1], Philippe Lachance[1], Dean T. Eurich[2], Henry T. Stelfox[3], R. T. Noel Gibney[1], Lisa Hartling[4], Robin Featherstone[4] and Sean M. Bagshaw[1]

QIs were classified as related to:

- structure (*n* = 4, 22.2 %),
- care processes (*n* = 9, 50.0 %), and
- outcomes (*n* = 5, 27.8 %).

The most commonly mentioned QIs focused on:

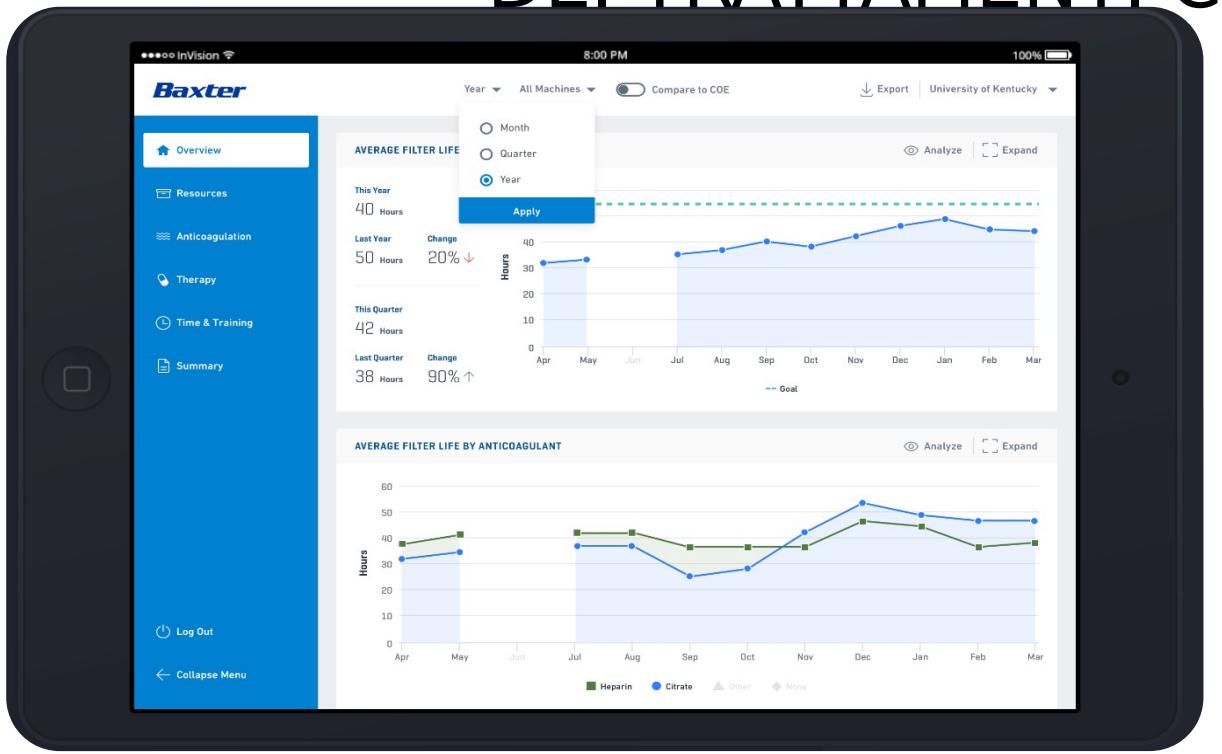
- filter lifespan (*n* = 98),
- small solute clearance (*n* = 46)
- bleeding (*n* = 30),
- delivered dose (*n* = 19), and
- treatment interruption (*n* = 5)

Across studies, the definitions used for QIs evaluating similar constructs varied considerably. When identified, QIs were most commonly described as important (n = 144, 48.3 %), scientifically acceptable (n = 32, 10.7 %), and useable and/or feasible (n = 17, 5.7 %) by their primary study authors.

2 MONITORAGGIO E ANALISI

TRUEVUE ANALYTICS™ PERMETTE DI MISURARE LE METRICHE CHIAVE DEI TRATTAMENTI CRR

Baxter
TrueVue Therapy Management



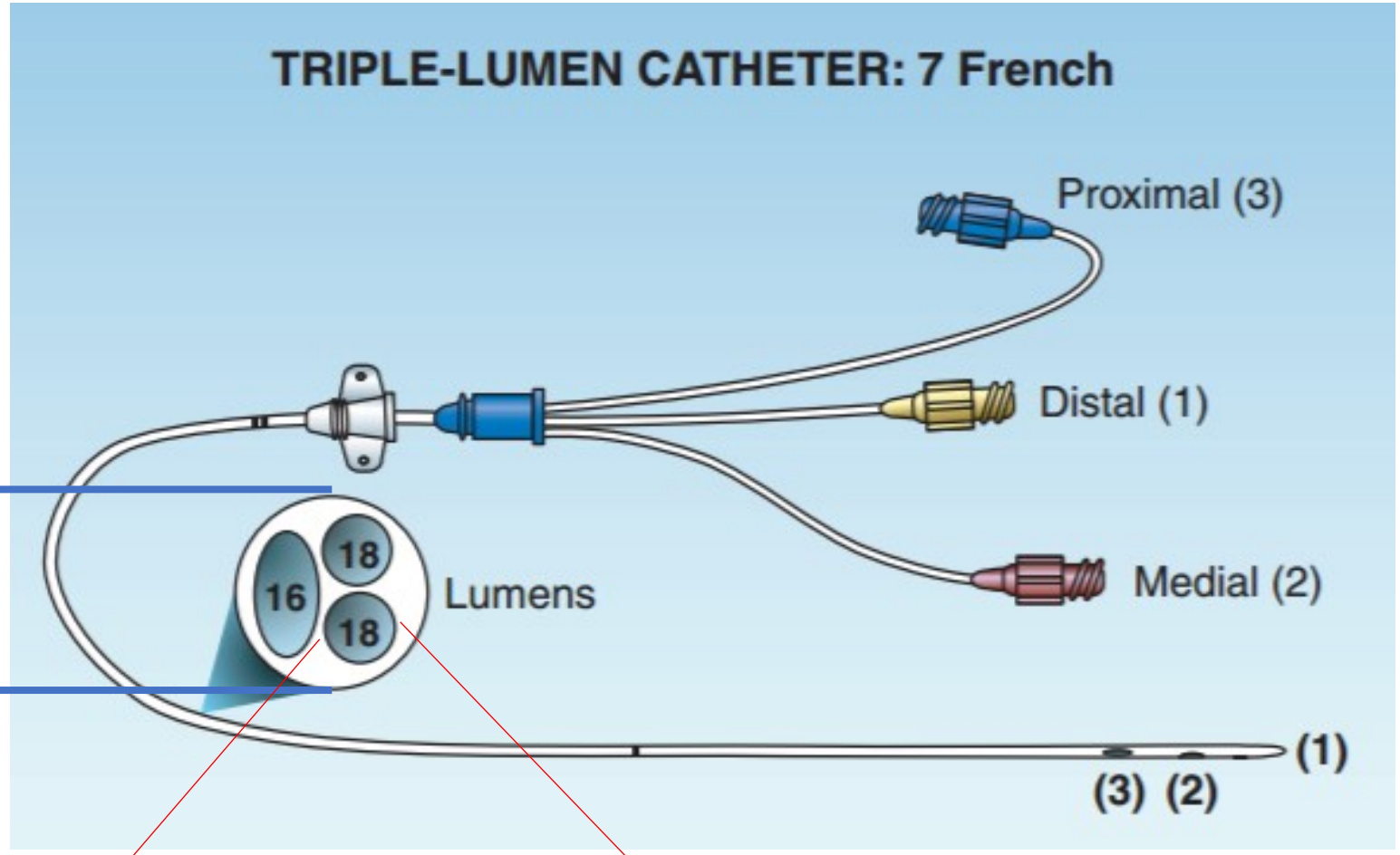
TrueVue Analytics riceve i dati dal cloud e popola una dashboard CRRT che misura e traccia le **metriche chiave** come la **durata del filtro**, **gli allarmi** e **la dose erogata**.

TrueVue Analytics :

CONSENTE ai medici di valutare i trend e le metriche di performance del proprio centro rispetto a degli obiettivi.

FAVORISCE l'individuazione di indicatori e standard di qualità interni

Central Venous Catheters



maximize blood flow while minimizing vessel trauma

Rheology
Poiseville Low

The largest and shortest catheter should be best

Hagen-Poiseuille equation (4).
$Q = \Delta P \times (\pi r 4 / 8\mu L)$

Patient

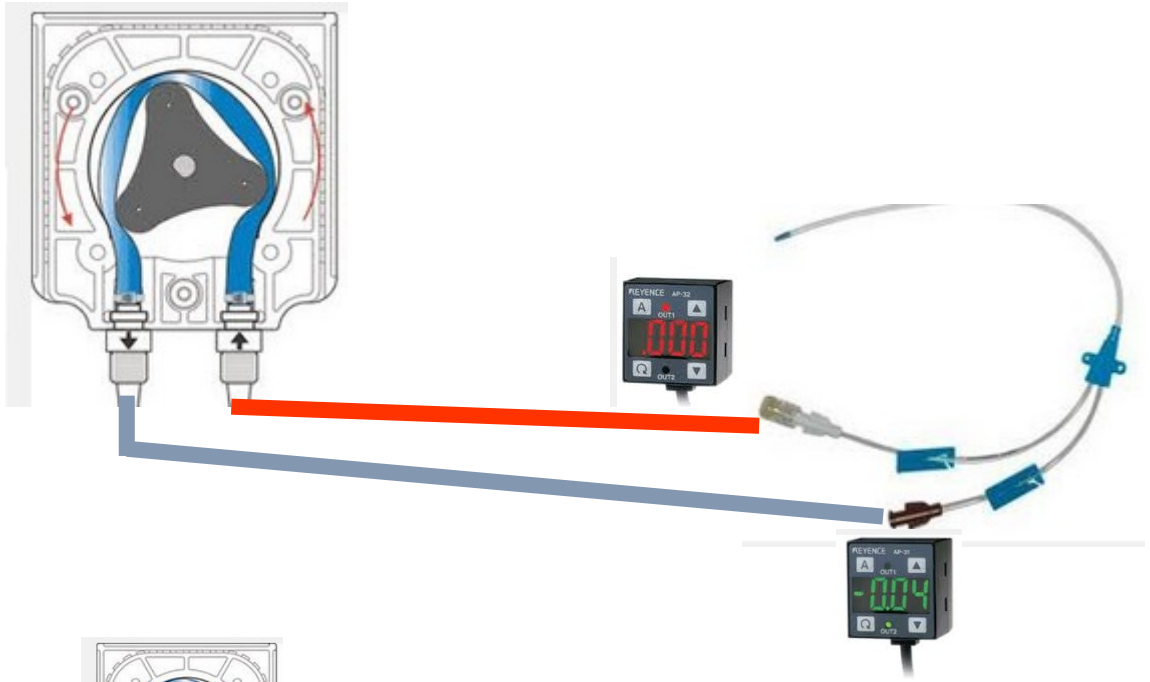
The thinner and longer catheter should be best

French ~ 3 x diameter of vessel

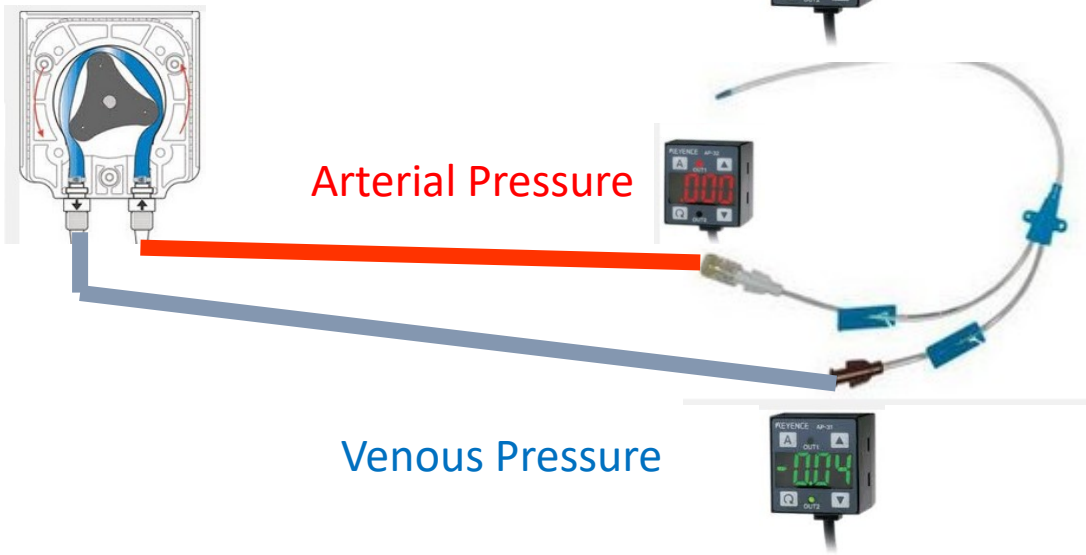
Pumps and catheters: effect on pressure variation

Classic Pump

Adults Chronic/Acute machine



Carpediem Pump

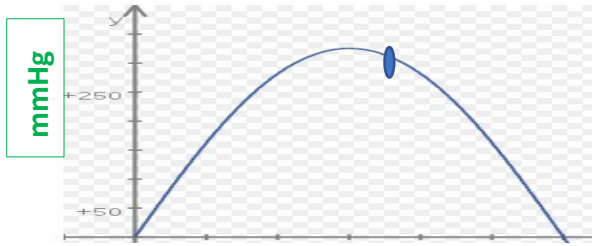


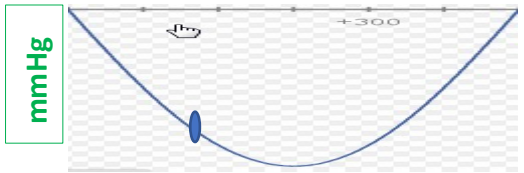
Catheter Size:

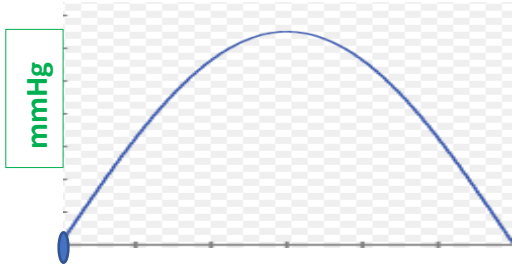
4 Fr and 5 Fr

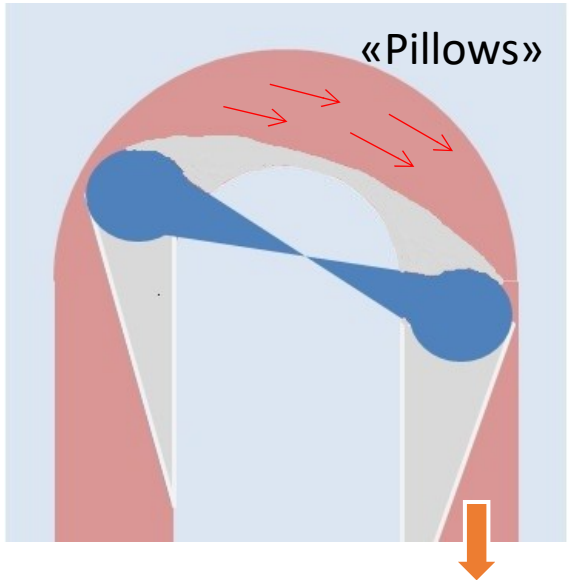
Flow in Peristaltic Pumping

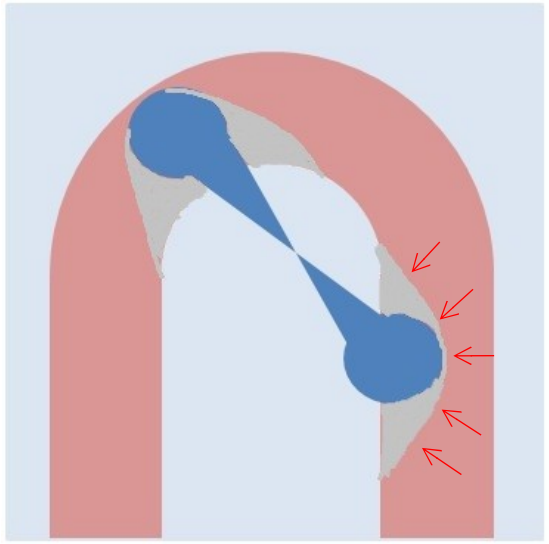
Alternating pillows and voids cause fluid flow to be pulsated, rather than smooth and continuous

