Extracorporeal Therapies and Antibiotics Management

- Why and which extracorporeal therapies?
- How do extracorporeal therapies affect the antibiotics management?
- How can we optimize the antibiotics management?

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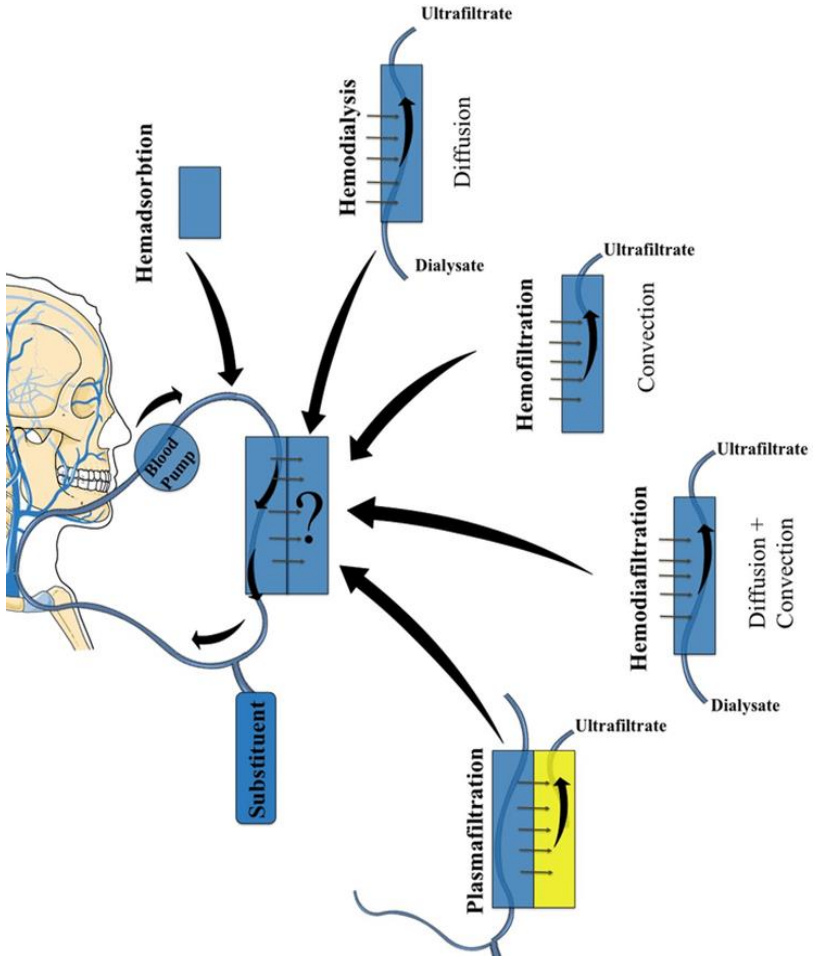
"Casa Sollievo della Sofferenza" Foundation, Scientific Institut for Reserch and Health Care
San Giovanni Rotondo ***Certified ISO 9001:2015***

The Blood Purification Therapies

Extracorporeal blood purification therapies are life-saving procedures that use advanced technologies for organ support