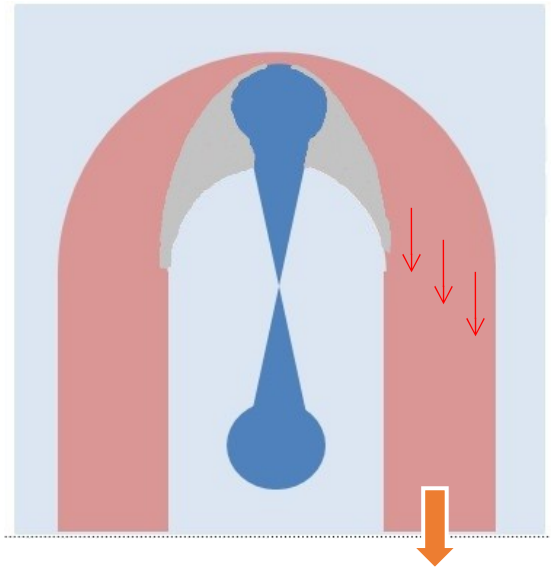






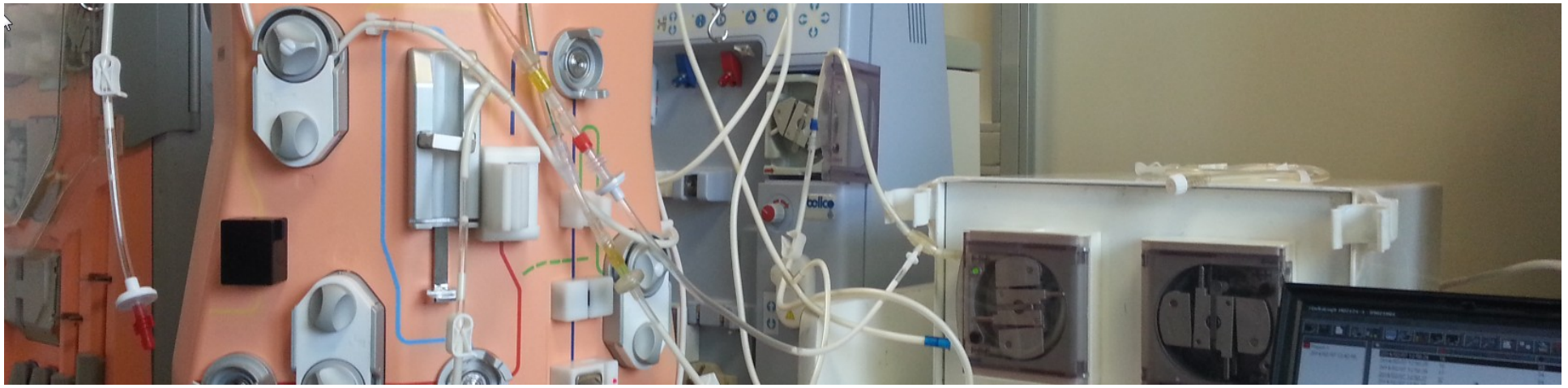


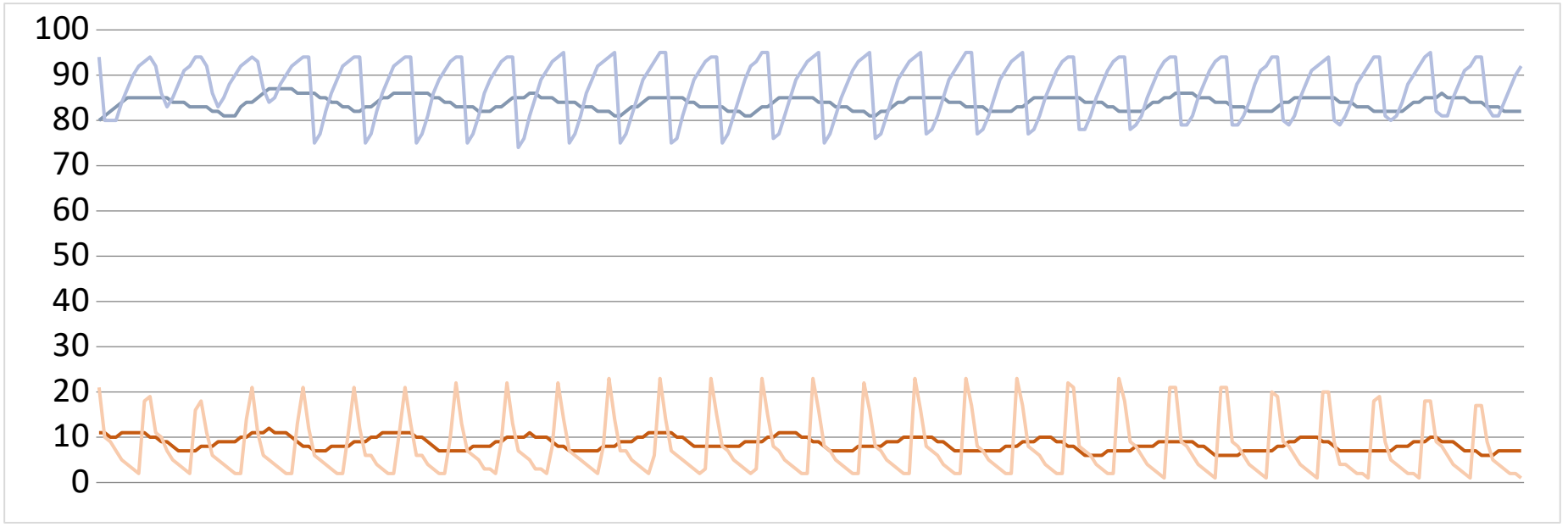


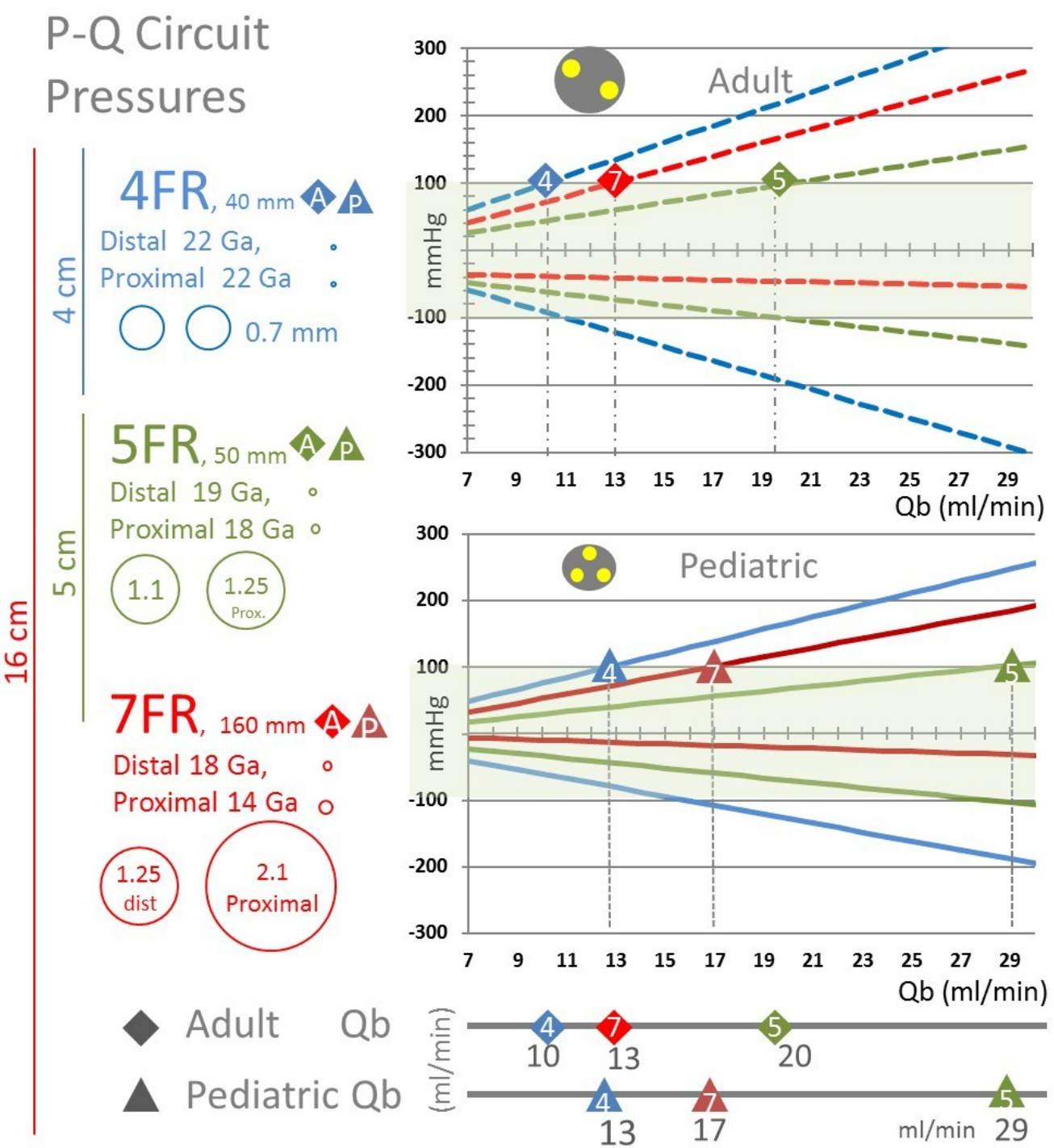


Tubing behind the rollers recovers its shape.

Big Pump VS Small Pump





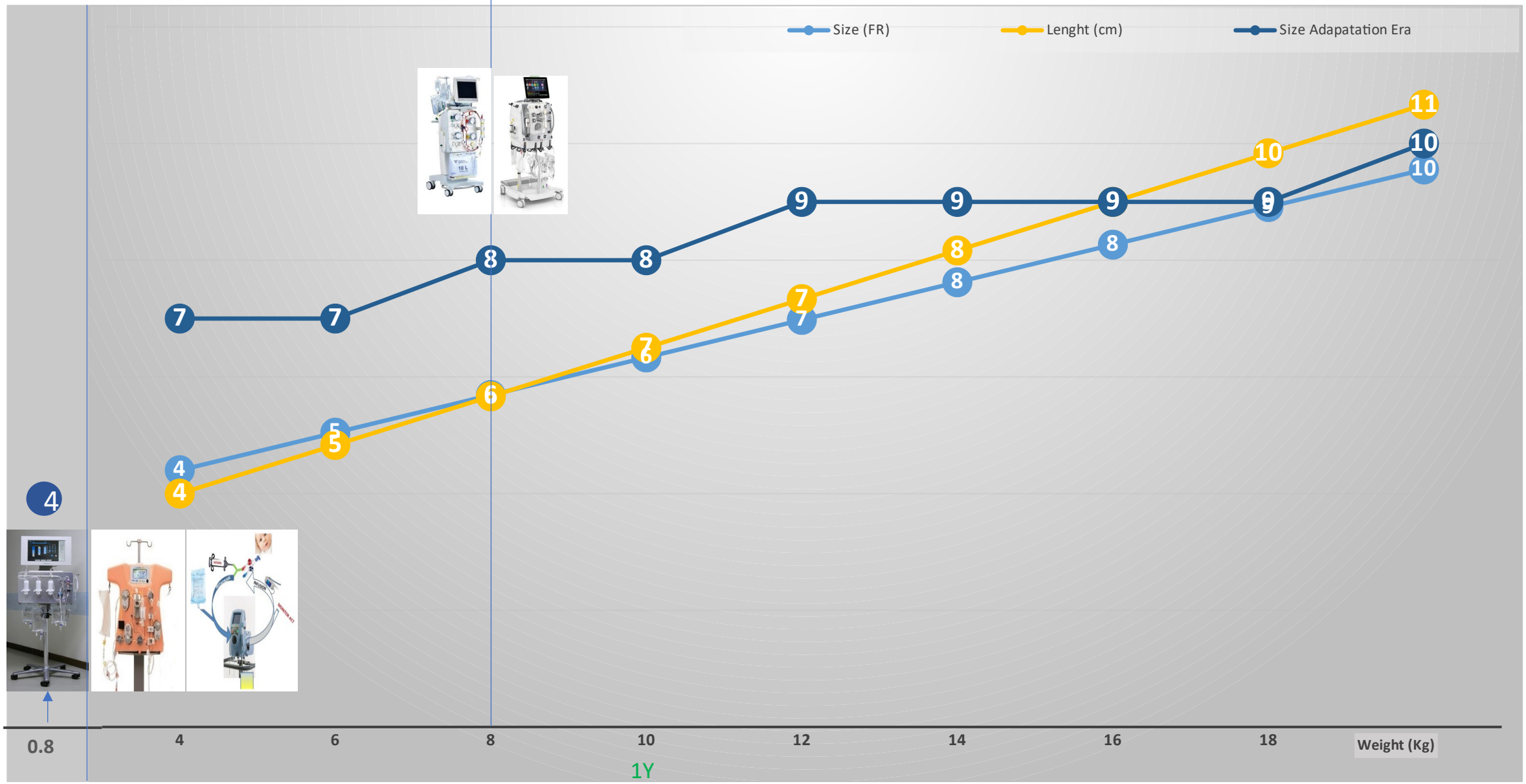


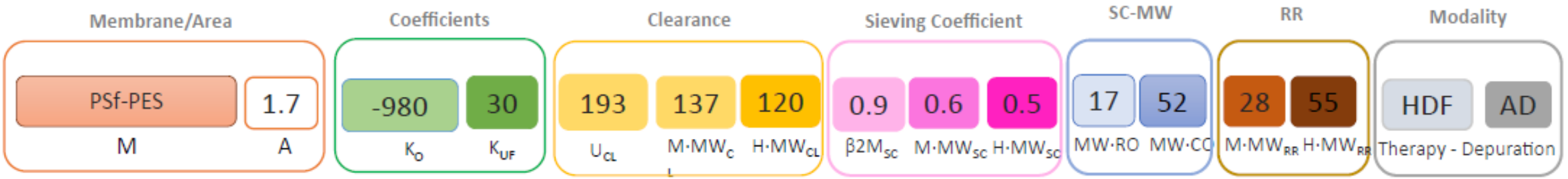
Online Laboratory Investigation

Choice of Catheter Size for Infants in Continuous Renal Replacement Therapy: Bigger Is Not Always Better*

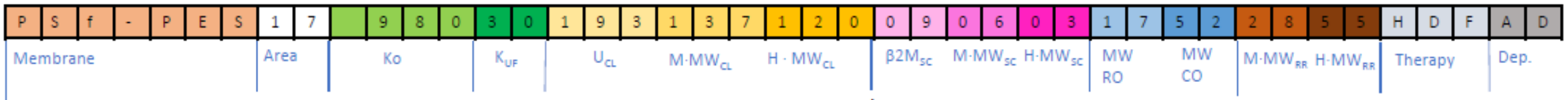
Francesco Garzotto, MSc[1–3]; Marta Zaccaria, MSc[4]; Enrico Vidal, MD, PhD[5]; Zaccaria Ricci, MD[6]; Anna Lorenzin, MSc[4]; Mauro Neri, MSc[4]; Luisa Murer, MD[5]; Federico Nalesso, MD, PhD[3,4]; Alfredo Ruggeri, MSc[7]; Claudio Ronco, MD[3,4]

The optimal access for CRRT





DIC 43 digits



M Membrane Material/s
A Area (m^2)
K_O urea mass transfer coefficient*
K_{UF} (mL/h/ mmHg)*
U_{CL} Urea Clearance (mL/min)*
$M{\cdot}MW_{CL}$ Middle MW Clearance** (mL/min)
$H{\cdot}MW_{CL}$ High MW Clearance*** (mL/min)
$\beta2M_{SC}$ β2M Sieving Coefficient
$M{\cdot}MW_{SC}$ Middle MW Sieving Coefficient**
$H{\cdot}MW_{SC}$ High MW Sieving Coefficient***
MW·RO MW Retention Onset (Kda)
MW·CO MW Cut-Off (Kda)
$M{\cdot}MW_{RR}$ Middle MW Reduction Rate**
$H{\cdot}MW_{RR}$ High MW Reduction Rate***

$$RR(\%) = \left(1 - \frac{C_{Post}}{C_{Pre}}\right) \times 100$$

*SC QB=300 mL/min; QUF=0.2*QB (ISO8637); Kuf: HCT 32%, 37°C*
** KO ,Clearance (QB = 300 mL/min, QD = 500mL/min, QUF=0)*
***MW ≥ 17 KDa (the molecule used has to be specified for standardization)*
****MW ≥ 40 KDa (the molecule used has to be specified for standardization)*

Legend: SC Sieving Coefficient, RR Reduction Rate (%), MW Molecular Weight (KDa)

Membrane:
CTA cellulose triacetate
CUP Cuprophan
PES Polyethersulfone
PMMA Polymethylm methacrylate
PSf Polysulfone

Therapy
HD Hemodyalisis
HDx Expanded HD
HFD HighFluxDialysis
HDF Hemodiafiltration
HF Hemofiltration
HFR HF with endogenous reinfusion
AFB Acetate Free Biofiltration

Main depuration process
DI Diffusion
CO Convection
AD Adsorption
IF Internal-Filtration
RO Replacement On-Line
RB Replacement Bag
RE Replacement Endogenous

***MMW: Myoglobin (17.2 kDa)
****HMW : sFLC λ (50 kDa)

Artificial Organs
WILEY

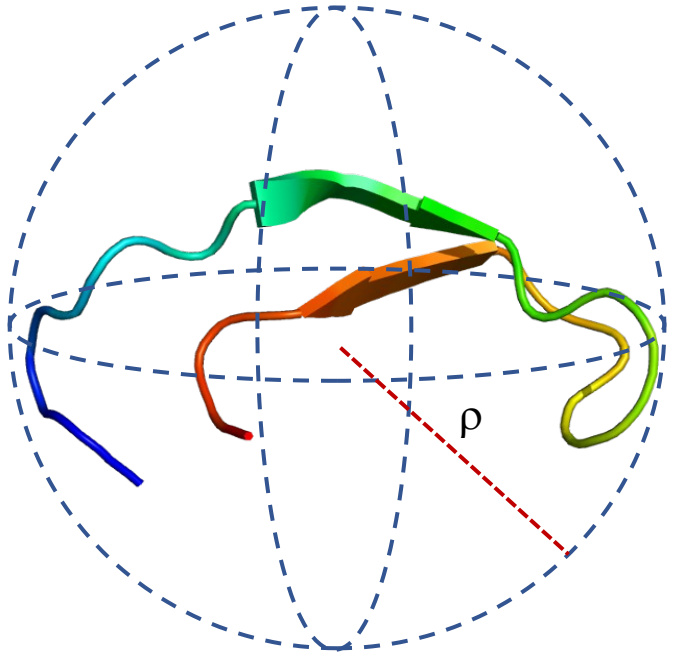
THOUGHTS AND PROGRESS

The Dialyzer Identification Code (DIC): A filter characteristics codification for dialyzer choice in renal replacement therapy

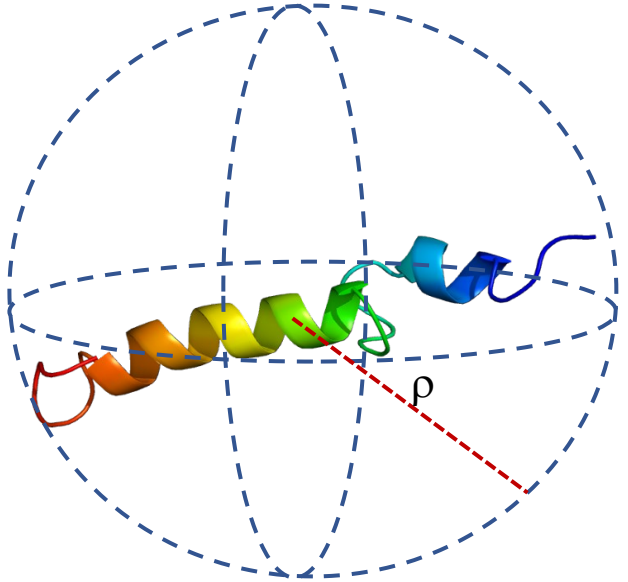
Federico Nalesso[1] | **Leda Cattarin**[1] | **Lorenzo Arcangelo Calò**[1] | **Francesco Garzotto**[2]

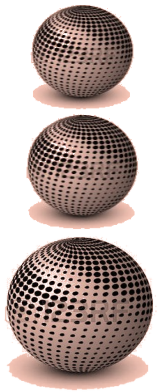
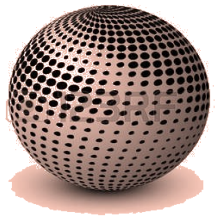
The Molecular Radius

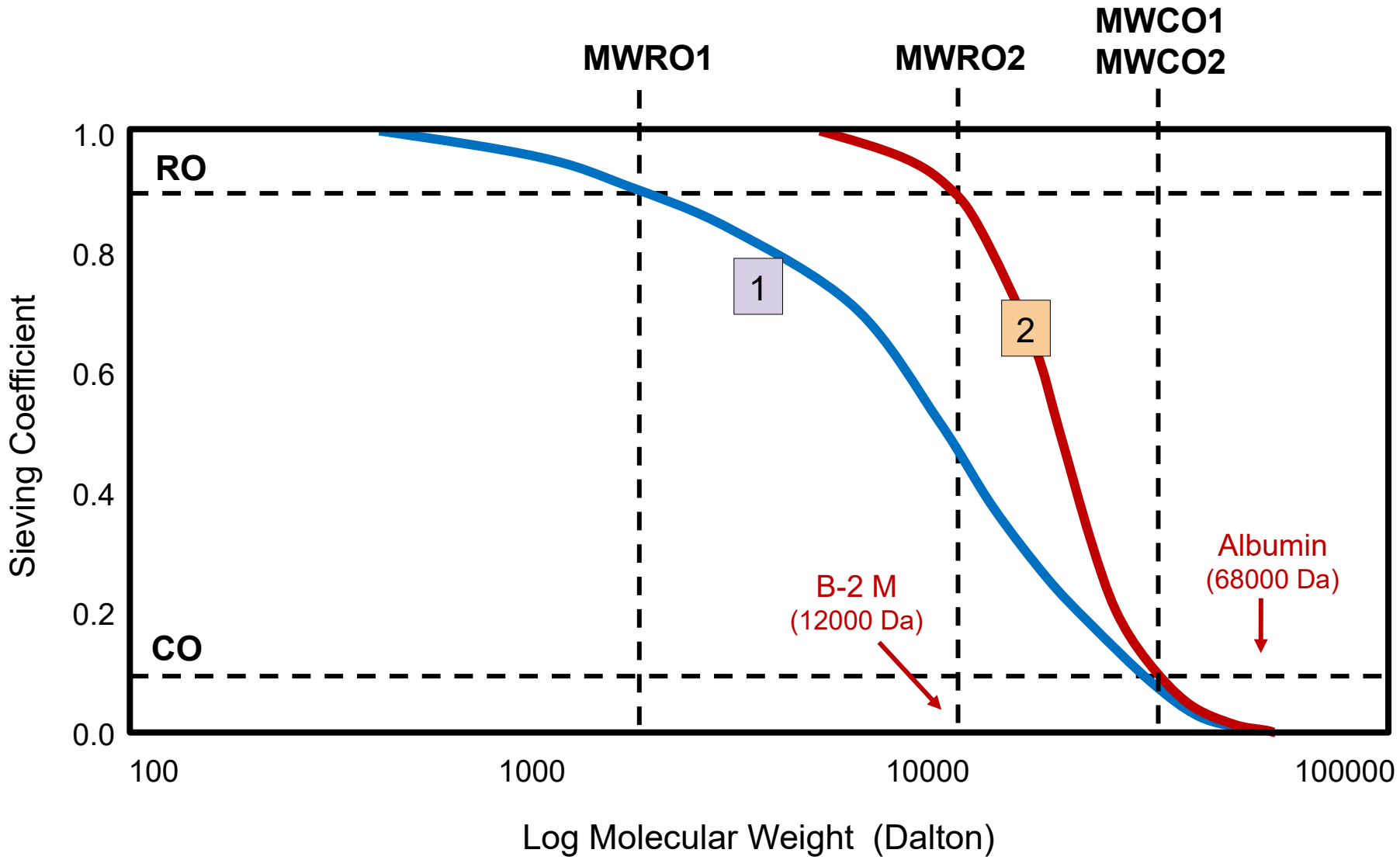
Hepcidin Anti Microbial Peptide
MW: 27000 Da