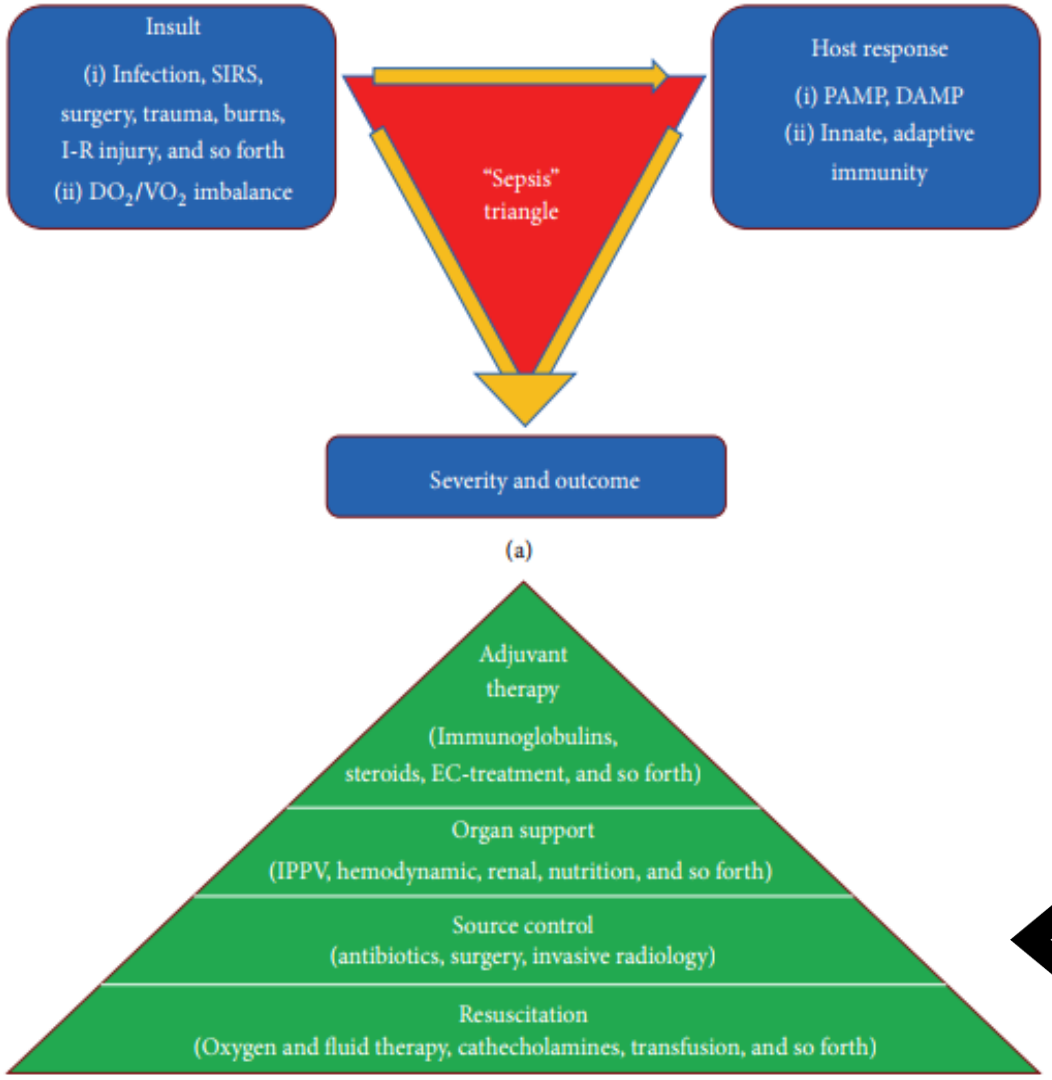
- **MULTI-ORGAN SUPPORT:**

- Acute Kidney Injury (AKI): **renal replacement therapy** (continuous or intermittent)
- Respiratory insufficiency: extracorporeal CO2 removal (ECCO2), extracorporeal membrane oxygenation (ECMO).
- Liver dysfunction
- Inflammatory Systemic Response: modulation of cytokines cascade

- **METABOLIC SUPPORT:**

- Acid-base imbalance: metabolic acidosis and high lactacidaemia
- Electrolytes disturbances

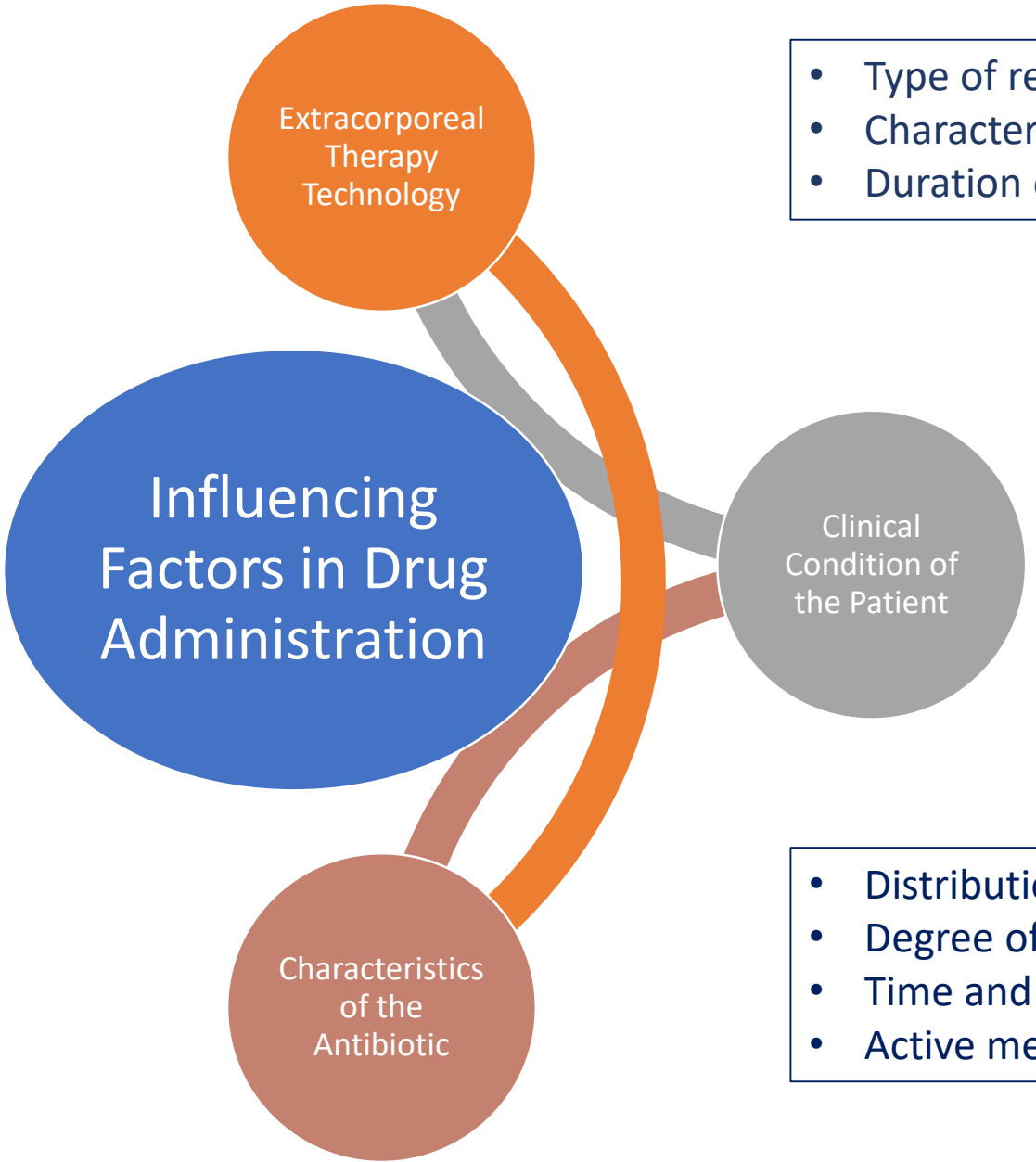
Antibiotic Therapy



Current guidelines and expert opinion recommend using a structured approach to sepsis treatment that consists of rapid recognition, timely use of antibiotics and control of the source of the infection.

Antibiotic therapy is the main weapon to combat sepsis.