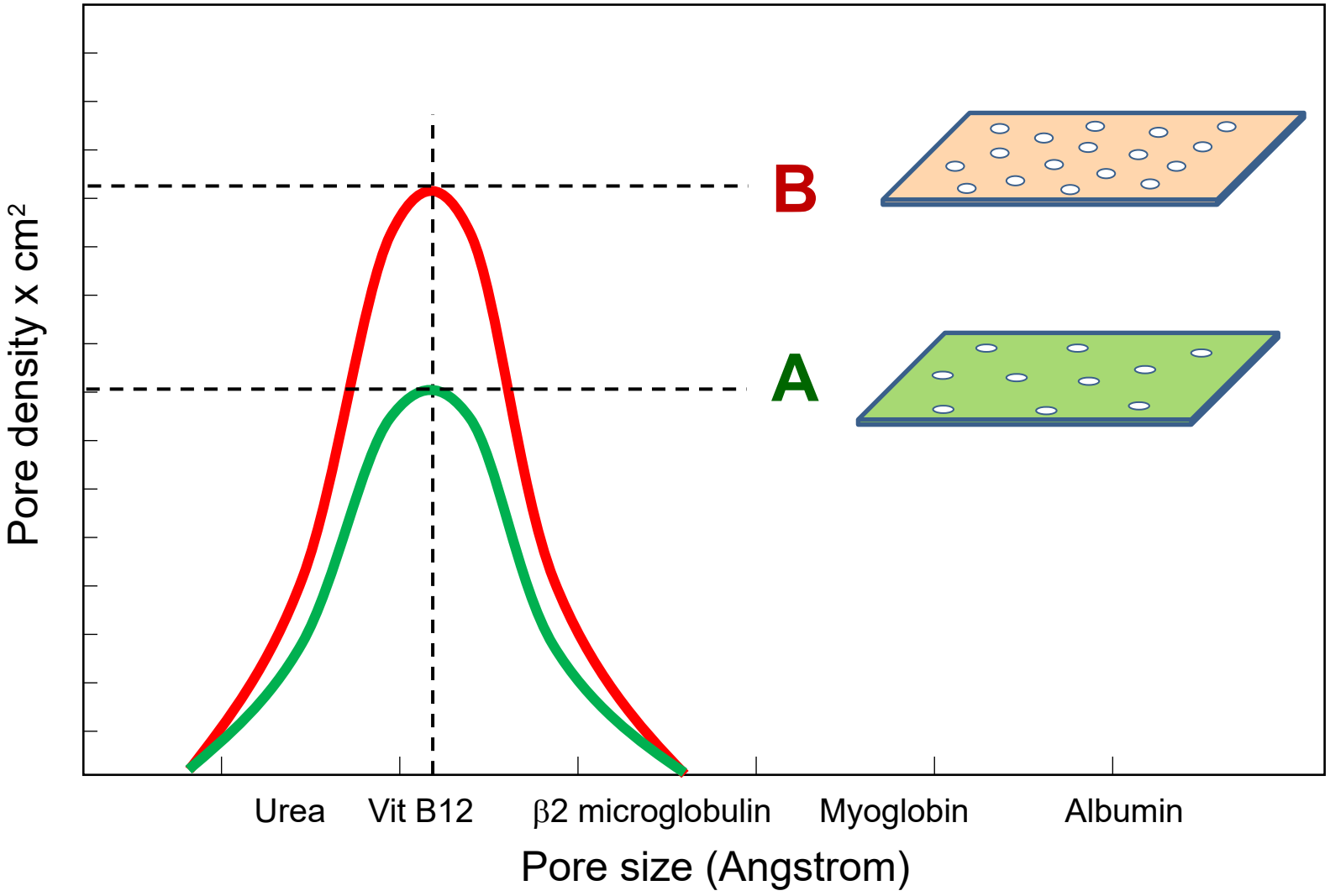
Parathyroid Hormon
MW: 9300 Da



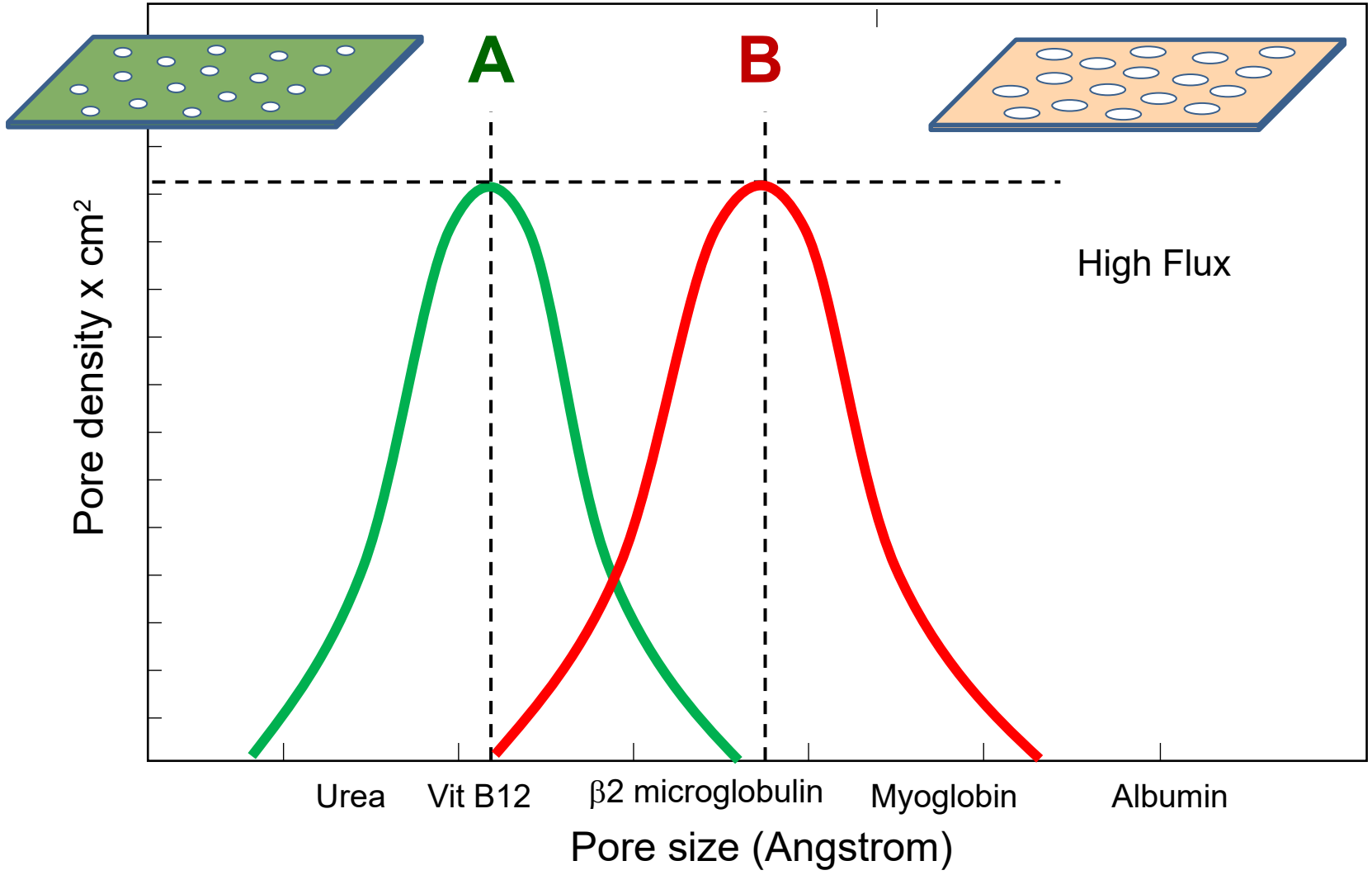
	SOLUTE	MW (Da)	Class	Action/Effect
	Urea	60	Small	General toxicity
	Creatinine	125		
	Vitamin B12	1250		
	β 2 M	12000	Middle	Amiloidosis CTS
	Leptin	16000		Malnutrition
	Myoglobin	17000		Organ damage
	κ-FLC	23000	Large	Toxicity
	Prolactin	23000		Infertility
	Interleukin-6	25000		Inflammation
	Hepcidin	27000		Anemia
	Bound P-Cresol	33500		CV Toxicity
	Pentraxin-3	43000		Acute Phase Prot.
	λ-FLC	45000		CV Toxicity
	TNF-α (Trim)	51000		Inflammation
	Albumin	68000	Essential protein	Toxin binding capacity


MWRO1
MWRO2
MWCO1
MWCO2
1.0
RO
0.8
0.6
0.4
0.2
CO
0.0
Sieving Coefficient
1
2
B-2 M
(12000 Da)
Albumin
(68000 Da)
100
1000
10000
100000
Log Molecular Weight (Dalton)

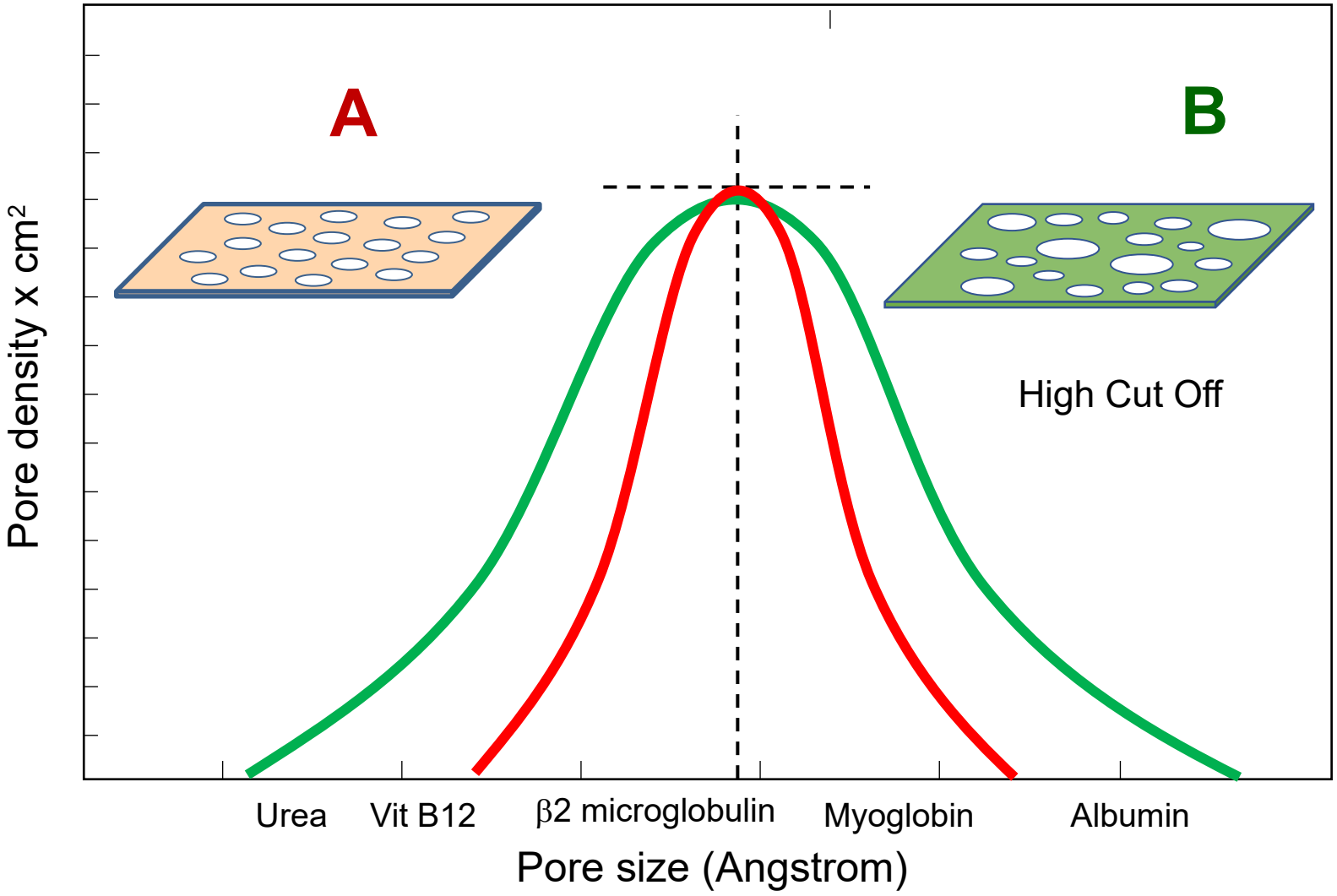
Membrane Pore Density

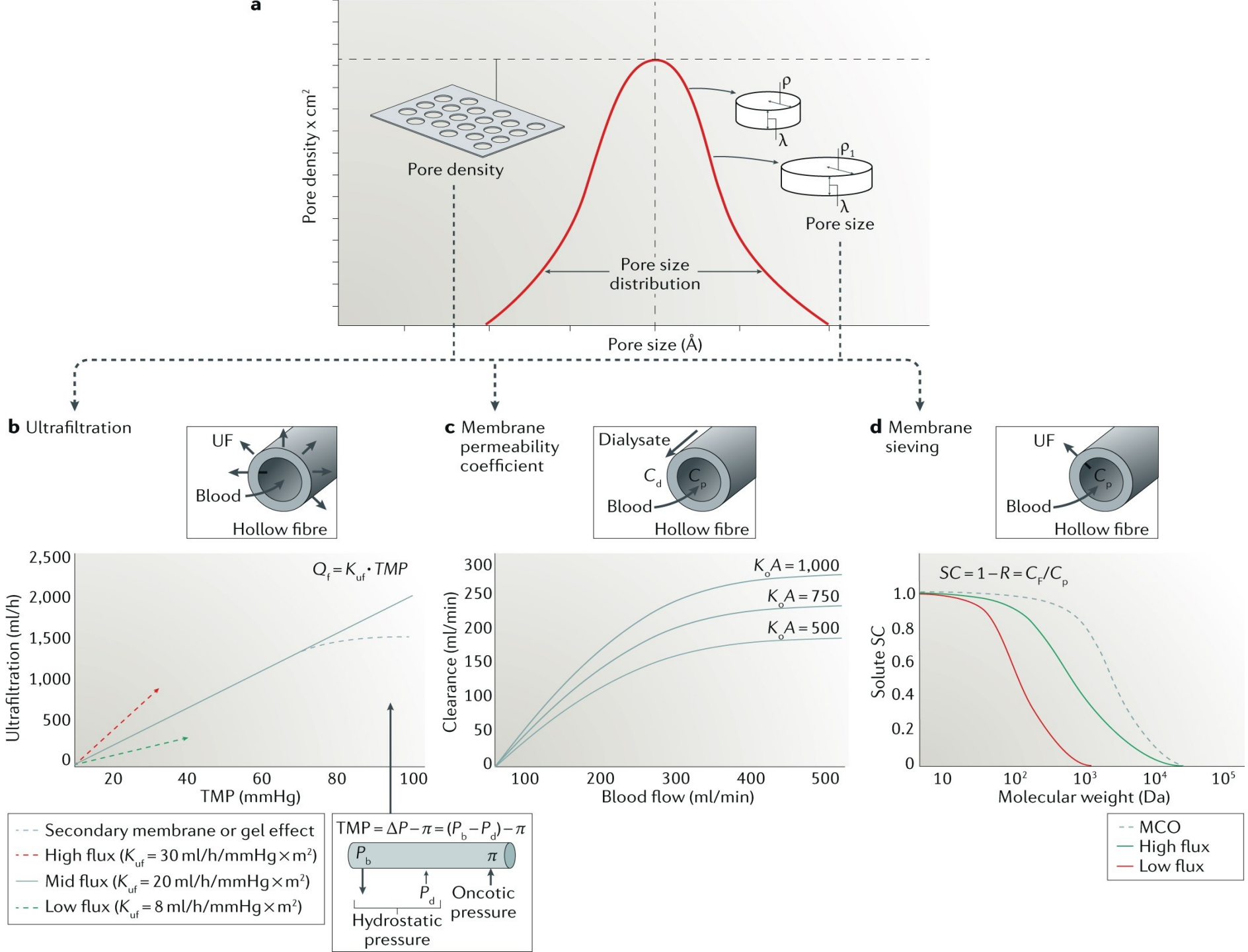


Membrane Pore Size

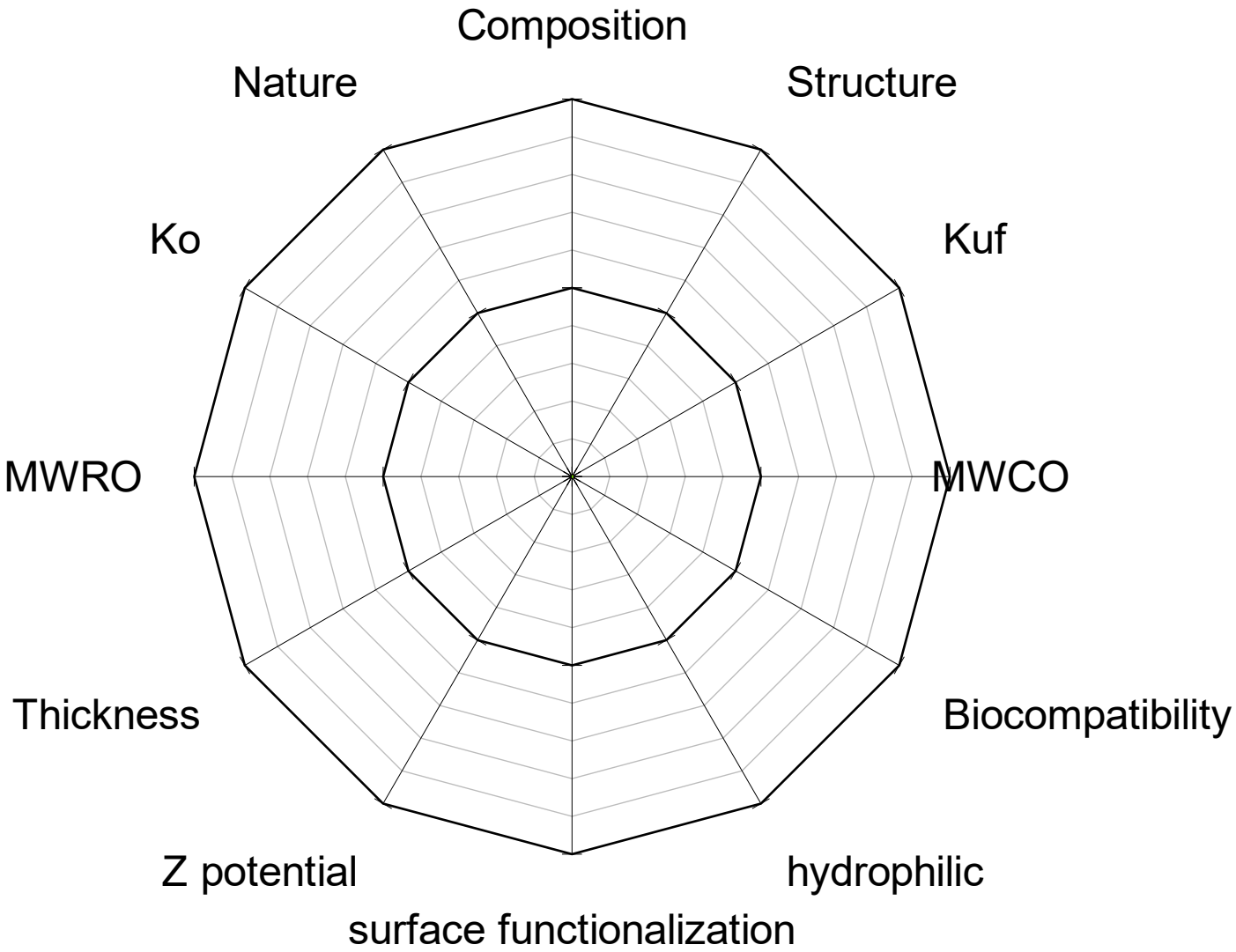


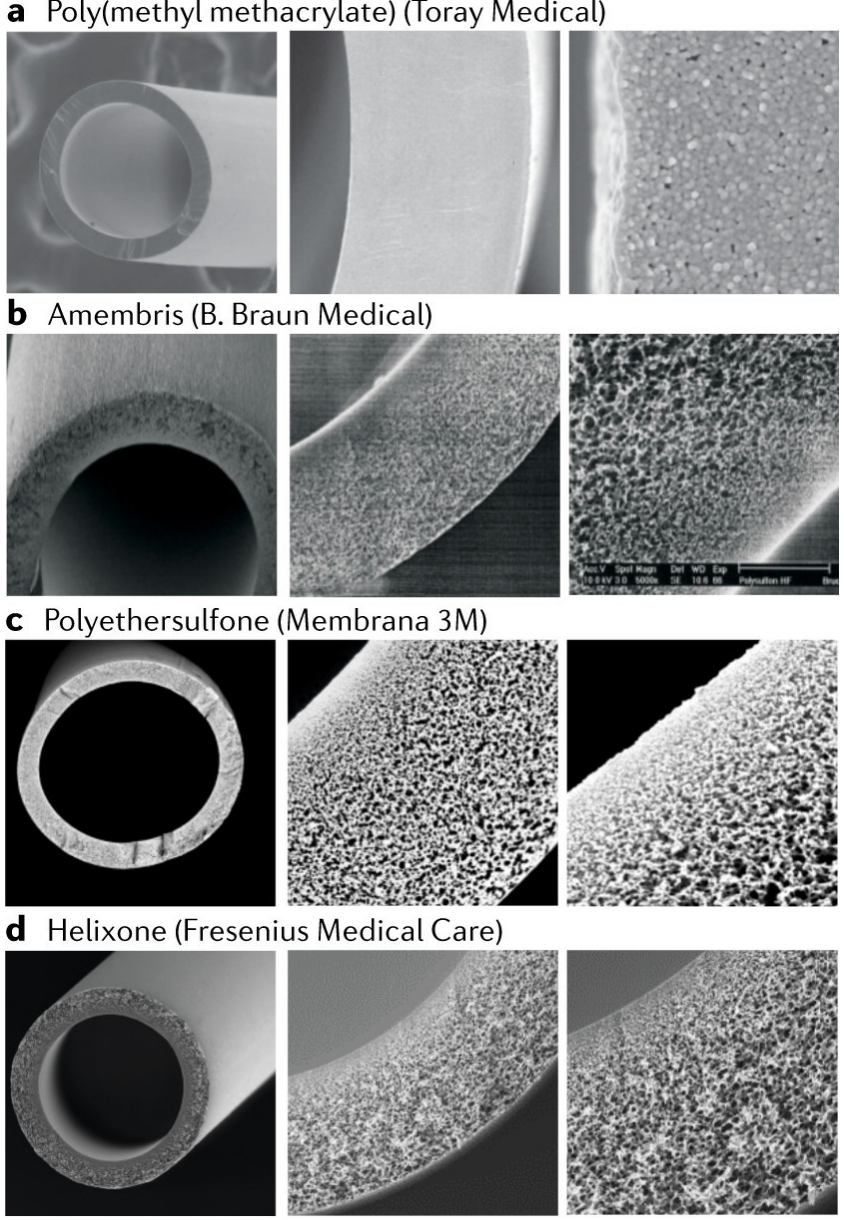
Membrane Pore Size Distribution

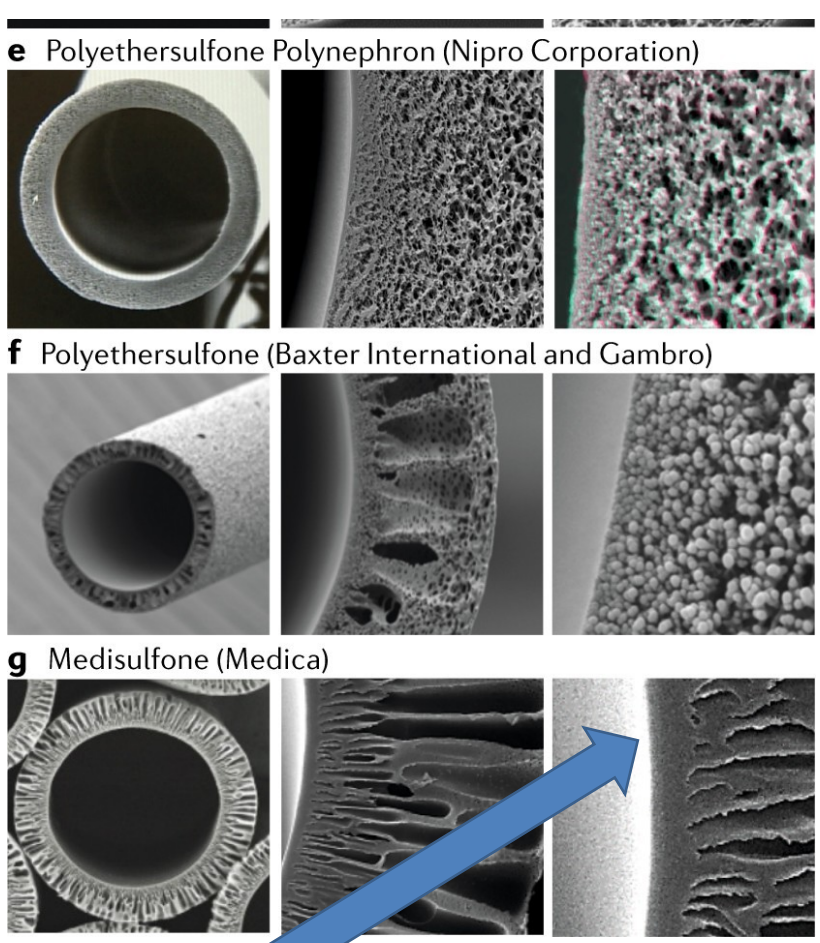



a
Pore density x cm²
Pore density
ρ
λ
ρ1
λ
Pore size
Pore size distribution
Pore size (Å)
b Ultrafiltration
UF
Blood
Hollow fibre
Ultrafiltration (ml/h)
Qf = Kuf · TMP
TMP (mmHg)
Secondary membrane or gel effect
High flux (Kuf = 30 ml/h/mmHg × m²)
Mid flux (Kuf = 20 ml/h/mmHg × m²)
Low flux (Kuf = 8 ml/h/mmHg × m²)
TMP = ΔP − π = (Pb − Pd) − π
Pb
π
Pd
Oncotic pressure
Hydrostatic pressure
c Membrane permeability coefficient
Dialysate
Cd
Cp
Blood
Hollow fibre
Clearance (ml/min)
KoA = 1,000
KoA = 750
KoA = 500
Blood flow (ml/min)
d Membrane sieving
UF
Cp
Blood
Hollow fibre
SC = 1 − R = CF/Cp
Solute SC
Molecular weight (Da)
MCO
High flux
Low flux

Multidimensional Membrane Evaluation







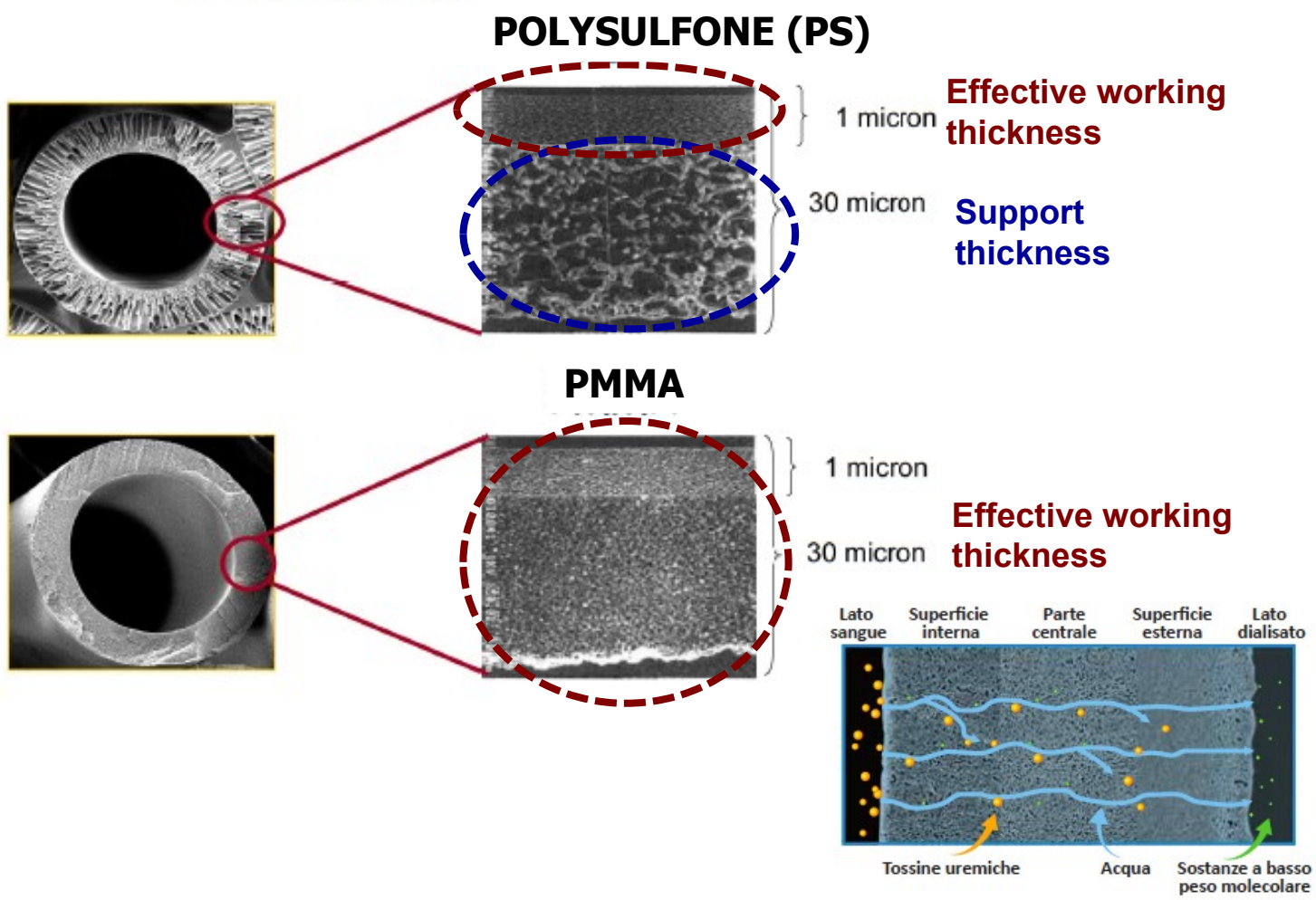
Thin inner ‘skin’ layer (width approximately ≤ 1 µm) at the membrane–blood interface serves as the primary size-discriminating element in solute removal.

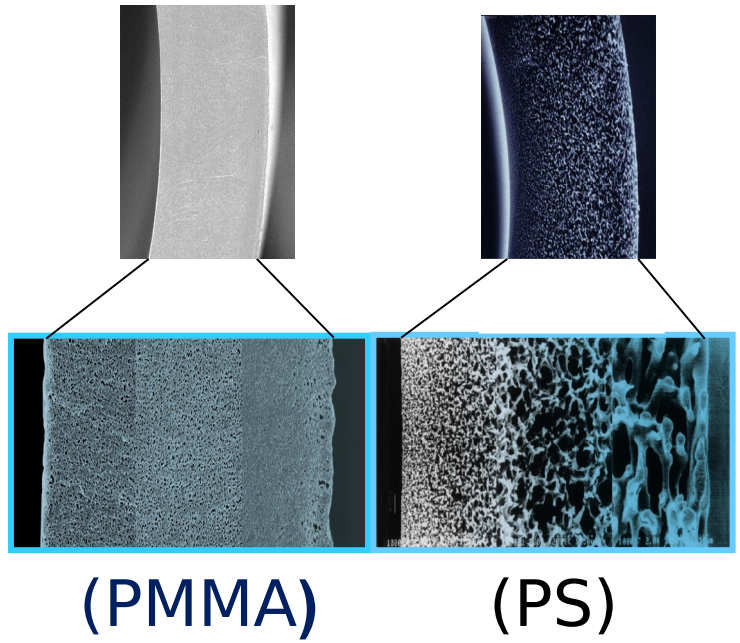
The remaining wall thickness (the ‘stroma’) acts as a support structure that also provides a substantial surface area for the removal of molecules by adsorption. As opposed to the compact nature of the skin layer, the structure of the stroma is relatively open (‘macroporous’) and typically has a sponge-like or finger-type structure

Haemodialysis membranes, Ronco

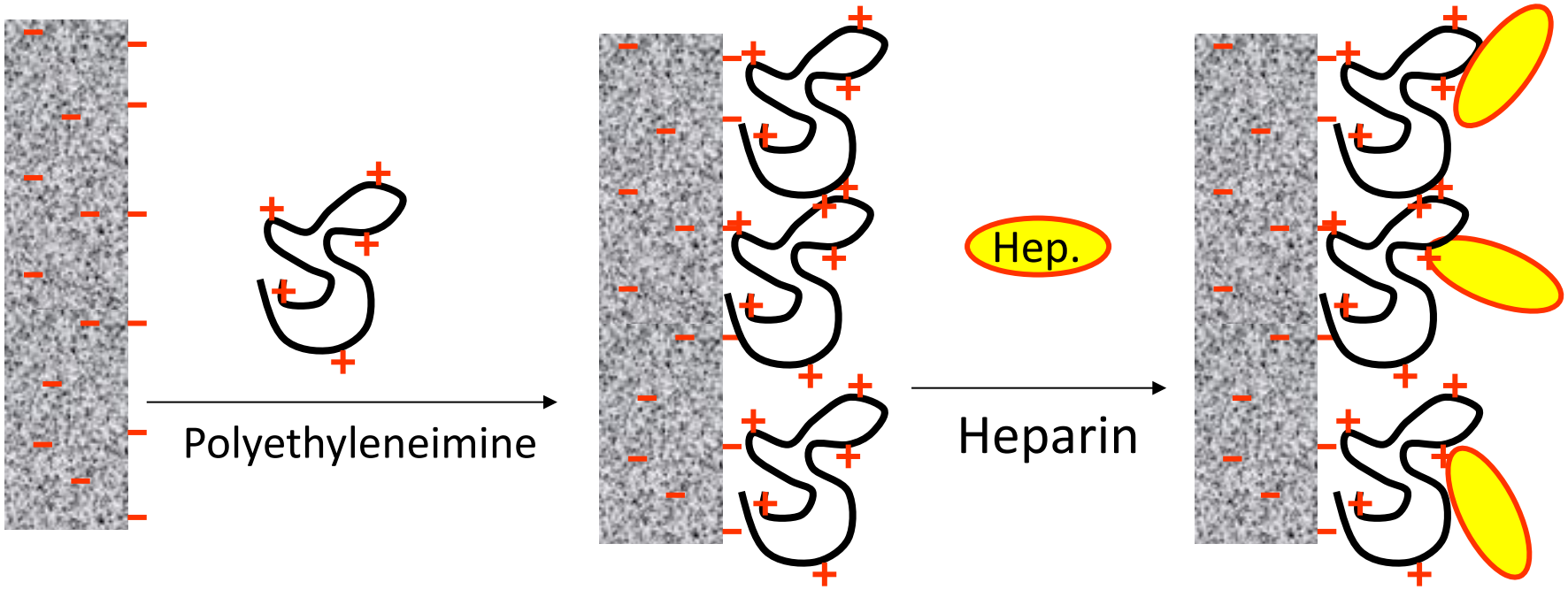
DIALYZER STRUCTURE AND MEMBRANE COMPATIBILITY
Are all dialytic membranes the same?

POLYMETHYLMETHACRYLATE (PMMA) – MEMBRANE STRUCTURE

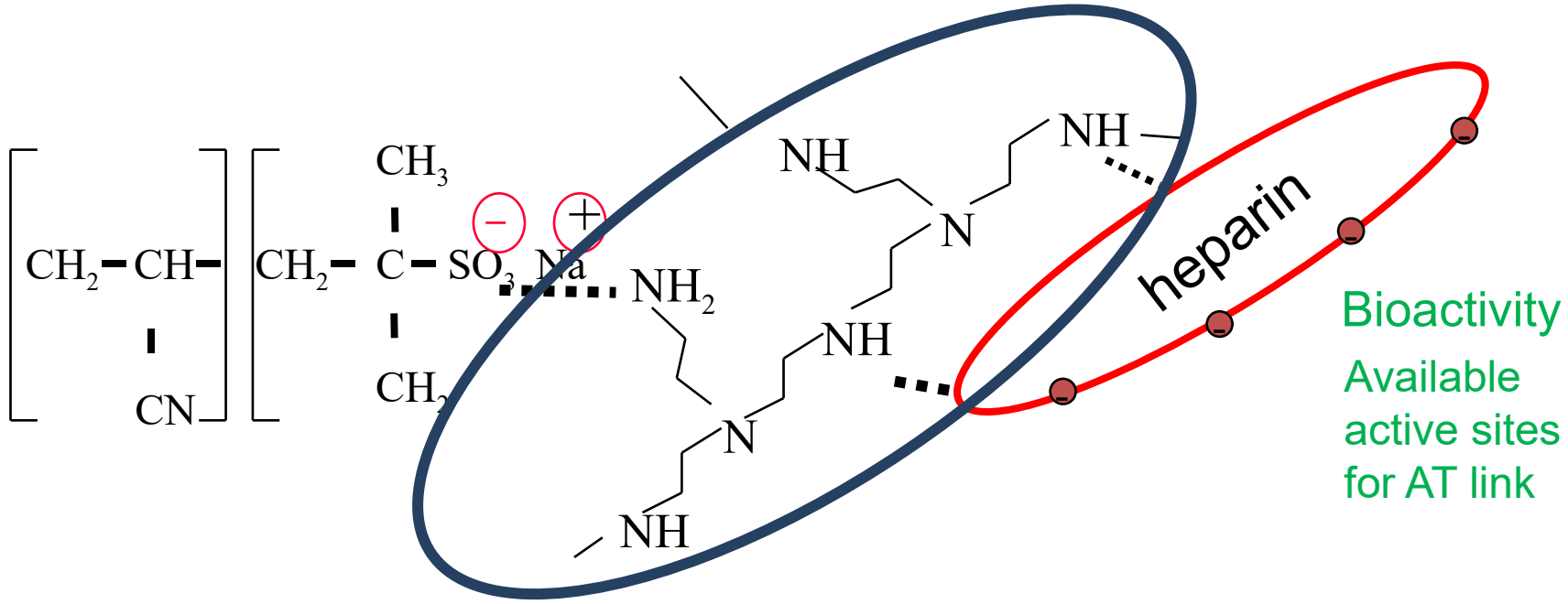




AN69 ST* and Heparin Adsorption



oXiris Membrane - Material



Membrane separation VS solute adsorption

Extracorporeal blood purification can be achieved by different mass separation processes:
Diffusion, as in standard hemodialysis or CVVHD
convection as in hemofiltration CVVH
or their combination as in hemodiafiltration (HDF) CVVHDF

While these techniques are based on membrane separation, a third mechanism, solute adsorption, is based on mass separation by a solid agent (sorbent)

Understanding of critical care pathophysiology and hyperinfammatory diseases, each patient requires a tailored approach

Sorbents

Sorbents are generally produced in granules, beads, or fibers.
They are solid particles with a diameter generally ranging between 50 µm and 1.2 cm.
The surface-area-tovolume ratio (S/V) is extremely high with a surface area varying from 300 to 1200 m2 /g.
Sorbents are classifed according to the size of the pores of their inner structure as a) Macro-porous (Pore size>500 Å), b) Mesoporous (Pore size 20–500 Å) and c) Micro-porous (Pore size <20 Å)

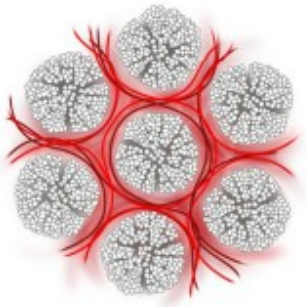
Table 1 Development of sorbents and application in extracorporeal therapies

1850 First inorganic aluminosilicates (zeolites) used to exchange NH_4 and Ca^{++}
1910 Water softeners using zeolites display instability in the presence of mineral acids
1935 Adams and Holmes synthesize the first organic polymer ion exchange resin
1948 First published application of hemoperfusion using an ionic resin to treat uremia in dogs
1950s Application of synthetic porous polymers (trade names: Amberlyte, Duolite, Dowex) to experimental blood purification
1958. Use of ion exchange resin to treat a patient with barbiturate poisoning
1960s Clinical use of hemoperfusion with ion exchange resins to remove salicylate and phenobarbital in dogs
1970s Widespread application of coated charcoal and resins to the treatment of poisoning
1980s Application of coated charcoal and resins to the treatment of a variety of conditions (liver disease, vasculitis, and autoimmune diseases)
1990s Decreased interest in hemoperfusion with charcoal and resins and side effects reported more frequently with greater use
2000s Continued decrease in the use of hemoperfusion as dialysis membranes achieve better clearance, greater biocompatibility and lower cost and continuous renal replacement therapy spreads
2010s Improvements in coating and manufacturing and positive experimental work restore interest in hemoperfusion with growing numbers of reports
2020s Application of hemoperfusion to the management if inflammatory and/or septic states becomes more common

Ronco and Bellomo Critical Care (2022)

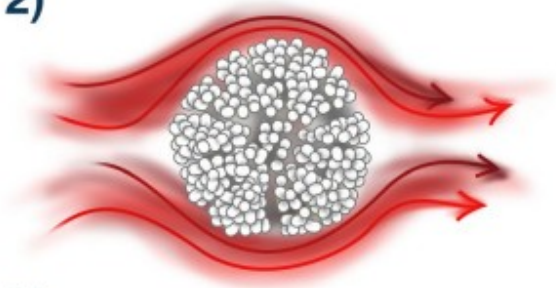
Permeation of the blood into the interparticle space – tortous channels (spece between beads). Characterized by the density of the beads and the density of the sorbent. The flow depends on the interparticle porosity and on the blood viscosity.

1)



Blood flow through the tortuous pathway
(**interparticle**)

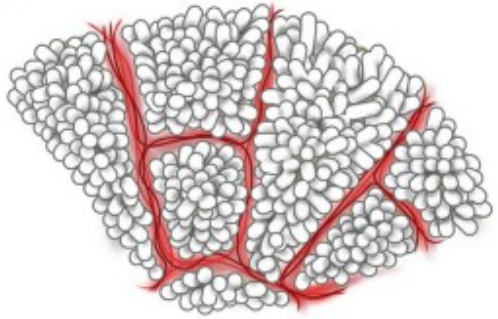
2)



Blood flow on the external surface of the bead
(**interphase**)

External mass transfer of the solute from the bulk fluid by convection through a thin film or boundary layers, to the outer surface of the sorbent

3)



Blood flow on the internal part of the bead
(**intraphase**)

Internal mass transfer of the solute by pore diffusion from the outer surface of the adsorbent to the INNER surface of the internal porous structure

Hemoperfusion in the intensive care unit Zaccaria et Al Intensive Care Med (2022) 48:1397–1408

Hemoperfusion

Multiple organ failure following a septic event derives from immune dysregulation. Many of the mediators of this
process are humoral factors (cytokines), which could theoretically be cleared by direct adsorption through a process
called hemoperfusion.