Antibiotic Therapy and Extracorporeal Therapies



- Type of removal technology
- Characteristics of the materials
- Duration of treatment

- AKI and MOF
- Altered distribution volume associated with increased micro-vascular permeability

- Distribution Volume V_D
- Degree of protein binding
- Time and way of dosing
- Active metabolites of the parent drug

Factor influencing Antibiotic Removal

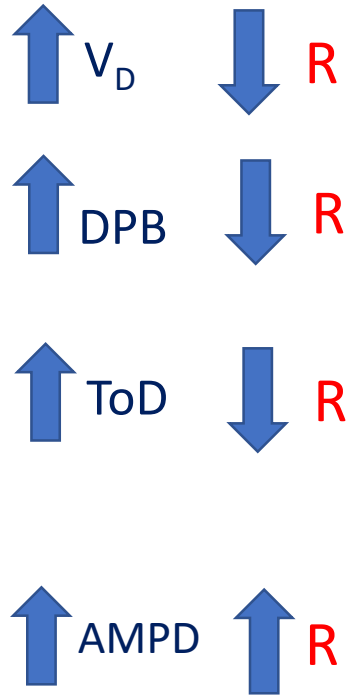
Distribution Volume (V_D): Larger it is, lower the removal is

Degree of protein binding (DPB): Strong protein binding mean less available free drug for removal

Time (and way) of dosing (ToD): Drugs reaching the distribution in all the body are less exposed to removal rates compared drugs just injected into the blood

Active metabolites of the parent drug (AMPD): drugs with fast conversion to active and smaller metabolites are more available for remouval

The balance between flow rates through filters or sorbents cartridge and the speed of metabolism to active metabolite(s) have clinical relevance



Free, non protein bound drugs are easierly removed.

The removal rate is higher :

- ***With Drug having short half-life and rapidly converted in active, low MW metabolite***
- ***At the moment of the injection, before the diffusion on total Vd***

ANTIMICROBIAL DOSE ADJUSTMENT DURING RRT

Which RRT?

Intermittent/prolonged HD

- two different PK phases (intradialytic and interdialytic).

CRRT

- constant CL of drugs (performed under optimal operative conditions)

Which bactericidal effect?

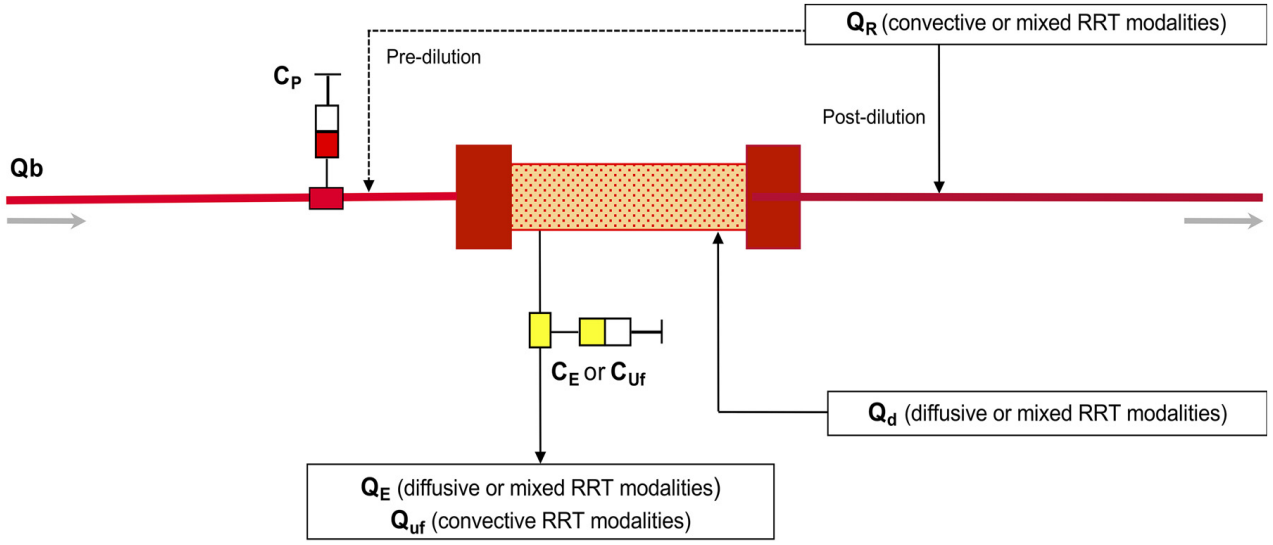
Time-dependent

- The drug need a concentration steadily abobe the MIC;
- Modify the single dose without any variation in time interval.
- EG: beta-lactams, lipopeptides.

Concentration-dependent

- The effect is related to Cmax/MIC or other PK/PD parameters;
- Modulate dosing interval without changes in single doses.
- EG: aminoglycosides, quinolones.

Different technology mean different interaction: the CRRT



CONVECTIVE RRT MODALITIES	DIFFUSIVE RRT MODALITIES	MIXED RRT MODALITIES
$Cl_{convective}$ (post-dilution) = SC x Q_{Uf} $Cl_{convective}$ (pre-dilution) = SC x Q_{Uf} x [Qb/(Qb+Q_R)]	$Cl_{diffusive}$ = SA x Q_E	Cl_{mixed} (post-dilution) = SA x Q_E Cl_{mixed} (pre-dilution) = SA x Q_E x [Qb/(Qb+Q_R)]

Qb: blood flow rate; Q_d: dialysate flow rate; Q_R: reinfusion flow rate; Q_{uf}: ultrafiltrate flow rate; Q_E: effluent flow rate = Q_{Uf} + Q_d

C_P: plasma solute concentration; C_{uf}: ultrafiltrate solute concentration; C_E: effluent solute concentration

SC: sieving coefficient = C_{Uf} / C_P **SA**: saturation coefficient = C_E / C_P

Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal Replacement Therapy. Antimicrob Agents Chemother. 2019 Jul 25;63(8):e00583-19. doi: 10.1128/AAC.00583-19. PMID: 31109983; PMCID: PMC6658763.

Remotion Factors related to CRRT

- CRRT mode: diffusive, convective (pre-dilution or post-dilution) mixed
- Dialytic dose: Duration of treatment, Flows
- Characteristics of the membrane used

❖ **"Constant" clearance during the treatment**

CVVH

- Use the **convective transport** of solutes. The elimination of a solute by convection depends on **the pressure gradient** applied, characteristics of the membrane used and the relative cut-off.