Table 1 Currently available technologies

Sorbent polymer	Commercial name (manufacturer)	Amount of sorbent	Coating
Norit charcoal	Adsorba (Gambro)	100–300 g	Cellulose acetate
Polymyxin B	Toraymyxin (Estor)	–	–
Spherical charcoal	Hemosorba (Asahi)	170 g	Polyhema
Polystyrene divinyl benzene	HA 130/230/330 (Jafron)	–	None
Polystyrene divinyl benzene	Cytosorb (Aferetica)	300 g	None
Ultra-high molecular weight polyethylene beads with end-point-attached heparin	Seraph-100 (ExThera Medical)	–	–

Hemoperfusion through devices:
bind specific molecules like endotoxin or theoretically provide **non-specific adsorption of pro-inflammatory mediators**

More recently, technological evolution has led to the increasing application of adsorption due to more biocompatible and possibly more efficient biomaterials

Hemoperfusion in the intensive care unit Zaccaria et Al Intensive Care Med (2022) 48:1397–1408

Hemoperfusion in the intensive care unit Zaccaria Ricci et Al Intensive Care Med (2022)

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Spherical charcoal	Hemosorba (Asahi)	170 g	Polyhema
Polystyrene divinyl benzene	HA 130/230/330 (Jafron)	–	None
Polystyrene divinyl benzene	Cytosorb (Aferetica)	300 g	None
Ultra-high molecular weight polyethylene beads with end-point-attached heparin	Seraph-100 (ExThera Medical) FMC	–	–
Synthetic peptide binds to Lipid A	LPS Adsorber (Alteco)		


NB Accertarsi che sia stato certificato l'utilizzo della cartuccia nel vostro device per CRRT/emoperfusione

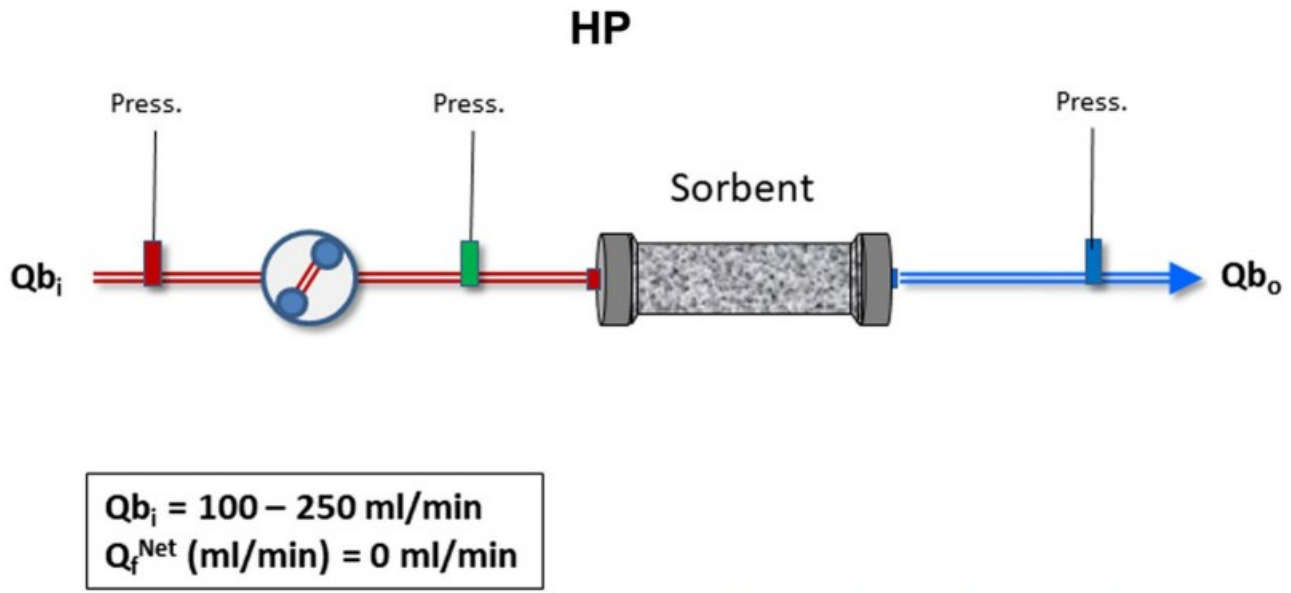


Fig. 1 Schematic configuration of direct hemoperfusion (HP). Qb_i = Blood flow at the inlet of the unit; Q_f^{Net} = net ultrafiltration

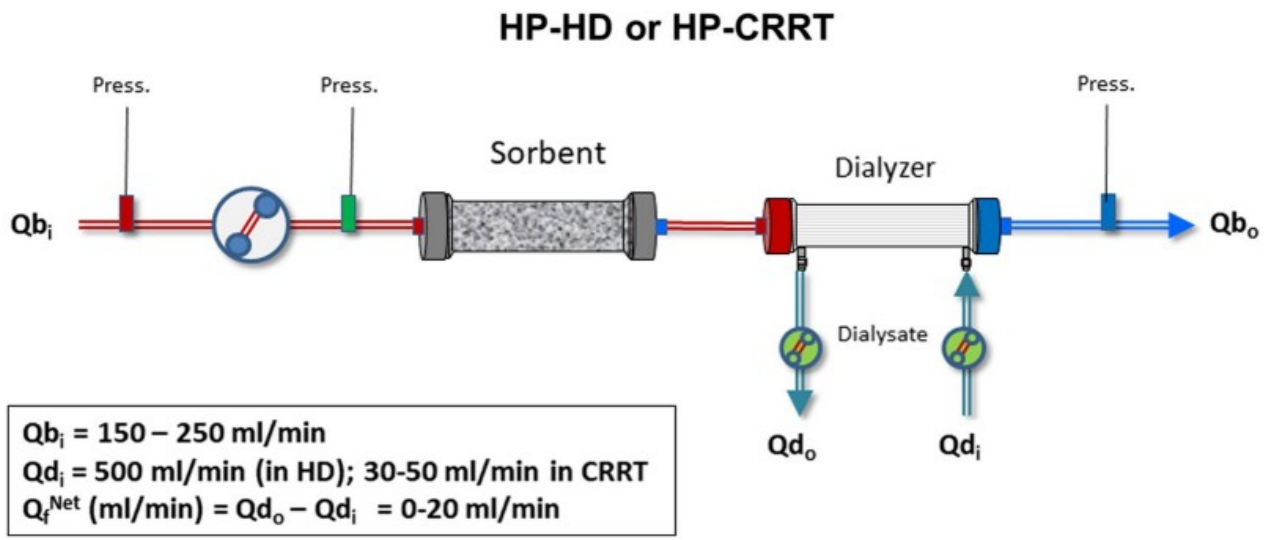


Fig. 2 Schematic configuration of hemoperfusion combined with hemodialysis (HP-HD) and hemoperfusion combined with continuous renal replacement therapy (HP – CRRT). Qb_i = Blood flow at the inlet of the unit; Qb_o = Blood flow at the outlet of the units; Qd_i = Dialysate flow at the inlet of the dialyzer; Qd_o = Dialysate flow at the outlet of the dialyzer; Q_f^{Net} = net ultrafiltration

Review

The Supporting Role of Combined and Sequential Extracorporeal Blood Purification Therapies in COVID-19 Patients in Intensive Care Unit

Federico Nalesso [1,*], Federica L. Stefanelli [1], Valentina Di Vico [1], Leda Cattarin [1], Irene Cirella [1], Giuseppe Scaparrotta [1], Francesco Garzotto [2] and Lorenzo A. Calò [1]

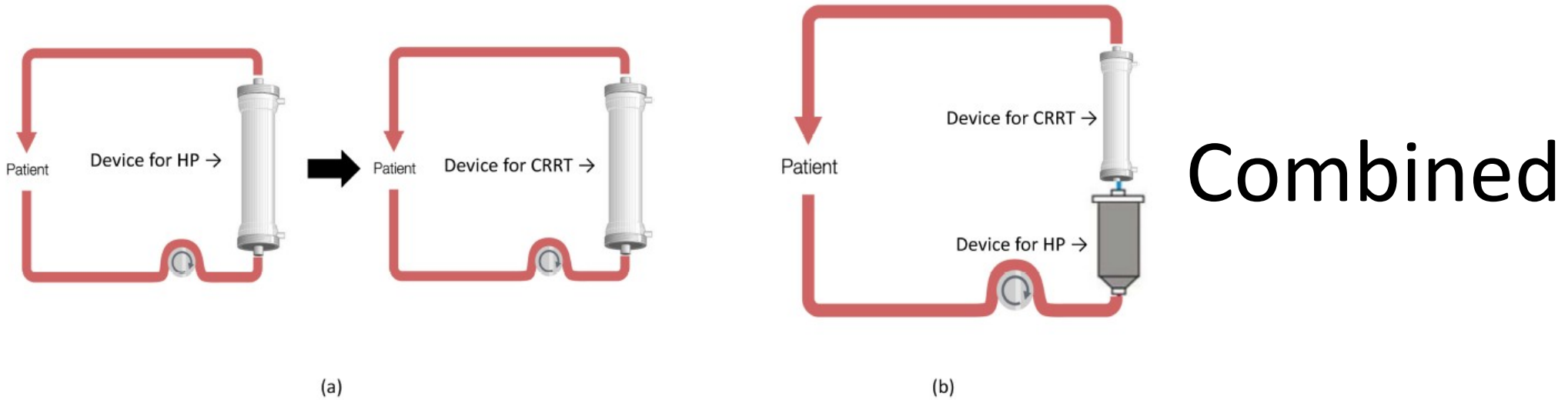


Figure 3. Sequential (**a**) and combined (**b**) treatments.

Combined

Sequential

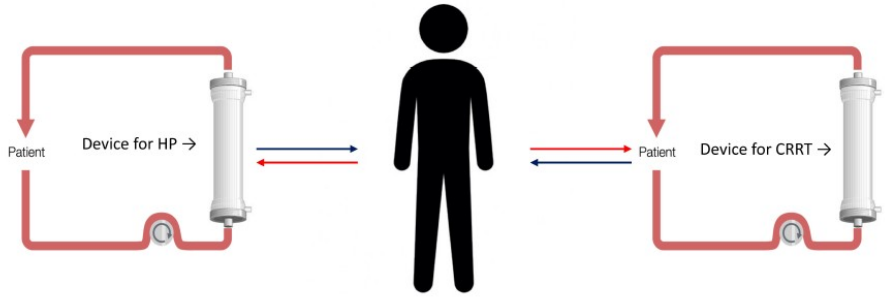
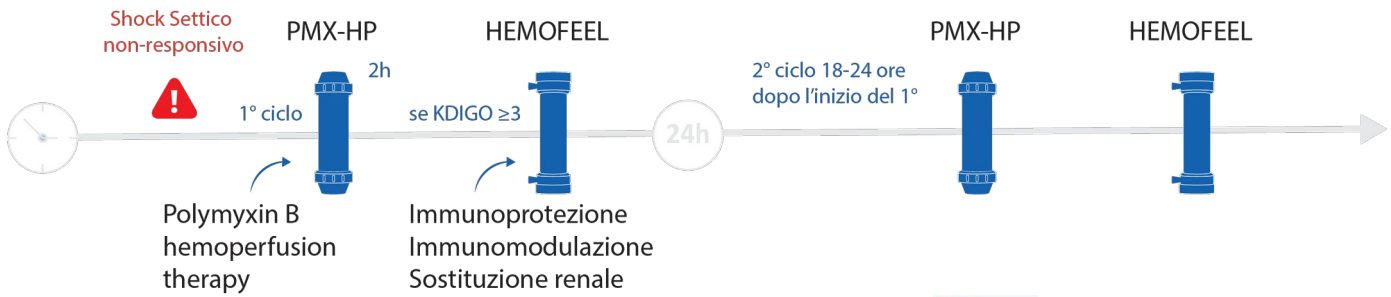


Figure 4. Hemoperfusion and continuous kidney replacement therapy (CRRT) with two different vascular accesses.

Sequential Therapies

Esempio di SETS in paziente in shock settico:

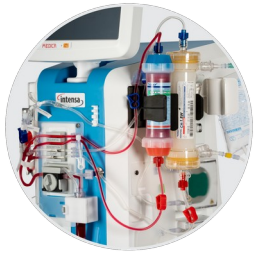


SETS

TORAYMYXIN®
Polymyxin B Hemoperfusion Therapy

+

HEMOFEEL®
PMMA membrane for continuous therapy



Sequential

Adsorption

Clamp

intensa

PLAY DIFFERENTLY,
LIVE **INTENSA®**

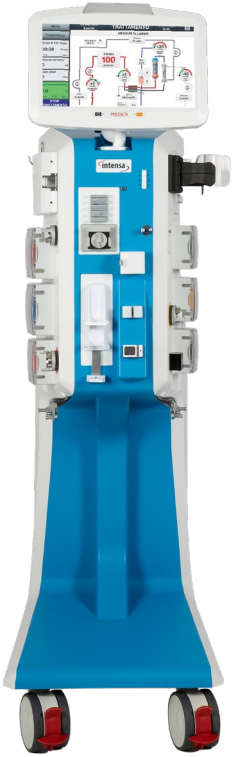


Table 1. EBPs comparison.

Device	Manufacturer	Composition	Device Type	Specificity If Removal	Target in COVID-19	Treatment Type	Blood Flow (mL/min)	Anticoagulation	Duration of Single Device	Use with Other Treatment
CytoSorb	CytoSorbents Corporation, Princenton, NJ, USA	beads in polystyrene divinylbenzene copolymer with a biocompatible polyvinylpyrrolidone coating	hemoadsorber	non-selective capacity	cytokines and inflammatory mediators	HP	150–500 mL/min (maximum flow 700 mL/min) with a minimum of 100 mL/min	Heparin; aPTT between 60 and 80 s (or ACT of 160–210 s)	24 h	CRRT/ECMO
HA-330	Jafron Biomedical Company, Zhuhai, China	neutro-macroporous resin adsorbing beads in non-ionic styrene divinylbenzene copolymers	hemoadsorber	non-selective capacity	hydrophobic or protein-bound exogenous substances, cytokines, protein-bound uremic toxins, middle uremic toxins, free hemoglobin, and myoglobin	HP	100–250 mL/min	Heparin; desired aPTT between 60 and 80 s (or ACT of 160–210 s)	24 h	CRRT/ECMO
Toraymyxin	Toray Industries Ltd., Tokyo, Japan	polymyxin B-immobilized on polystyrene derivative fibers	hemoadsorber	selective capacity	endotoxin (direct adsorption of inflammatory mediators, cytokines, and the activated monocytes and neutrophils apheresis)	HP	100–120 mL/min	Heparin; desired aPTT between 60 and 80 s	2 h	-
Septex	Baxter, Round Lake, IL, USA	polyarylethersulfone membrane of 1.1 m^2	High Cut-Off filter for CVVHD	non-selective capacity	cytokines and inflammatory mediators	CVVHD in RCA or with Heparin	80–200 mL/min	Trisodium citrate or heparin	72 h	-
Emic-2	Fresenius Medical Care, Bad Homburg, Germany	polysulfone membrane of 1.8 m^2	High Cut-Off filter for CVVHD	non-selective capacity	cytokines and inflammatory mediators	CVVHD in RCA or with Heparin	100–200 mL/min	Trisodium citrate or heparin	72 h	-
oXiris	Baxter, Round Lake, IL, USA	acrylonitrile and sodium methallyl-sulfonate-copolymer and as surface treatment agent polyethyleneImine (PEI) and heparin	Filter for all CRRT	non-selective capacity	endotoxins, cytokines, and inflammatory mediators	CRRT in RCA or with Heparin	80–200 mL/min in RCA 120–200 mL/min with Heparin	Trisodium citrate or heparin	72 h	-

Review

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Review

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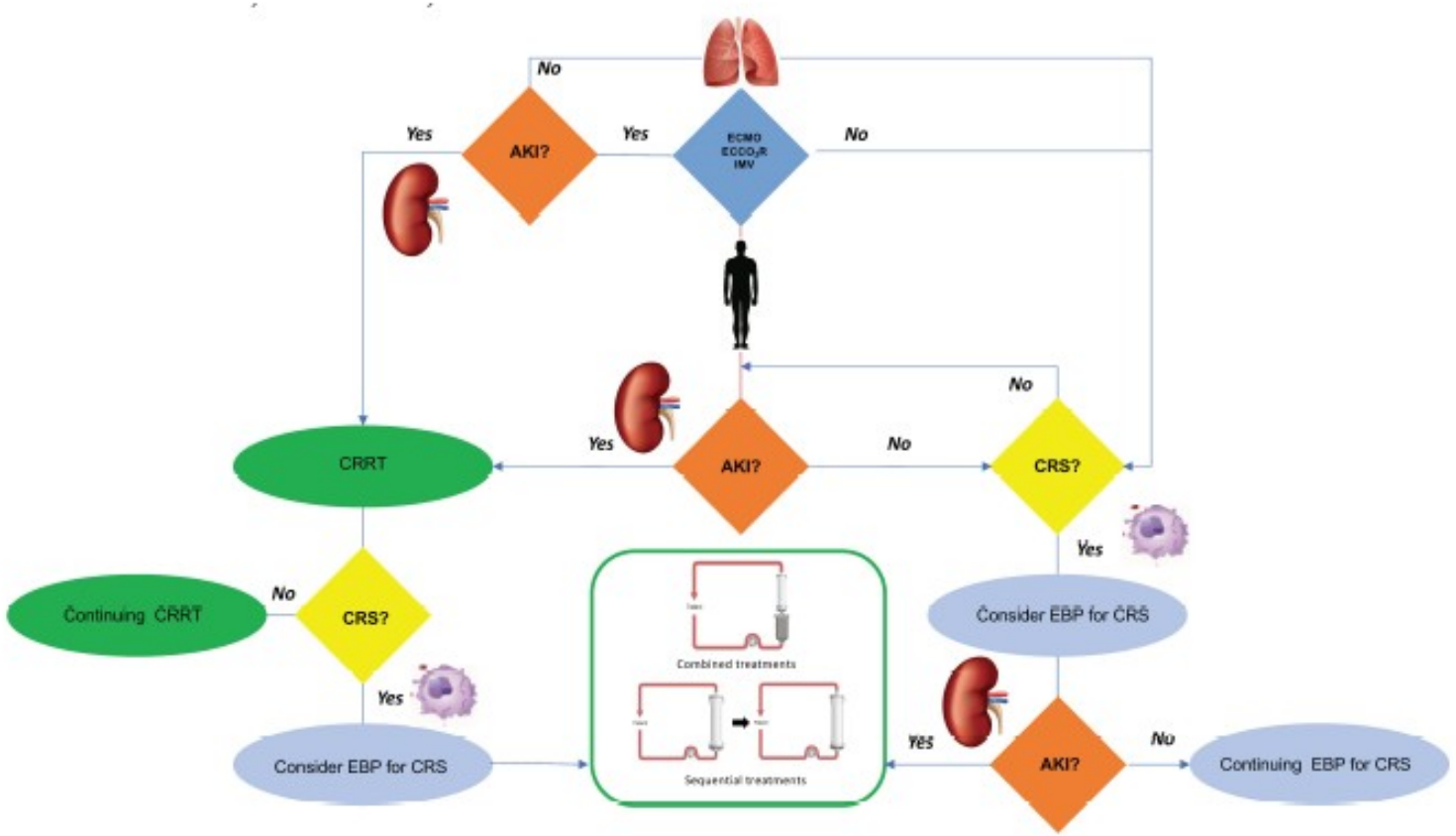


Figure 6. Algorithm to guide in the extracorporeal blood purification treatment in COVID-19 patients.

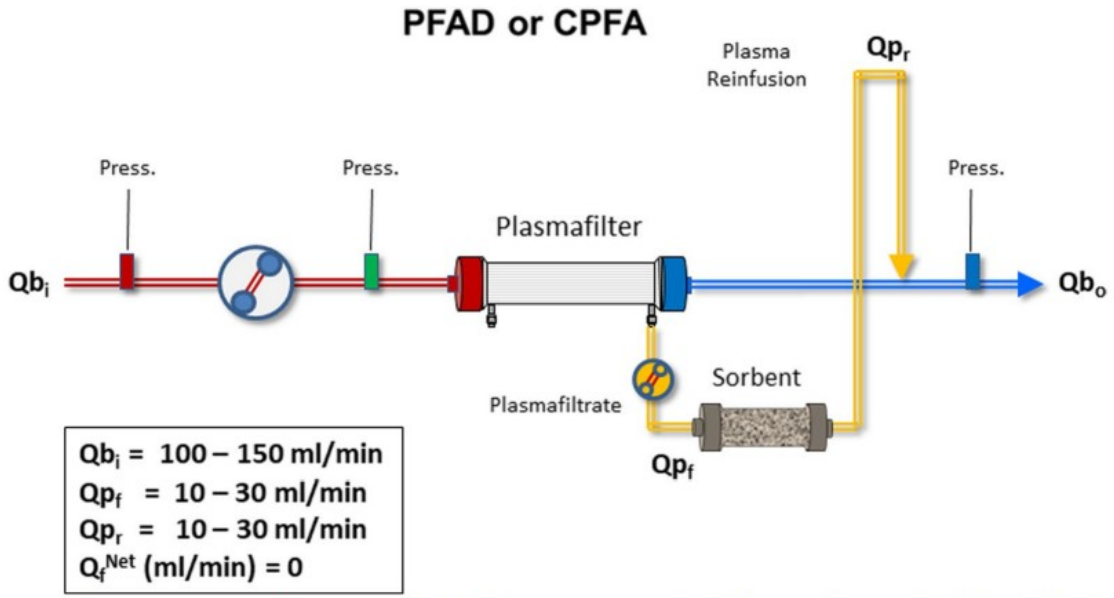


Fig. 3 Schematic configuration of plasmafiltration-adsorption (PFAD) or continuous plasmafiltration-adsorption (CPFA). Qb_i = Blood flow at the inlet of the plasmafilter; Qb_o = Blood flow at the outlet of the plasmafilter; Qp_f = Plasmafiltrate flow; Qp_r = Plasma Reinfusion flow; Q_f^{Net} = net ultrafiltration

Plasmafiltration-adsorption (PFAD) or continuous plasmafiltration-adsorption (CPFA

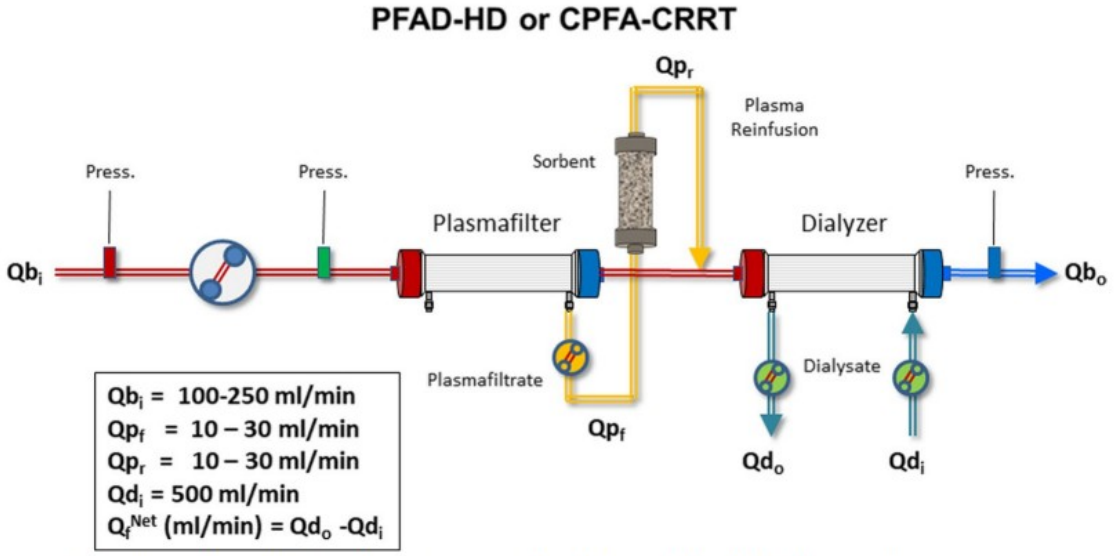


Fig. 4 Schematic configuration of plasmafiltration-adsorption combined with hemodialysis (PFAD-HD) or continuous plasmafiltration-adsorption combined with continuous renal replacement therapy (CPFA-CRRT). Qb_i = Blood flow at the inlet of the units; Qb_o = Blood flow at the outlet of the units; Qp_f = Plasmafiltrate flow; Qp_r = Plasma Reinfusion flow; Qd_i = Dialysate flow at the inlet of the dialyzer; Qd_o = Dialysate flow at the outlet of the dialyzer; Q_f^{Net} = net ultrafiltration

Plasmafiltration-adsorption combined with hemodialysis (PFAD-HD) or continuous plasmafiltration-adsorption combined with continuous renal replacement therapy (CPFA-CRRT)

Double plasmafiltration molecular adsorption system (DPMAS)