CVVHD

- Use the **diffusive transport**. The removal of a solute by diffusion depends on numerous factors: the diffusion coefficient, the temperature, the surface of the dialyzer, the **concentration gradient** and thickness of the membrane.

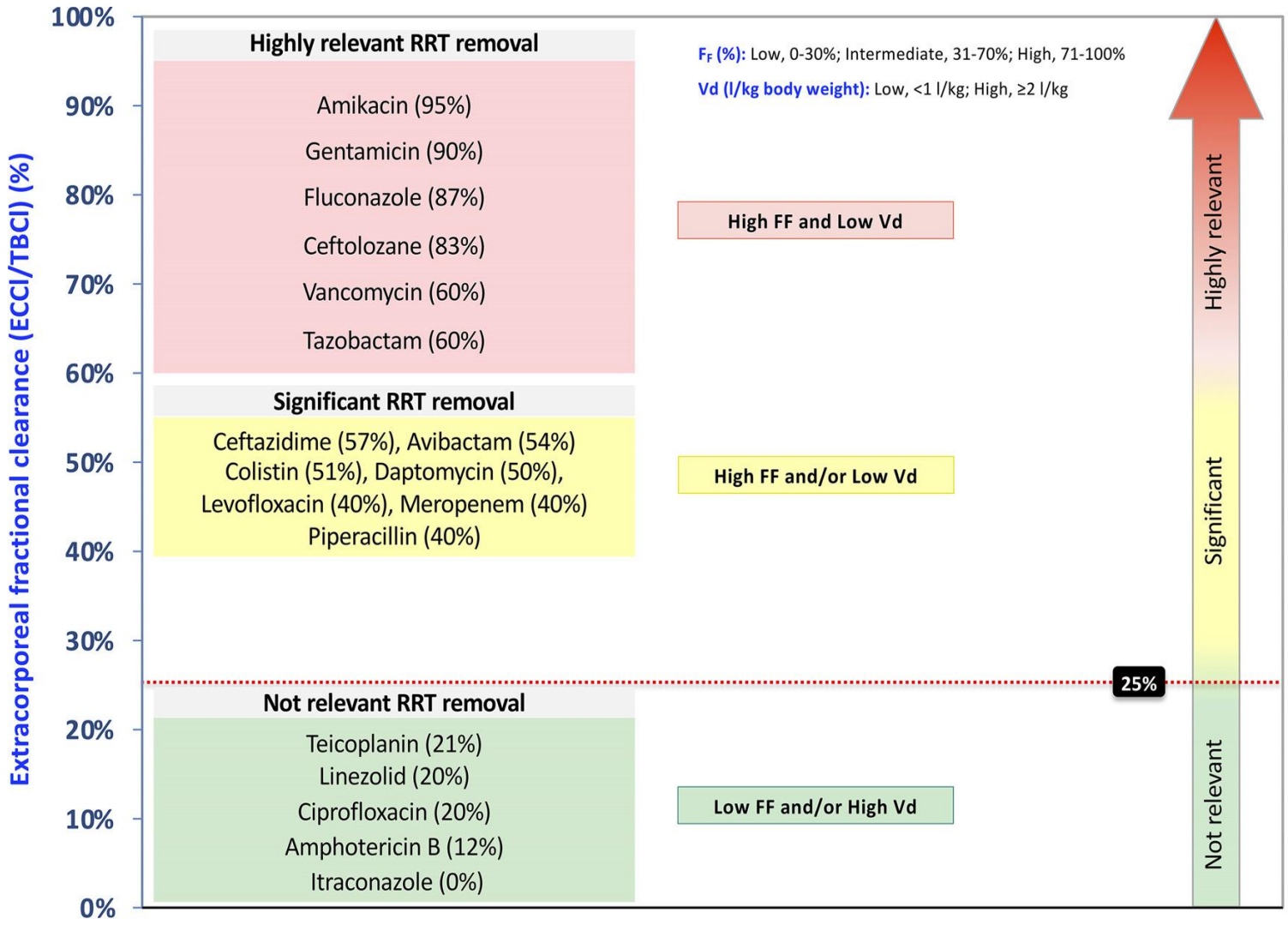
CVVHDF

- Modality that uses both **diffusion and convection exchange.**

CRRT and the removal of antibiotics

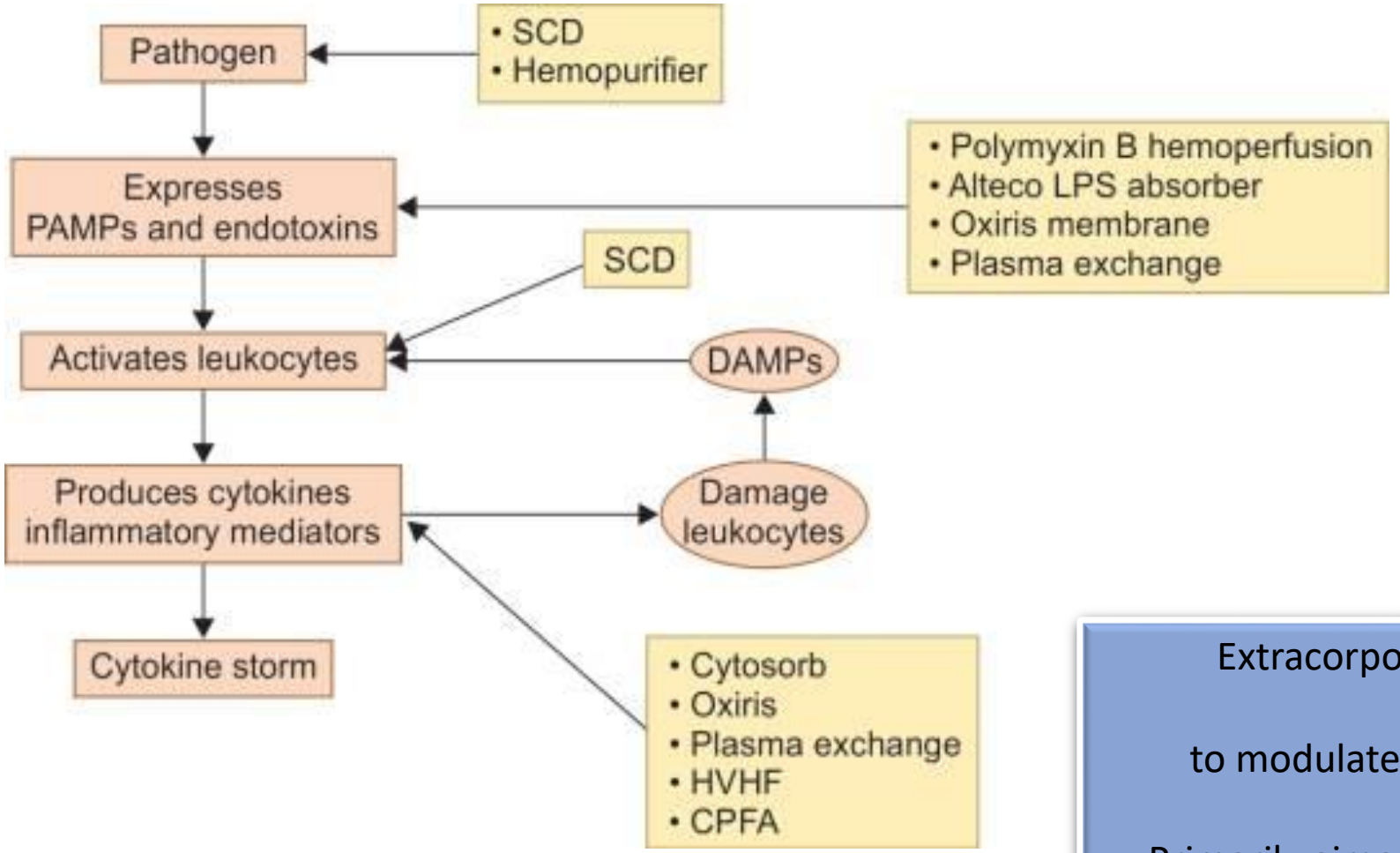
Antibiotic dose adjustments during CRRT

- **Linezolid**: No dosage adjustment is recommended
- **Vancomycin:** effectively removed