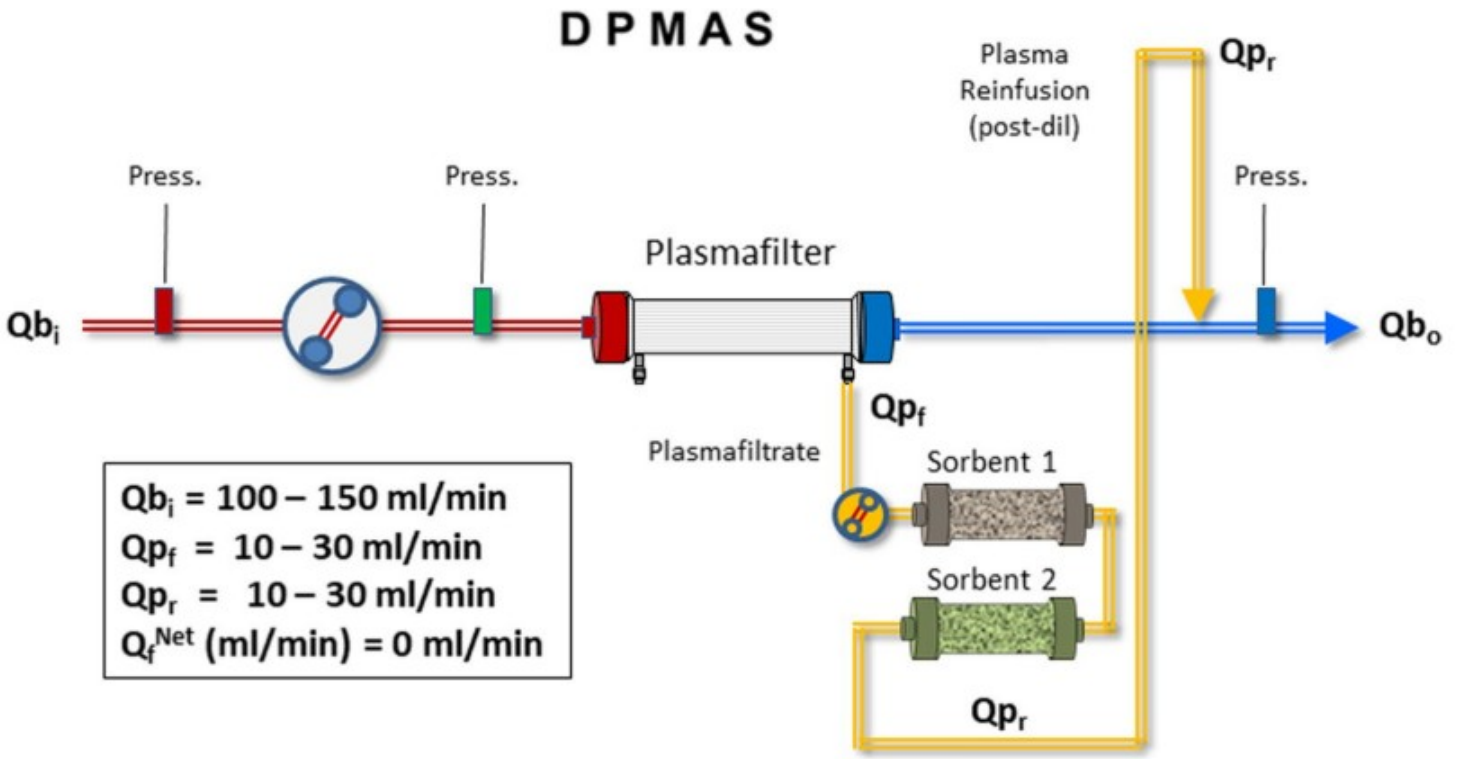


Fig. 5 Schematic configuration of double plasmafiltration molecular adsorption system (DPMAS). Qb_i = Blood flow at the inlet of the unit; Qb_o = Blood flow at the outlet of the plasmafilter; Qp_f = Plasmafiltrate flow; Qp_r = Plasma Reinfusion flow; Q_f^{Net} = net ultrafiltration

Combined CRRT with extracorporeal CO2 removal $ECCO_2R$

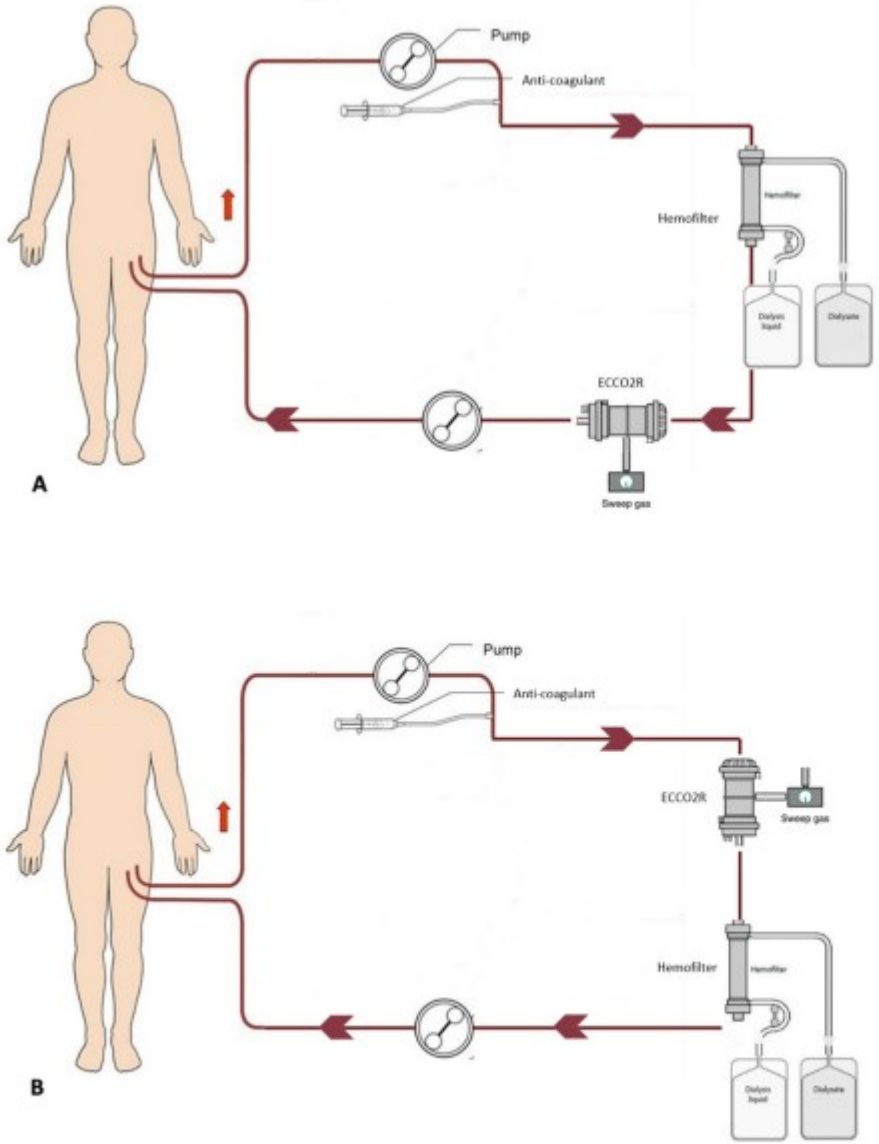


Figure 1. Exemplificative schemes of combined $ECCO_2R$–CRRT configurations. In the example CRRT is provided according to CVVHD modality. Membrane oxygenator for $ECCO_2R$ may be inserted either downstream (**A**) or upstream (**B**) of the hemofilter.

Review

Extracorporeal Carbon Dioxide Removal: From Pathophysiology to Clinical Applications; Focus on Combined Continuous Renal Replacement Therapy

Francesca Cappadona [1], Elisa Costa [2], Laura Mallia [2], Filippo Sangregorio [2], Lorenzo Nescis [2], Valentina Zanetti [2], Elisa Russo [2,3], Stefania Bianzina [4], Francesca Viazzi [1,2] and Pasquale Esposito [1,2,*]

Extracorporeal Lung Support (*carbon dioxide removal)*

The ability to efficiently remove CO_2 at lower blood flows has motivated use of extracorporeal CO_2 removal, or $ECCO_2R$, as an alternative or supplement to mechanical ventilation

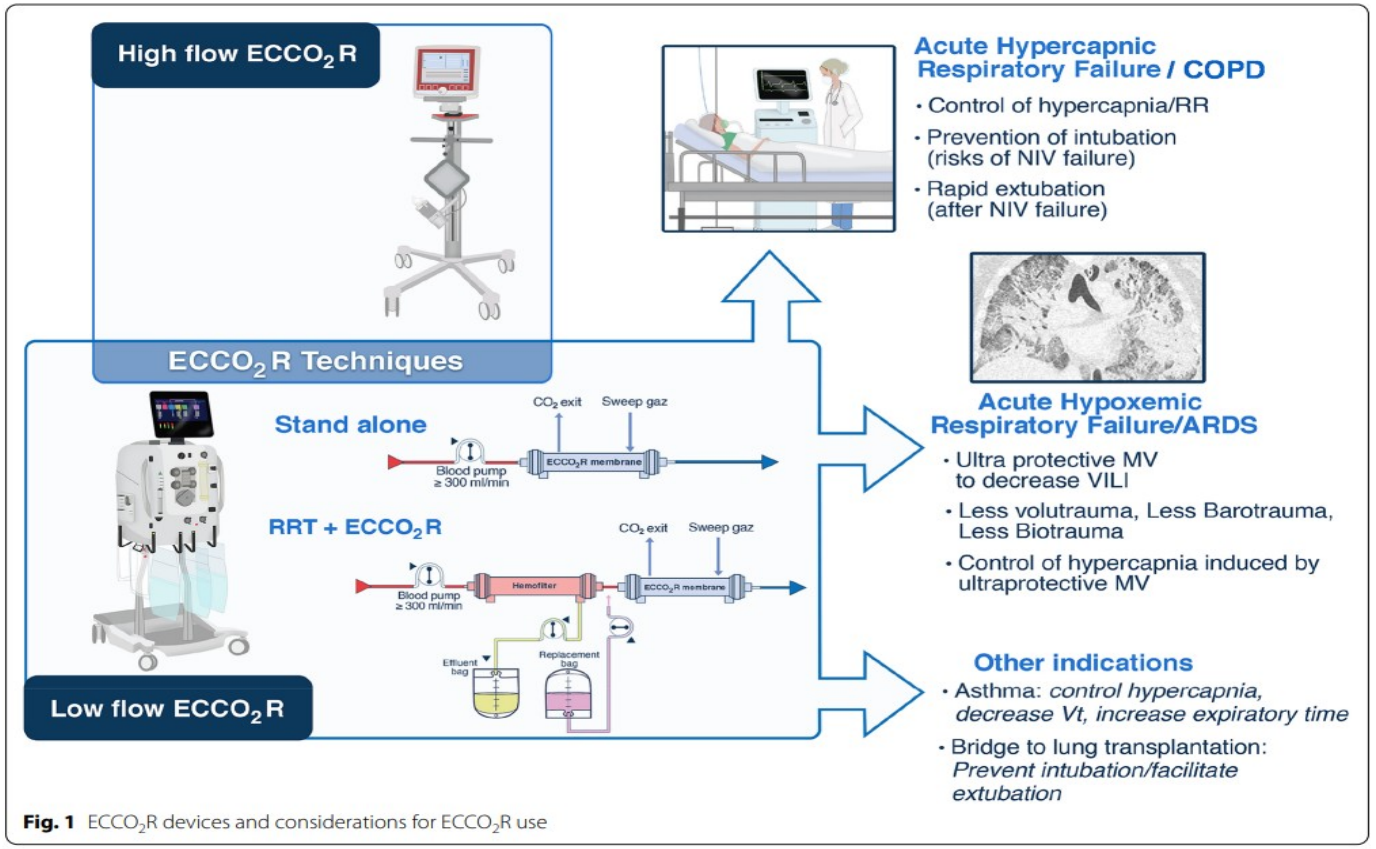
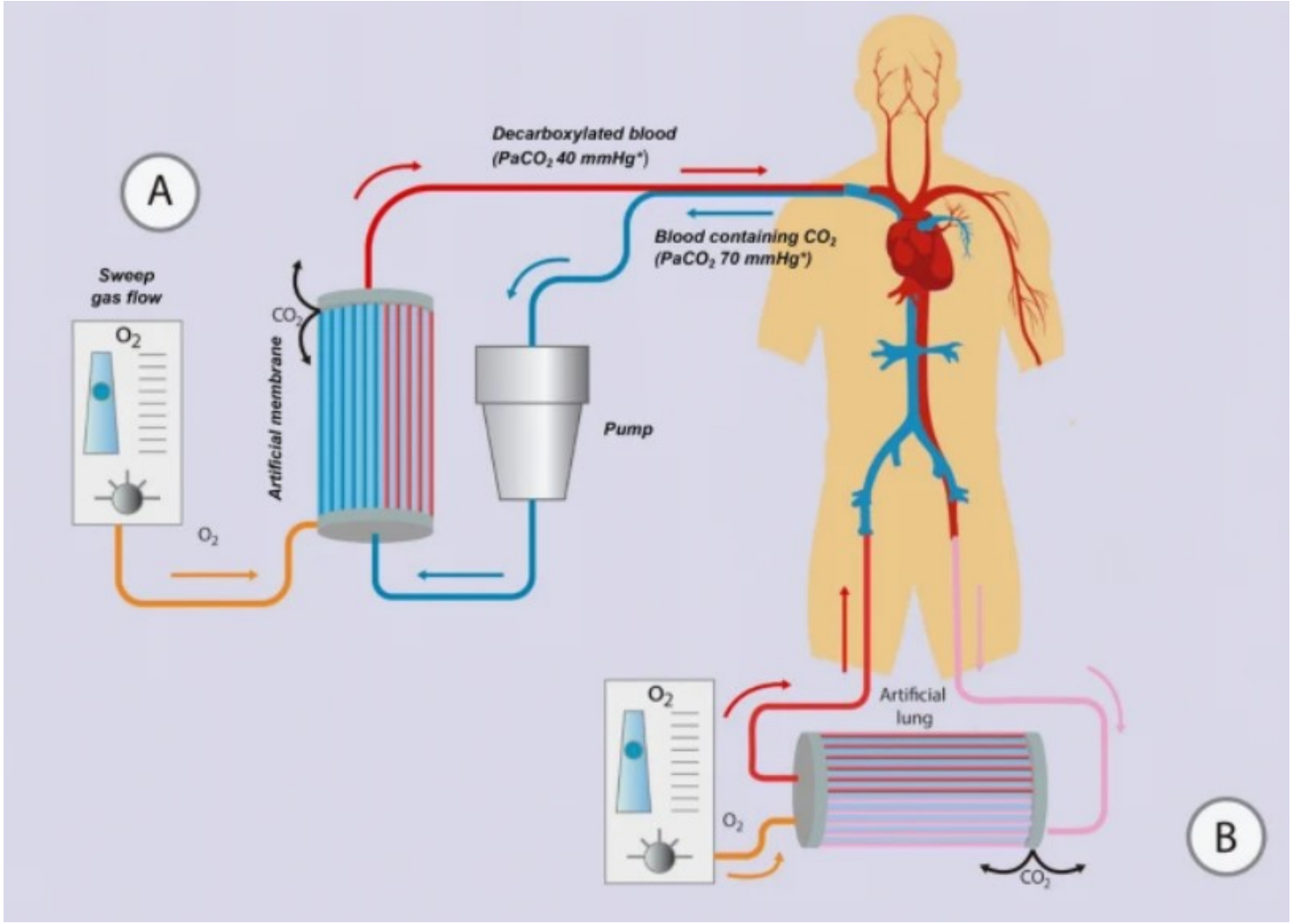
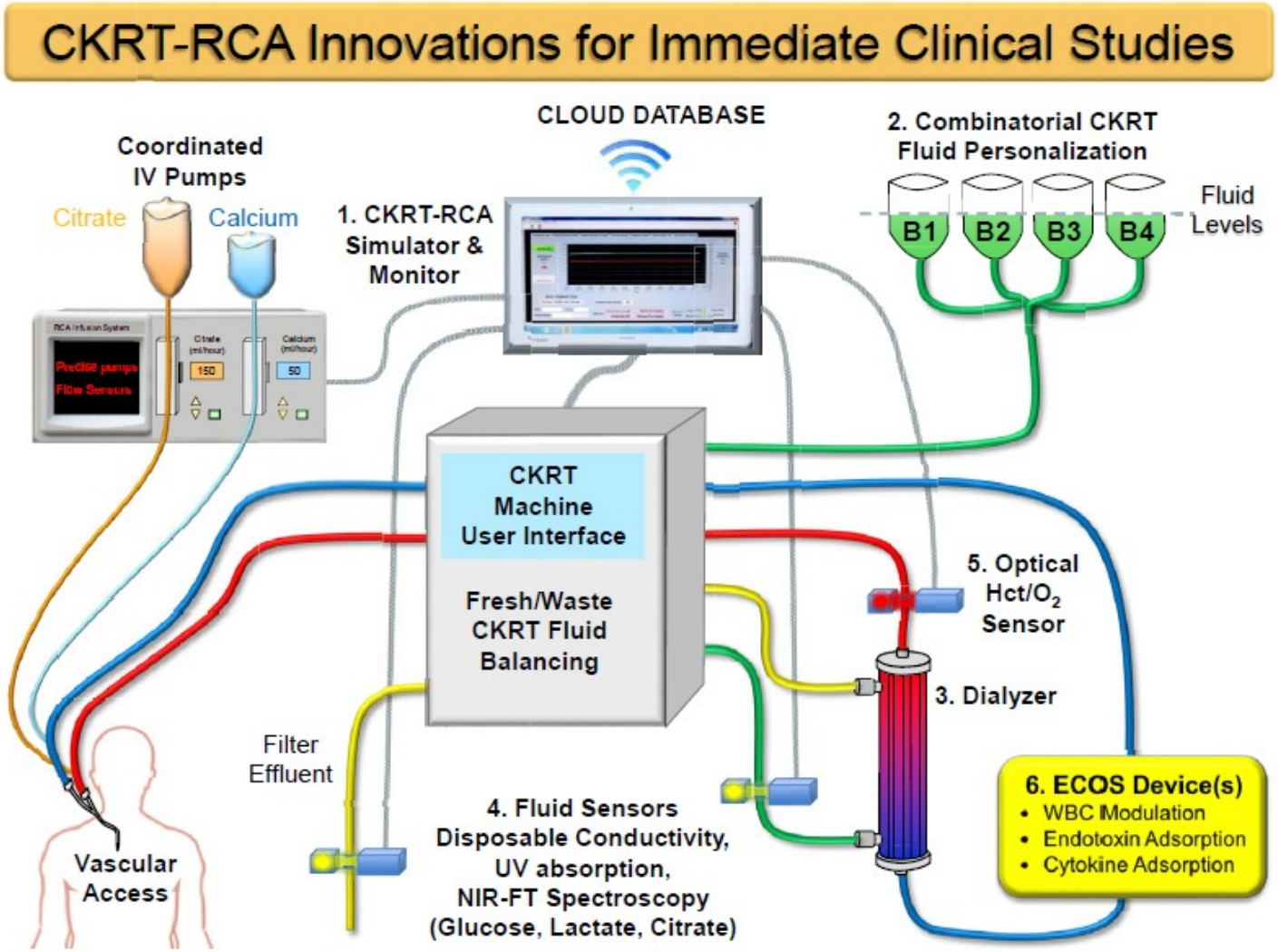


Fig. 1 $ECCO_2R$ devices and considerations for $ECCO_2R$ use

Extracorporeal carbon dioxide removal for acute respiratory failure: a review of potential indications, clinical practice and open research questions Alain Combes



Extracorporeal carbon dioxide removal for acute hypercapnic respiratory failure Luis Morales-Quinteros et Al Annals of Intensive Care



…the clinical feasibility and benefit of many of the envisioned improvements has not been established by clinical studies to date

Technology Innovations in Continuous Kidney Replacement Therapy: The Clinician's Perspective. Nada Hammouda and Javier A. Neyra AGKD

a Development of wearable sensors

Commercial
Research stage

- 1962 — First wearable sensor: Holter monitor for cardiac monitoring
- 1982 — Wireless heart rate monitor from Polar Electro
- 1999 — Conductive fabrics for smart textiles for temperature and motion sensing[283]
- 2002 — First commercial reverse iontophoresis-based sensing platform for non-invasive glucose determination ('GlucoWatch' by Cygnus)
- 2011 — Introduction of epidermal electronics[284]
- 2012 — Graphene-based biosensor integrated onto tooth enamel for bacteria detection[285]; Contact lens biosensors for non-invasive glucose monitoring
- 2014 — First wearable glucose monitoring system ('FreeStyle Libre' by Abbott)
- 2015 — Integrated mouthguard biosensor for salivary uric acid monitoring[286]
- 2016 — Integrated wearable sensor arrays for multiplexed perspiration analysis[10]; Glove-based biosensors for on-site detection of chemical threats[287]
- 2017 — Paper-based wearable sensors for continuous breath chemistry monitoring[99]
- 2018 — Smart face mask for respiration monitoring ('Spyras')
- 2019 — Smartwatches for the early detection of symptomatic and pre-symptomatic COVID-19 (refs.[12,13]); Microneedle biosensors for real-time, minimally invasive drug monitoring[244]
- 2020 — Passive perspiration biofuel cells for energy-autonomous wearable sensors[288]
- 2021 — Synthetic biology-enabled wearable biosensors[28]

b Building blocks of wearable sensors

Materials

Substrates
Natural materials
Synthetic polymers
Hydrogels
Inorganics

Electrodes
Metals
Carbon-based materials
Hydrogels

Decision-making unit
Data conversion
Data processing
Data transmission
Data storage