- **Voriconazole**: no significant removal and no dosage adjustment with administration of a dose of 6mg / kg).
- **Tigecycline**: No dosage adjustment is recommended
- **Caspofungin**: No dosage adjustment is recommended



*Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal Replacement Therapy. Antimicrob Agents Chemother. 2019 Jul 25;63(8):e00583-19. doi: 10.1128/AAC.00583-19.

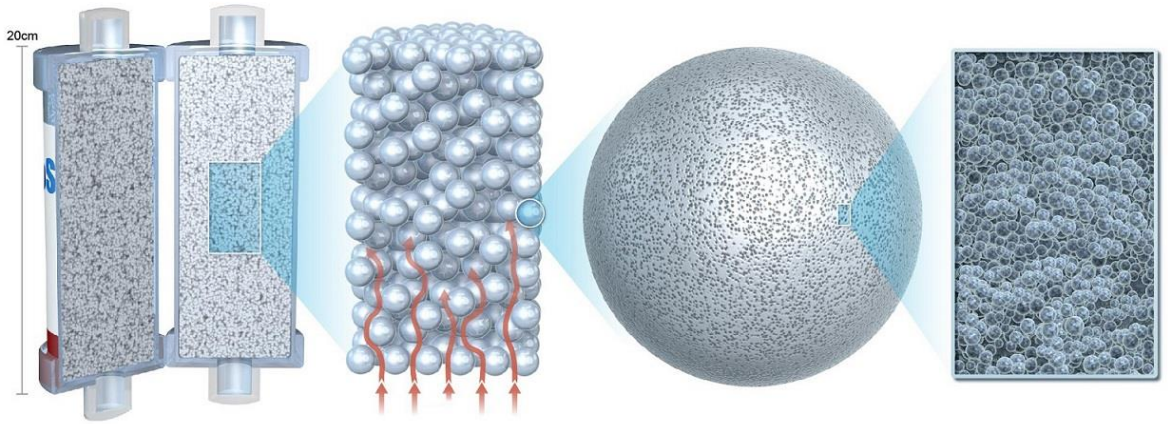
Blood purification techniques in sepsis



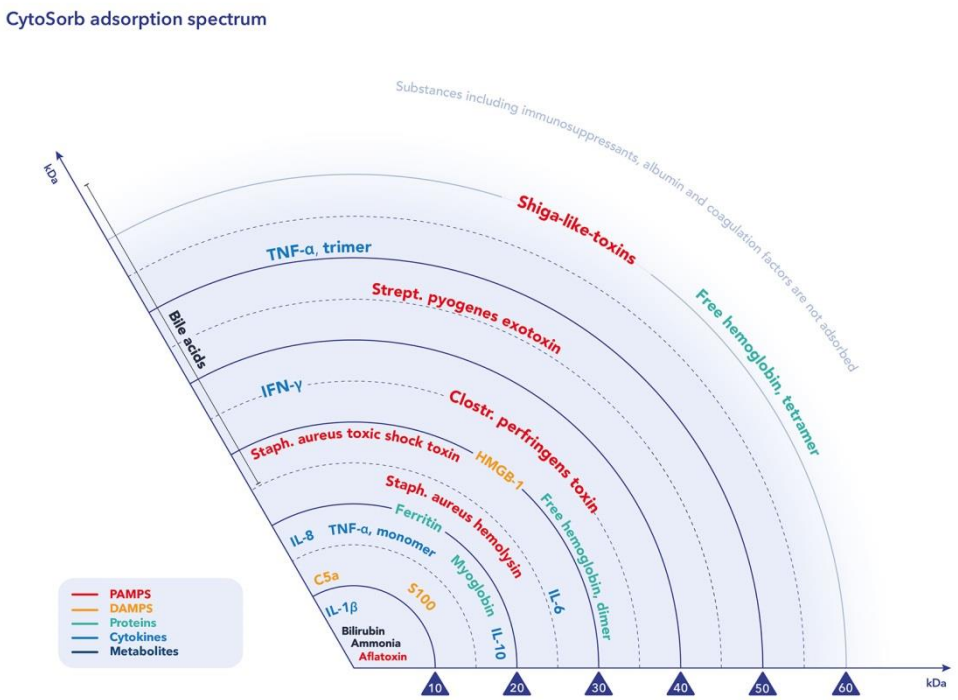
Extracorporeal blood purification therapies as **adjuvant therapies** to modulate the dysregulated immune response.