Power unit
Energy harvesting
Energy storage

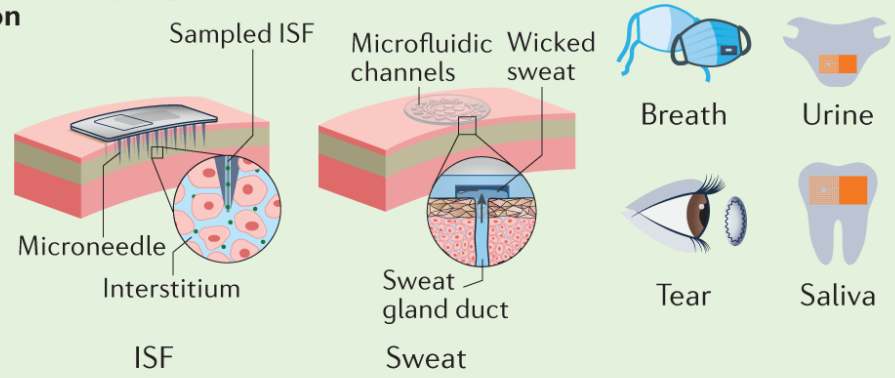
Sensing unit

Biorecognition elements
Enzymes
Affinity proteins
Peptides
Aptamers
CRISPR

Signal amplification
Chemical
Electrical
Digital

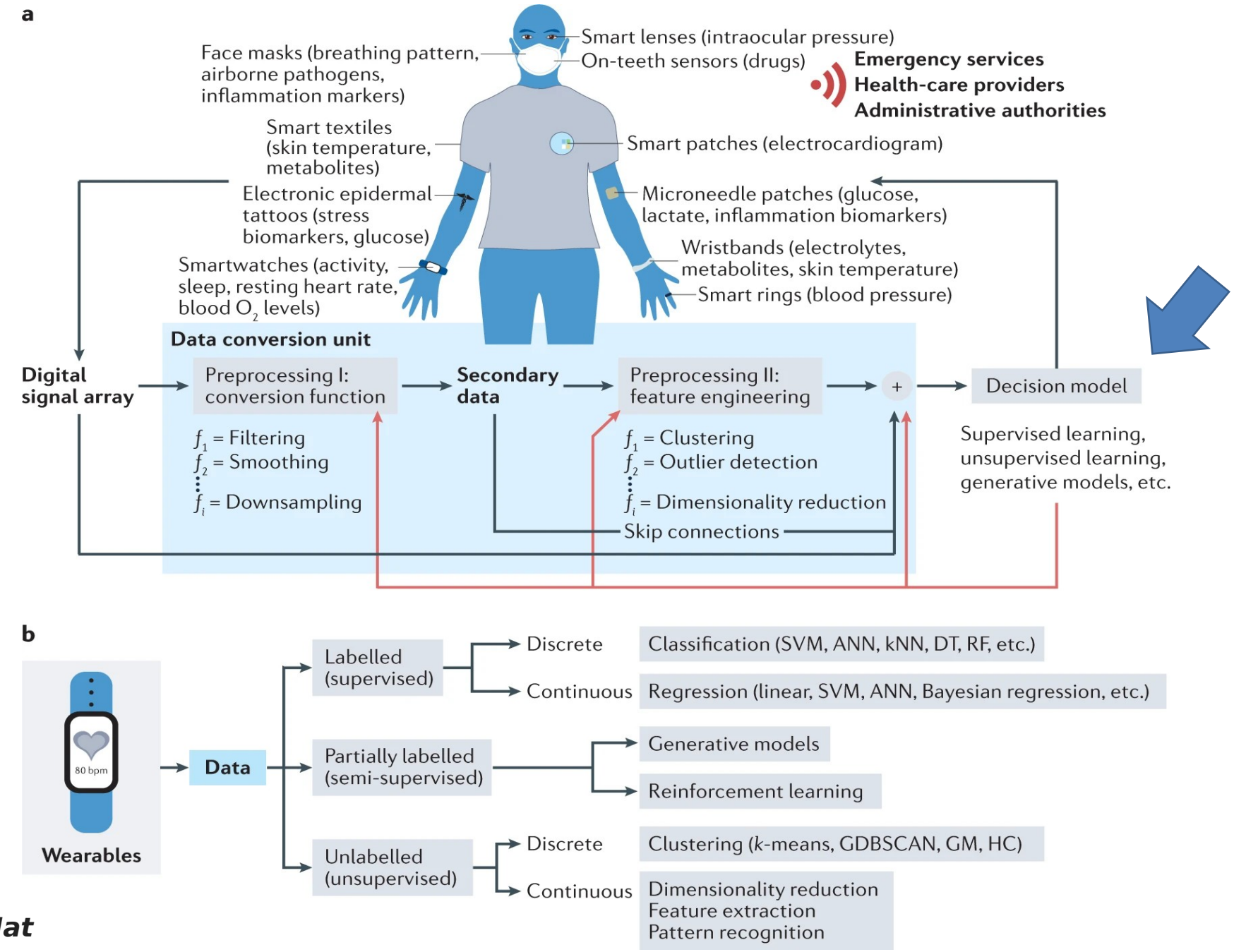
Signal transduction
Electromechanical
Electrical
Optical
Electrochemical

Sampling



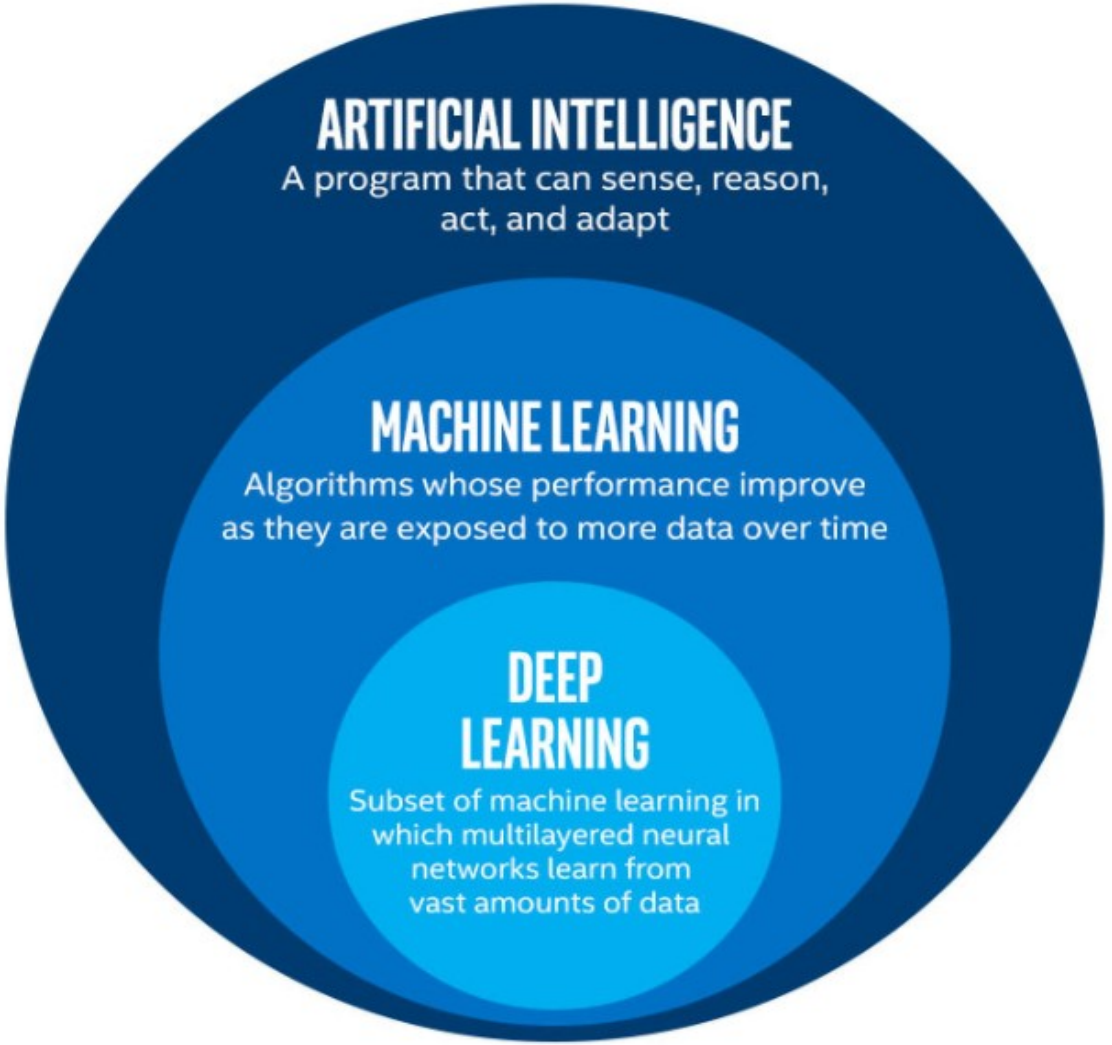
Ates, H.C., Nguyen, P.Q., Gonzalez-Macia, L. *et al.* End-to-end design of wearable sensors. *Nat Rev Mater* **7**, 887–907 (2022)

links between the measured signals and physiological status



Overview of data-driven methods. Post-processing of big data to explore the complex links between the measured signals and physiological status of individuals is possible with machine learning algorithms.

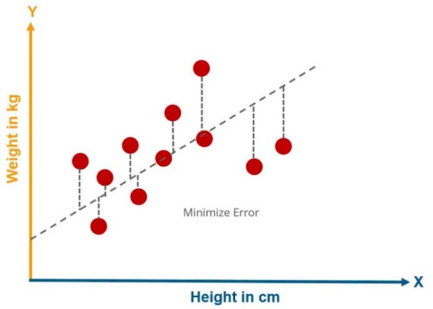
Ates, H.C. *et al.* End-to-end design of wearable sensors. *Nat Rev Mater* 7, 887–907 (2022)



AI: The study of the modelling of human mental functions by computer programs." — Collins Dictionary

AI: Theory and development of computer system to perform tasks that normally require human intelligence- McCarthy 1956

ML "Machine learning is the science of getting computers to act without being explicitly programmed." — Stanford University

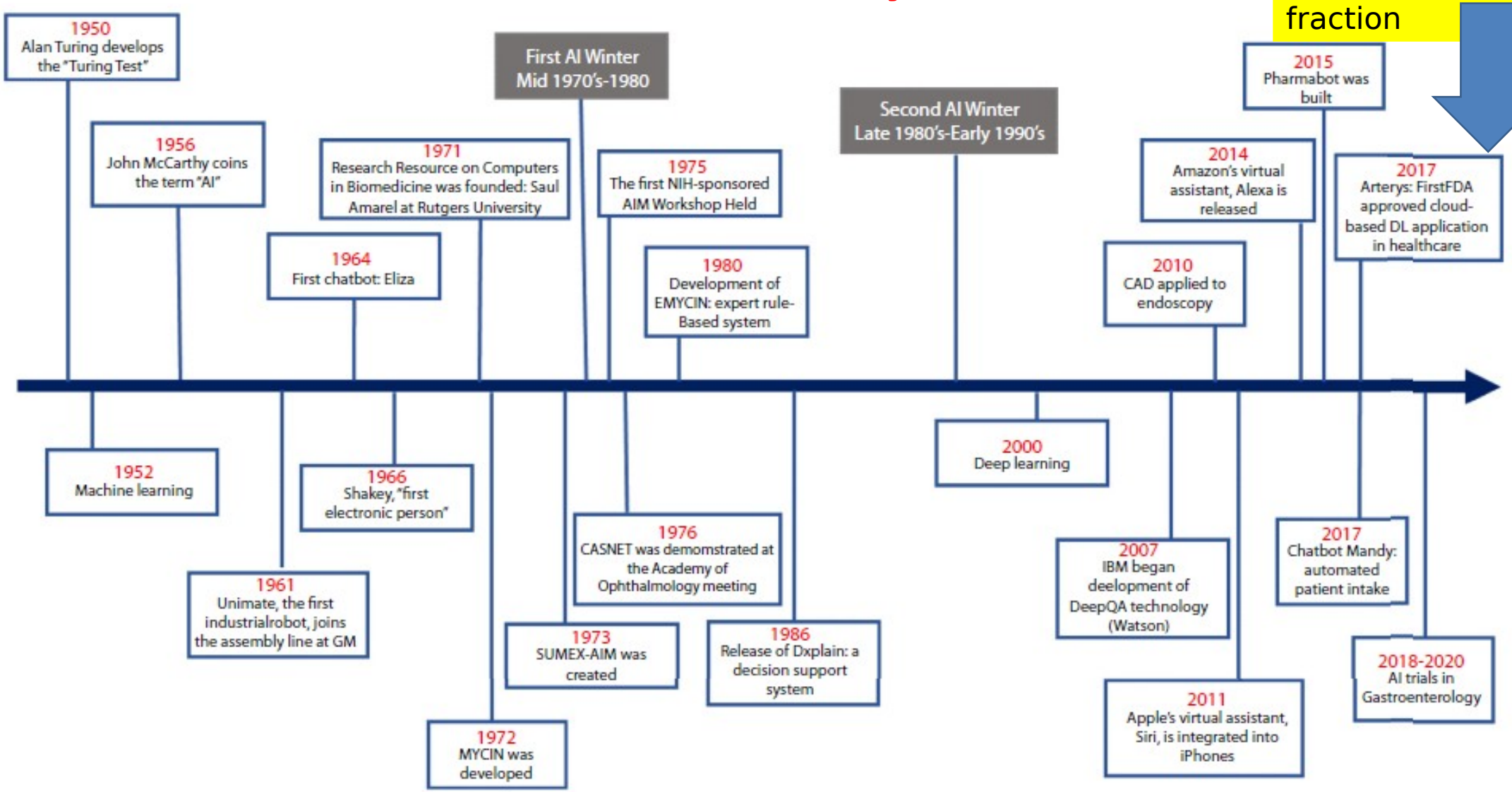


Linear Regression

"Deep Learning is a subfield of machine learning concerned with algorithms inspired by the structure and function of the brain called artificial neural networks".

AI…really new?

CardioAI
RM to cardiac ejection fraction



Kaul V, Enslin S, Gross SA. History of artificial intelligence in medicine. Gastrointest Endosc. 2020 Oct

Jakub Polec • 3rd+
Professional geek | Driving business growth through digital transform...
1mo • Edited •

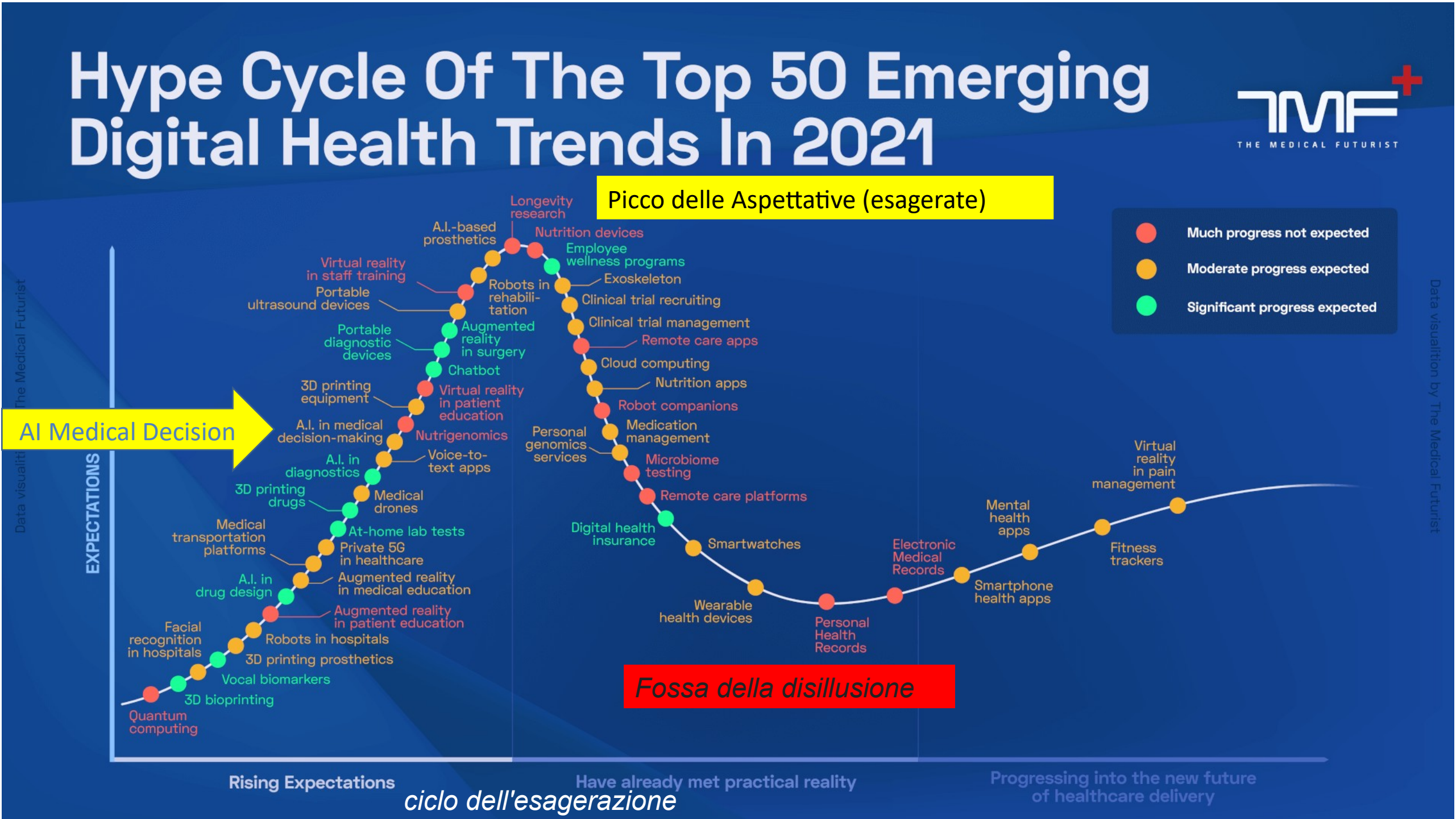
+ Follow

When I hear that Machine Learning is an emerging tech field and new technology, it freaks me out:

Logistic regression — 1958
Hidden Markov Model — 1960
Stochastic gradient descent — 1960
Support Vector Machine — 1963
k-nearest neighbours — 1967
Artificial Neural Networks — 1975
Expectation Maximization — 1977
Decision tree — 1986
Q-learning — 1989
Random forest — 1995

The logic seems to be: "if I didn't care about something important my whole life, but I care now, then it has to be emerging".

Hype Cycle Of The Top 50 Emerging Digital Health Trends In 2021



ciclo dell'esagerazione

Utilization of deep learning for subphenotype identification in sepsis-associated AKI

CJASN
Clinical Journal of American Society of Nephrology

Methods and Cohort

EHR data from ICUs in a tertiary care hospital

Adult patients with sepsis and AKI within 48h of ICU admission

Deep learning utilizing all available vital signs, labs, and comorbidities

K Means clustering to identify subphenotypes

Results

Patients with sepsis and AKI
N=4001

sepsis-associated AKI

	Mortality 28d post AKI	Dialysis requirement
Subphenotype 1 N=1443	23% Reference	4% Reference
Subphenotype 2 N=1898	35% aOR 1.4 (1.2-1.6)	7% NS
Subphenotype 3 N=660	49% aOR 1.9 (1.5-2.4)	26% aOR 3.6 (2.5-5.4)

had higher odds or mortality than subphenotype 1

Conclusion Utilizing routinely collected laboratory variables, vital signs, and comorbidities we were able to identify three distinct subphenotypes of sepsis-associated AKI with differing outcomes.

Kumardeep Chaudhary, Akhil Vaid, Áine Duffy, et al. ***Utilization of Deep Learning for Subphenotype Identification in Sepsis-Associated Acute Kidney Injury***. CJASN doi: 10.2215/CJN.09330819. **Visual Abstract by Beatrice Concepcion, MD**

higher mortality P<0.001 and more patients received dialysis

ACKD

Can Artificial Intelligence Assist in Delivering Continuous Renal Replacement Therapy?

Nada Hammouda and Javier A. Neyra

Access-related complications remain a common issue in establishing effective and sustained CRRT delivery

Circuit Clotting: There is no standardization on CRRT anticoagulation. While the use of predilution regional citrate anticoagulation (RCA) prolongs filter lifespan, it requires a specialized protocol and could also increase risk of
bleeding or other complications.

Solute Control: Electrolyte disturbances such as hypokalemia and hypophosphatemia are common complications during CRRT.