Primarily aimed at removing inflammatory mediators: **Cytokines, Endotoxins, PAMPs, or DAMPs from the blood.**

Different technology mean different interaction: Adsorption



CRRT exchanges via convection and diffusion using a second liquid. The exchange is conditioned by the flows and the filter type used.



CytoSorb acts by adsorption directly on whole blood. The adsorption will depend on:

- **Type**: The CytoSorb device is an adsorbent cartridge made up of highly biocompatible microspheres that interact exclusively with **hydrophobic molecules**
- **Size**: Adsorption takes place through a selective physico-chemical bond that exclusively involves molecules with a **molecular weight up to 60 kDa**.
- **Concentration**: The adsorption by CytoSorb is **concentration dependent**: higher removal with higher concentration of the target molecule.

In vitro experiences on the interaction of CytoSorb with anti-infective agents

Int J Artif Organs. 2019 Feb;42(2):57-64. doi: 10.1177/0391398818812601. Epub 2018 Dec 13.

In vitro removal of anti-infective agents by a novel cytokine adsorbent system

Christina König [1 2], Anka C Röhr [3], Otto R Frey [3], Alexander Brinkmann [4], Jason A Roberts [5 6 7], Dominic Wichmann [1], Stephan Braune [1], Stefan Kluge [1], Axel Nierhaus [1]

In **CytoSorb + CRRT in** Reconstituted blood

Blood	Continuous Infusion Rate (mg/h)	CL
meropenem	192	5.4 to 1.4
ciprofloxacin	30	6.3 to 4.3

Hemoperfusion In **normal saline 0.9%** and **human albumin 5%**

Drugs	Bolus Dose mg	CL (NaCL0.9%) l/h	CL (HA5%) l/h
vancomycin	40	1,19	1,28
gentamicin	20	1,13	1,25
meropenem	20	1,32	1,29
ciprofloxacin	15	1,32	1,24
piperacillin	80	1,29	1,44
flucloxacillin	80	1,17	1,2
voriconazole	10	1,18	1,41
Fluconazole	40	1,12	1,22

In contrast to CRRT where drugs are removed in a continuous fashion, the use of CytoSorb appeared to saturate the adsorbent surface leading to a reduction in CL over time. The administration of an additional dose within the first hours of CytoSorb treatment may be reasonable

Management of Vancomycin in conjunction with CytoSorb treatment

Artificial Organs

MAIN TEXT

Impact of CytoSorb on kinetics of vancomycin and bivalirudin in critically ill patients

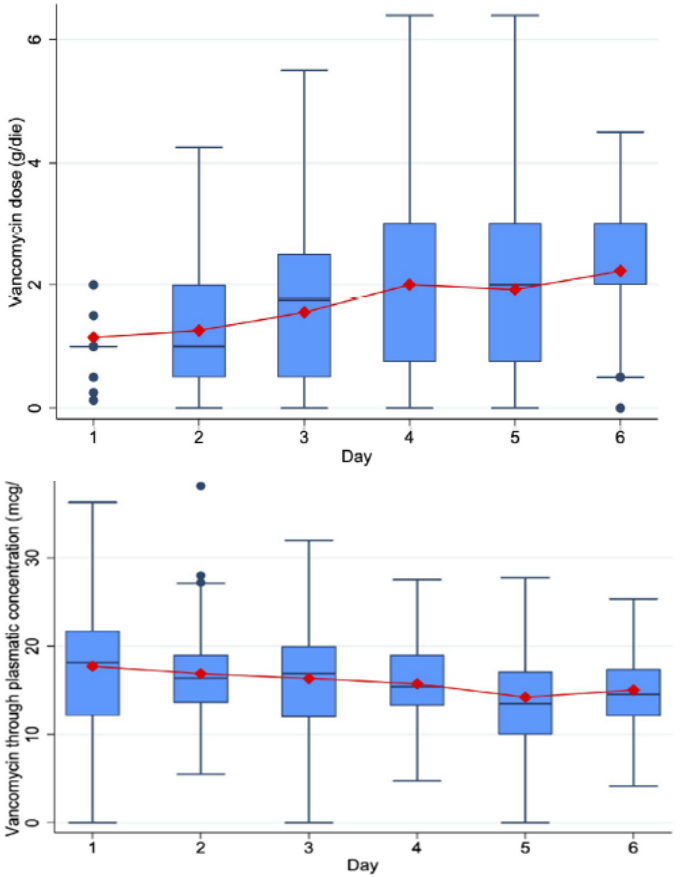
Anna Mara Scandroglio, Marina Pieri, Pasquale Nardelli, Evgeny Fominskiy, Maria Grazia Calabrò, Giulio Melisurgo, Silvia Ajello, Federico Pappalardo

First published: 09 March 2021 | https://doi.org/10.1111/aor.13952

Retrospective study 89 patients - 109 CytoSorb treatments

Post-operative cardiac surgery ICU patients

- 61 patients ECMO + CytoSorb
- 24 patients Mechanical Circulatory Support + CytoSorb
- 25 Patients CVVH + CytoSorb



Dose stabilization was achieved **1g** bolus administration and continuous infusion based on renal function**:**

2 g / day if creatinine clearance> 60 ml / min;
1.5 g / day if creatinine clearance <60 ml / min;
1 g / day if creatinine clearance <30 ml / min.

After dose stabilization, no relevant interaction was found.

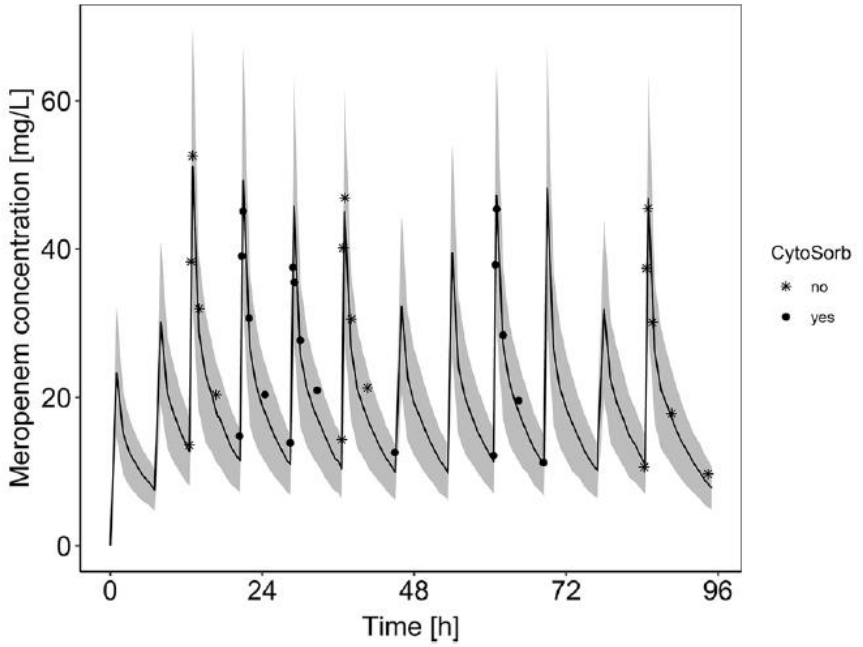
Management of meropenem during CytoSorb treatment

LETTER

No clinically relevant removal of meropenem by cytokine adsorber CytoSorb® in critically ill patients with sepsis or septic shock

Uwe Liebchen[1,2], Christina Scharf[1], Michael Zoller[1], Ferdinand Weinelt[2,3] and Charlotte Kloft[2*] on behalf of the CytoMero collaboration team

- Case series: 25 septic shock patients
- CytoSorb + CRRT or CRRT
- 44 CytoSorb Treatments
- Evaluation of the Meropenem trend under treatment



Observed meropenem concentrations and meropenem concentration–time profile predicted on the basis of a pharmacokinetic model excluding CytoSorb® samples. The profile refers to one patient from the dataset.

No clinically relevant adsorption was observed from a comparison of critically ill patients undergoing **hemodialysis** with and without treatment with **CytoSorb®**.

There is no need for overdose and more frequent drug monitoring.

Linezolid management during CytoSorb therapy

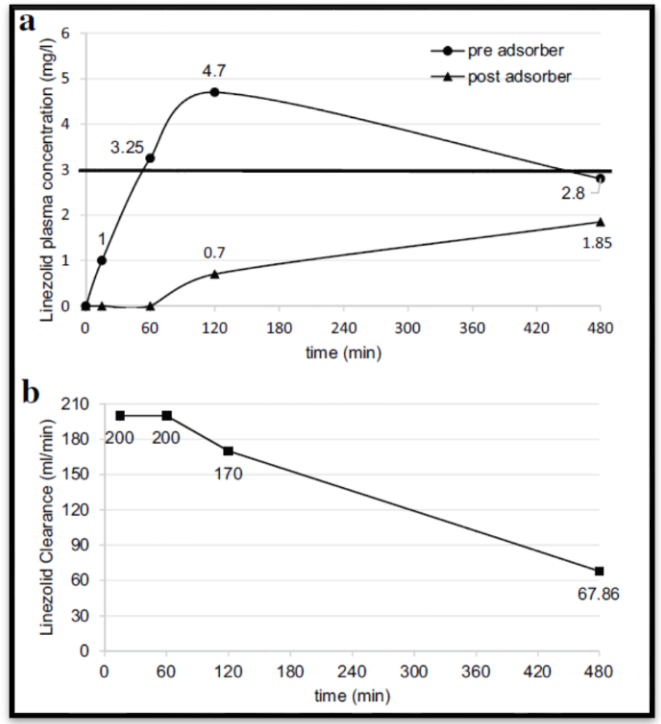
J Artif Organs. 2022; 25(1): 86–90.
Published online 2021 May 28. doi: 10.1007/s10047-021-01274-4
PMCID: PMC8866295
PMID: 34047868

Hemoadsorption with CytoSorb® and the early course of linezolid plasma concentration during septic shock

Thomas Köhler,[1] Elke Schwier,[1] Carmen Kirchner,[2] Günther Winde,[2] Dietrich Henzler,[1] and Claas Eickmeyer[1]

- *61 year-old woman*
- *Postoperative septic shock*
- *Vasopressor high dose support*
- *CVVHD+CytoSorb therapy over 94h*
- *5 sorbents used*

- *Infusion start with a new sorbent connection 600 mg/300 ml/60 min.*



Linezolid:
antibiotic levels tend to decrease during treatment and stabilize allowing for adequate therapy.

an additional loading dose of 600 mg would have been required at the start of therapy with CytoSorb® or after cartridge change.

The '' renal task force of Brescia '' group, suggested a therapeutic dose of **600 mg every 12 hours**.

Other clinical experience in the management of antibiotic therapy in conjunction with CytoSorb

New Generation Antibiotics

Cefotaxime, Ceftizoxime, Ceftriaxone, Cefepime, Cefclidina, Cefpirome, Cefquinome, Ceftolozane, Ceftazidime etc. are all antibiotics belonging to the family of cephalosporins, broad-spectrum Beta-lactams.
There are few studies on single drugs, therefore we can only refer to what is known for the cephalosporin family for which **has not been identified a significant interaction with the CytoSorb sorbent while important removals with dialysis therapies are reported**, given their molecular weight*.