Quality Assurance: Lack of oversight and standardized protocols have been shown to cause treatment interruptions, poor solute clearance, and off-target fluid management or effluent dose delivery

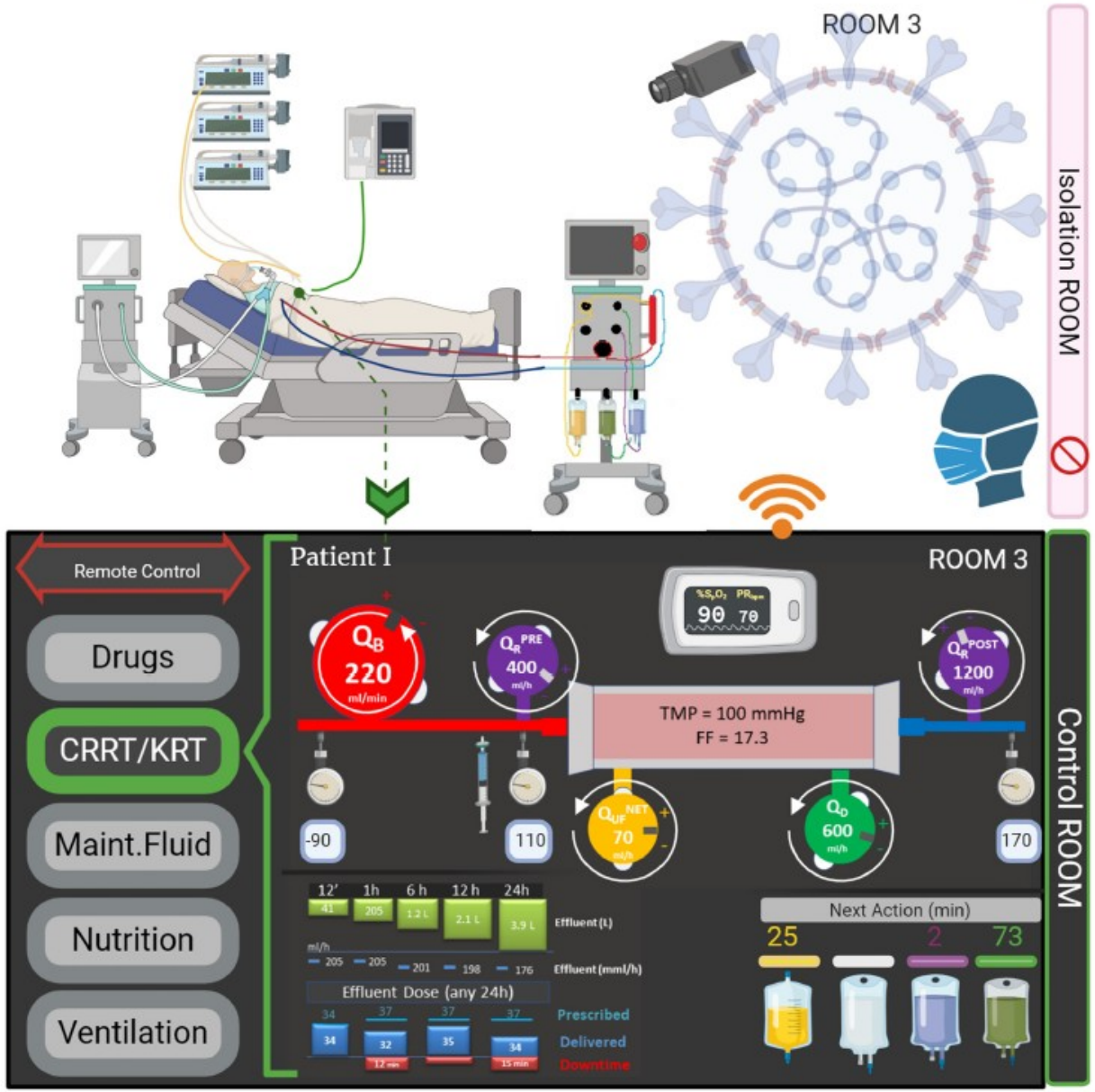


Fig. 1. Remote Control of Medical Devices in ICUs. Example of implementation of remote control and monitoring in an ICU setting. The control panel, located in a separate control room, is connected to the devices (RRT in the current image). Modification of parameters can be undertaken by medical personnel, without the need to enter the patient's room.

Monitoraggio Remoto

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Preventing infectious diseases in Intensive Care Unit by medical devices remote control: Lessons from COVID-19

Francesco Garzotto [a,b,*], Rosanna Irene Comoretto [b], Marlies Ostermann [c], Federico Nalesso [d], Dario Gregori [b], Maria Giuseppina Bonavina [a], Giorgio Zanardo [e], Gaudenzio Meneghesso [f]

Medical Device Regulation 2017/745

Documento 32017R0745

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.)

GU L 117 del 5.5.2017, pagg. 1–175 (BG, ES, CS, DA, DE, ET, EL, EN, FR, GA, HR, IT, LV, LT, HU, MT, NL, PL, PT, RO, SK, SL, FI, SV)

In vigore: Questo atto è stato modificato. Versione consolidata attuale: 24/04/2020

ELI: http://data.europa.eu/eli/reg/2017/745/oj

MDD vs MDR

Medical Device Directive

Directive: Sets out general rules that are transferred to national law by each member state

60 Pages
20 Articles
12 Annexes

Medical Device Regulation

Regulation: Directly applicable in all EU Member states. Leaves no room for local interpretation

369 Pages
97 Articles
16 Annexes

B BRAUN
SHARING EXPERTISE

Medical Device Regulation

Information on the Medical Device Regulation

The new European Medical Device Regulation (MDR) with many new rules is a challenge for all involved. B. Braun is preparing intensely and wants to apply the new requirements as soon as possible. Here we have compiled some information about the MDR for you.

For MDR certified Fresenius Medical Care products, instructions for use (IFU) will be provided online, in addition to the printed version. The instructions for use of MDR certified products can be found here.

Fresenius Medical Care Product Information

Library for product-related documents compliant with the Medical Device Regulation (MDR):

Updates of product information (e.g., user information, Instructions for Use (IFU), Manuals and Declarations of Conformity (DoC)) are made available to the user via this website. The documents can be searched in the database using the search function and the product name or the article number. Instructions for Use are provided in different languages depending on the relevant legislation and are indicated as two-letter language codes according to ISO 639.
The documents published on this website correspond to those approved according to the new Regulation (EU) 2017/745 (MDR) for medical devices. In case you are looking for older Instructions for Use, Manuals or Declarations of Conformity, please contact the local Fresenius Medical Care organization in your country.

Instructions for Use	Reference no. of finished product	Language	Edition date	Version/Software-Version	Declaration of Conformity
Ci-Ca Dialysate K2 Plus 5000 mL	F00009645	pl, hu, sk, sl, sr, el, ro, bg	2022-05	01	DoC
Ci-Ca Dialysate K4 5000 mL	F00009644	pl, hu, sk, sl, sr, el, ro, bg	2022-05	01	DoC

Unique Device Identification UDI

European Commission

Unique Device Identification (UDI) System

under the EU medical devices Regulations 2017/745 and 2017/746

MEDICAL DEVICES CHANGE OF LEGISLATION

What you need to know!

Introduction to the new UDI system and the obligations of operators

The existing regulatory framework on medical devices dates back to the 1990s and consists of three Directives. Two new Regulations (Regulation (EU) 745/2017 on medical devices and Regulation (EU) 746/2017 on *In Vitro* diagnostic medical devices) were adopted in April 2017 and entered into force on 25 May 2017. The general application dates of the two Regulations are 26 May 2021 for medical devices and 26 May 2022 for *In Vitro* diagnostic medical devices, though different timelines apply for certain specific provisions.

These Regulations introduce an EU identification system for medical devices based on a Unique Device Identifier (UDI)

3. Which products are subject to the UDI system?

The UDI system should apply to all devices, except custom-made and performance study/investigational devices.

The obligation for placing the UDI carrier applies according to the following timelines:

Device as per Regulation (EU) 2017/745 (MDR)	Implantable devices and Class III devices	Class IIa and Class IIb devices	Class I devices
Placing UDI-carriers on the labels of devices MDR Article 123(3)(f), Article 27(4)	26 May 2021	26 May 2023	26 May 2025
Direct marking of the reusable devices MDR Article 123(3)(g), Article 27(4)	26 May 2023	26 May 2025	26 May 2027

Clinical investigation and evaluation

Guidance - MDCG endorsed documents and other guidance

Reference	Title	
MDCG 2021-28 EN •••	**Substantial modification** of clinical investigation under Medical Device Regulation	December 2021
MDCG 2021-20 EN •••	Instructions for **generating CIV-ID** for MDR Clinical Investigations	July 2021
MDCG 2021-8 EN •••	Clinical investigation **application/notification documents**	May 2021
MDCG 2021-6 EN •••	Regulation (EU) 2017/745 – **Questions & Answers** regarding **clinical investigation**	April 2021
MDCG 2020-13 EN ••• - Word version EN •••	**Clinical evaluation assessment report template**	July 2020
MDCG 2020-10/1 Rev.1 EN ••• MDCG 2020-10/2 Rev. 1 EN •••	Guidance on **safety reporting** in clinical investigations Appendix: Clinical investigation summary safety report form	October 2022 October 2022
MDCG 2020-8 EN •••	Guidance on **PMCF evaluation report** template	April 2020
MDCG 2020-7 EN •••	Guidance on **PMCF plan** template	April 2020

2.3 Clinical evaluation and investigation

For any device regardless of class, the manufacturer must ensure the general safety and performance requirements are satisfied (MDR Article 5, MDR Annex I). This includes carrying out a clinical evaluation (MDR Article 5 (3), MDR Article 61, MDR Annex XIV. For implantable devices and class III devices, a premarket clinical investigation is compulsory, with some exceptions such as modifications of an existing device, demonstrated equivalence to CE-marked device, placed on the market under Directive 90/385/EEC or Directive 93/42/EEC for which sufficient clinical data is already available, and specific exemptions laid down in Article 61(6)(b). The conditions for starting a clinical investigation vary depending on the class of the device (see MDR Article 70(7) and Article 78). According to Article 61(10), if demonstration of conformity with Annex I requirements based on clinical data is not deemed appropriate, the manufacturer shall justify this in the technical documentation.

For class III implantable devices and class IIb active devices intended to administer or remove a medicinal product, the notified body must also follow the clinical evaluation consultation procedure where certain documentation including the clinical evaluation report is submitted for review by expert panels (MDR Article 54 and Section 5.1 of Annex IX). It must notify the Member State competent authorities of the certificates it has granted for these types of devices (MDR Article 55). The manufacturer may consult an expert panel on their clinical development strategy prior to performing the clinical evaluation and/or investigation (MDR Article 61(2)). See also MDCG Guideline 2019-3[5] for interpretation of Article 54.

For implantable devices and class III devices, other than custom-made or investigational devices, the manufacturer must update the post-market clinical follow-up evaluation report as it will serve an input for the writing of the Periodic Safety Update Report, and, if indicated, the summary of safety and clinical performance[6] (MDR Article 32).

MDCG 2020-7

Post-market clinical follow-up (PMCF) Plan Template

A guide for manufacturers and notified bodies

April 2020

MDCG 2020-8

Post-market clinical follow-up (PMCF) Evaluation Report Template
A guide for manufacturers and notified bodies

April 2020

The aim of the PMCF plan is:

- confirming the safety[1] and performance, including the clinical benefit if applicable, of the device throughout its expected lifetime;
- identifying previously unknown side-effects and monitor the identified side-effects and contraindications;
- identifying and analysing emergent risks on the basis of factual evidence;
- ensuring the continued acceptability of the benefit-risk ratio, referred to in Section 1 and 9 of Annex I in the MDR;
- identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.

The PMCF plan shall be part of the post-market surveillance plan.

PMCF

Section C. Activities related to PMCF: general and specific methods and procedures

In this section it is expected to describe the different activities that will be conducted in post-market, including general and specific methods / procedures to conduct in relation to the product covered by the scope of PMCF, also the aim of each activity described and the rational for the appropriateness of the chosen general and specific methods to achieve those objectives as well as the known limitations of the planned activities such as for example incomplete follow up, missing data and so on. The timelines of those activities shall be also defined quarterly or at least yearly.

Here are some examples of different activities related to PMCF:

- A manufacturer **device registry** (specific for the type of device or the group of the medical devices the product belongs to) can be indicated together with a description and a summary of the plan. A pre-specification of what quality and quantity data – based on the risk of the device(s) and the associated accessories – to be collected and analysed shall be included. Any possible evaluation of suitable **national public registries** with clinical data on the manufacturer's own device and/or on similar devices could be specified in this section, identifying the expected quantity and quality of data to be gathered and the search protocols to be adopted.
- **PMCF studies** planned could be indicated in this section, together with a summary of the plan including the design, sample size, the endpoints, the inclusion/exclusion criteria (e.g. extended follow up of patients included in the pre-market clinical investigations, new clinical investigations within the intended use, retrospective studies). In case of implantable devices and class III devices where clinical investigations have not been performed pursuant to Article 61 (4), the PMCF plan shall include post market studies to confirm the safety and performance of the device.
- Planned **Real-world evidence** (RWE) analyses could be indicated in this section, together with a summary of the plan including the design, sample size, the endpoints, and analysis population. The real-world data (RWD) from which these analyses are based on should be of sufficient quality and come from reliable data sources.
- **Surveys** planned to collect information about the use of the concerned medical device could be described.

Each activity will be developed in a different subsection (e.g. C.1, C.2, …), and for which the manufacturer will:

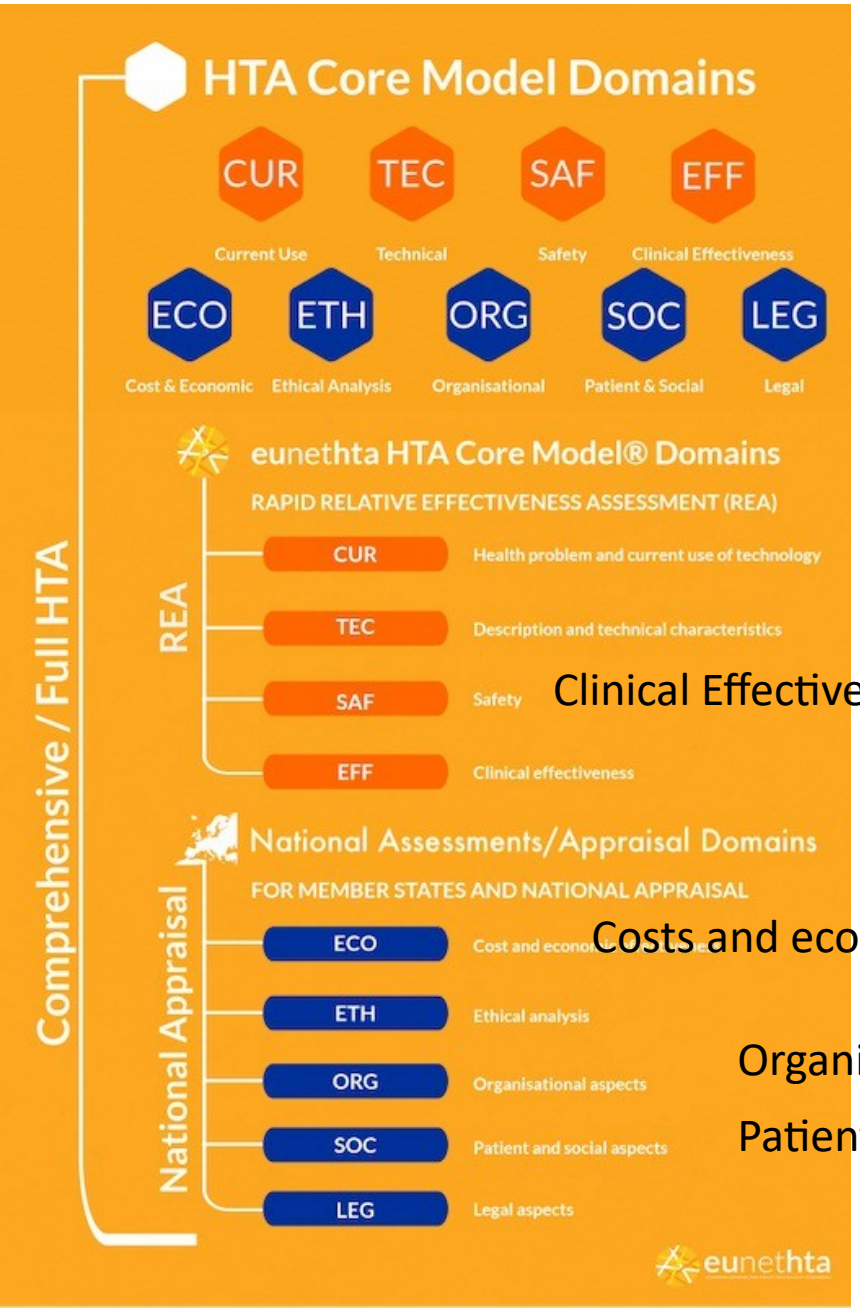
- Define where the need of conducting the PMCF activity is coming from (requested by notified body, clinical evaluation report, PMS, risk management report, previous PMCF report, etc…)
- Provide the description of activity, and if it is a general or specific procedure / method.
- Define the aim of this activity:
  - confirming the safety of the medical device
  - confirming the performance of the medical device
  - identifying previously unknown side-effects (related to the procedures or to the medical devices).
  - monitoring the identified side-effects and contraindications
  - identifying and analysing emergent risks
  - ensuring the continued acceptability of the benefit-risk ratio
  - identifying possible systematic misuse or off-label use of the device

- Describe the different procedures which will be used as part of PMCF:
  - screening of scientific literature and other sources of clinical data
  - post-market studies
  - collecting data in registries
  - survey from health care professional
  - survey from patients/users
  - review of case reports which may reveal misuse or off-label use

- Describe the rationale for the appropriateness of the chosen methods/procedures, including:
  - the justification for sample size, timescales and endpoints
  - justification for comparator, on the basis of intended purpose and state of the art
  - justification of the study design on the basis of all of the above, and why it is sufficient to ensure representative patient populations and provide for adequate controls on sources of bias (an evaluation of the potential sources of bias should form part of this)
  - a statistical justification for the expected quality of outcomes, and justification for why this is satisfactory in light of the residual risks. This is an important consideration. For example, retrospective surveys with no justification other than “this should demonstrate the expected quality of evidence that we require,” but without showing a statistical rationale, are not acceptable.

- Provide the timelines of the activity. A detailed and adequately justified time schedule for PMCF activities, such as the analysis of PMCF data and reporting, shall be described.

Organizational and economic impact of IT reports of KPI for HTA



What governments measure (...or would like.)

REGULATIONS

REGULATION (EU) 2021/2282 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2021

on health technology assessment and amending Directive 2011/24/EU

Clinical Effectivenss

Health technology assessment (HTA) is a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing health technologies. HTA focuses specifically on the added value of a health technology in comparison with other new or existing health technologies.

Costs and economics effectiveness

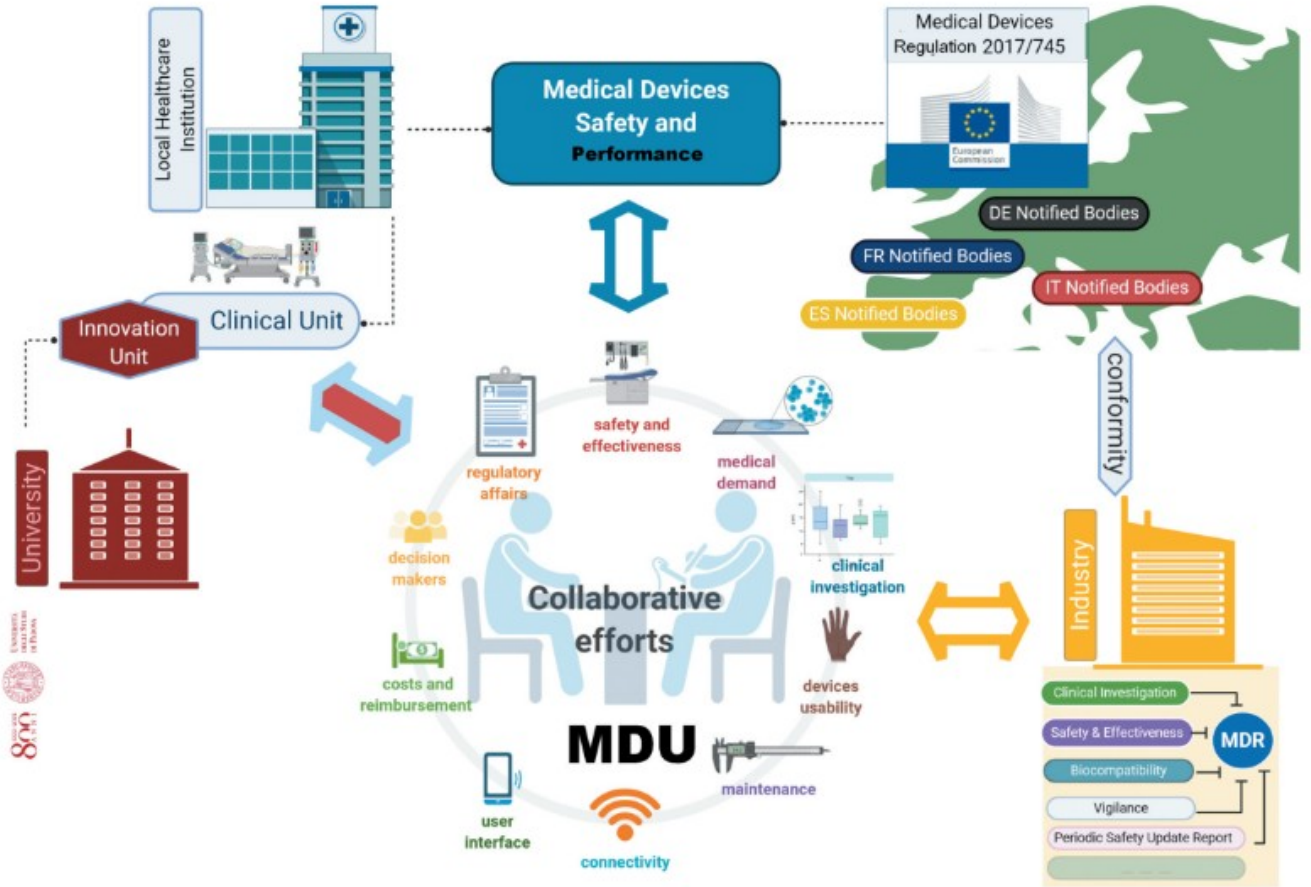
Organizational Aspects

Patient and Social Aspects

Preparing healthcare, academic institutions, and notified bodies for their involvement in the innovation of medical devices under the new European regulation

Francesco Garzotto [a,b,c], Rosanna Irene Comoretto [a,d], Lorenzo Dorigo [c], Dario Gregori [a], Alessandro Zotti [e], Gaudenzio Meneghesso [f], Gino Gerosa [g] and Mauro Bonin [h]

Start-ups and small companies might not be able to cope with the increasing complexity and the required changes of perspective. Health-care institutions are facing an increasing availability of complex technologies, while data on their clinical efficacy and cost-effectiveness are rarely provided.



A partnership/collaboration between health-care institutions, academia, and private industries will enhance their own specific interests with the common goal of improving overall health and quality of life.