For drugs with no pharmacokinetic data available during CytoSorb treatment, pharmacokinetic principles like **molecular weight**, **hydrophobicity, Vd**, **half-life** and **protein binding** can help determine the likelihood of significant removal.

* Polain A, Gorham J, Romeo I, Belliato M, Peluso L, Partipilo F, Njimi H, Brasseur A, Jacobs F, Creteur J, Hites M, Taccone FS. Prediction of Insufficient Beta-Lactam Concentrations in Extracorporeal Membranous Oxygenation Patients. Microorganisms. 2021 Oct 25;9(11):2219.
Gatti M, Pea F. Antimicrobial Dose Reduction in Continuous Renal Replacement Therapy: Myth or Real Need? A Practical Approach for Guiding Dose Optimization of Novel Antibiotics. Clin Pharmacokinet. 2021 Oct;60(10):1271-1289.
Abdulla A, Dijkstra A, Hunfeld NGM, Endeman H, Bahmany S, Ewoldt TMJ, Muller AE, van Gelder T, Gommers D, Koch BCP. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: a two-center prospective study (EXPAT). Crit Care. 2020 Sep 15;24(1):558.

Understanding of the Effects of CytoSorb on Antibiotic Therapy and Subsequent Adjustments

The interaction of the CytoSorb device with antibiotic, antiviral and antifungal agents has been extensively studied both through preliminary in vitro studies and through in vivo clinical experiences

In vivo removal less than 30%	In vitro removal less than 30%	In vitro removal greater than 30%	In vivo removal greater than 30%
Anidulafungin	Amikacin	Gentamicina	Amphotericin
Cefepime		Remdesivir	Fluconazole
Ceftriaxone		Voriconazolo	Linezolid
Ciprofloxacin			Posaconazolo
Clarithromycin			Teicoplanin
Clindamycina			Tobramycin
Flucloxacillin			Vancomycin
Ganciclovir			
Meropenem			
Metronidazolo			
Piperacillin			

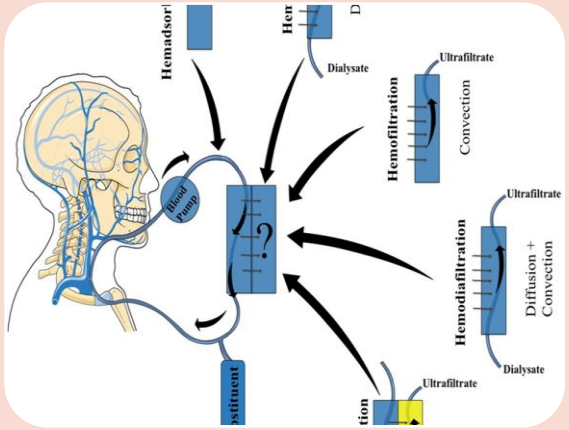
Scheier, Joerg MD[1]; Nelson, Peter J. MD, FASN[2]; Schneider, Antoine MD, PhD[3–4]; Colombier, Sébastien MD[5]; Kindgen-Milles, Detlef MD, PhD[6]; Deliargyris, Efthymios N. MD, FACC, FESC, FSCAI[2]; Nolin, Thomas D. PharmD, PhD[7]. Mechanistic Considerations and Pharmacokinetic Implications on Concomitant Drug Administration During CytoSorb Therapy. Critical Care Explorations: May 2022 - Volume 4 - Issue 5 - p e0688 doi: 10.1097/CCE.0000000000000688

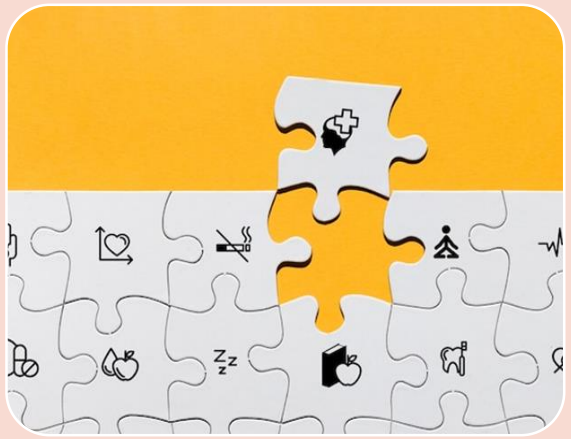
CRRT Vs Adsorbtion

NOME	Rimozione da CRRT	Rimozione da CytoSorb
Amikacina	A[1,16]	B[2]
Amfotericina	B[16]	A[2]
Anidulafungina	B[16]	B[2]
Cefepima	M[16]	B[2]
Ceftriaxone	B[16]	B[2]
Ceftazidime	M[16]	B[20]
Ciprofloxacina	B[16]	B[2]
Claritromicina	ND	B[2]
Clindamicina	B[18]	B[2,8]
Flucloxacillina	B[18]	B[2]
Fluconazole	A[16]	A[2]
Ganciclovir	M[1]	B[2]
Gentamicina	A[16]	M[2]
Linezolid	B[1]	A[2]
Meropenem	M[16]	B[2]
Metronidazolo	ND[1]	B[2]
Piperacillina	M[16]	B[2]
Posaconazole	B[16]	A[2]
Remdesivir	M[17]	M[2]
Teicoplanina	B[16]	A[2]
Tobramicina	ND	A[2]
Vancomicina	A[16]	A[2]

L < 30%
M > 30%; < 60%
H > 60%

CONCLUSIONS





Extracorporeal blood purification therapies

Advanced technologies to remove harmful substances and give functional support

All extracorporeal therapies can affect **antibiotics** dosage.

Multifactorial interaction between Drugs and ET

Factors influencing Drug dosage with ET:

- **Pharmacokinetics**:
Vd, binding degree, dosing time and mode, active metabolites

- **Clinical conditions:**
Vd alteration, MOF, AKI

- **Extracorporeal Therapy:**
Tipe, size, modes, flow

CONCLUSIONS

The management of antibiotic must be managed in a conscious way when are used in conjunction of Extracorporeal Purification Therapies

starting from

CRRT

up to

Hemoperfusion