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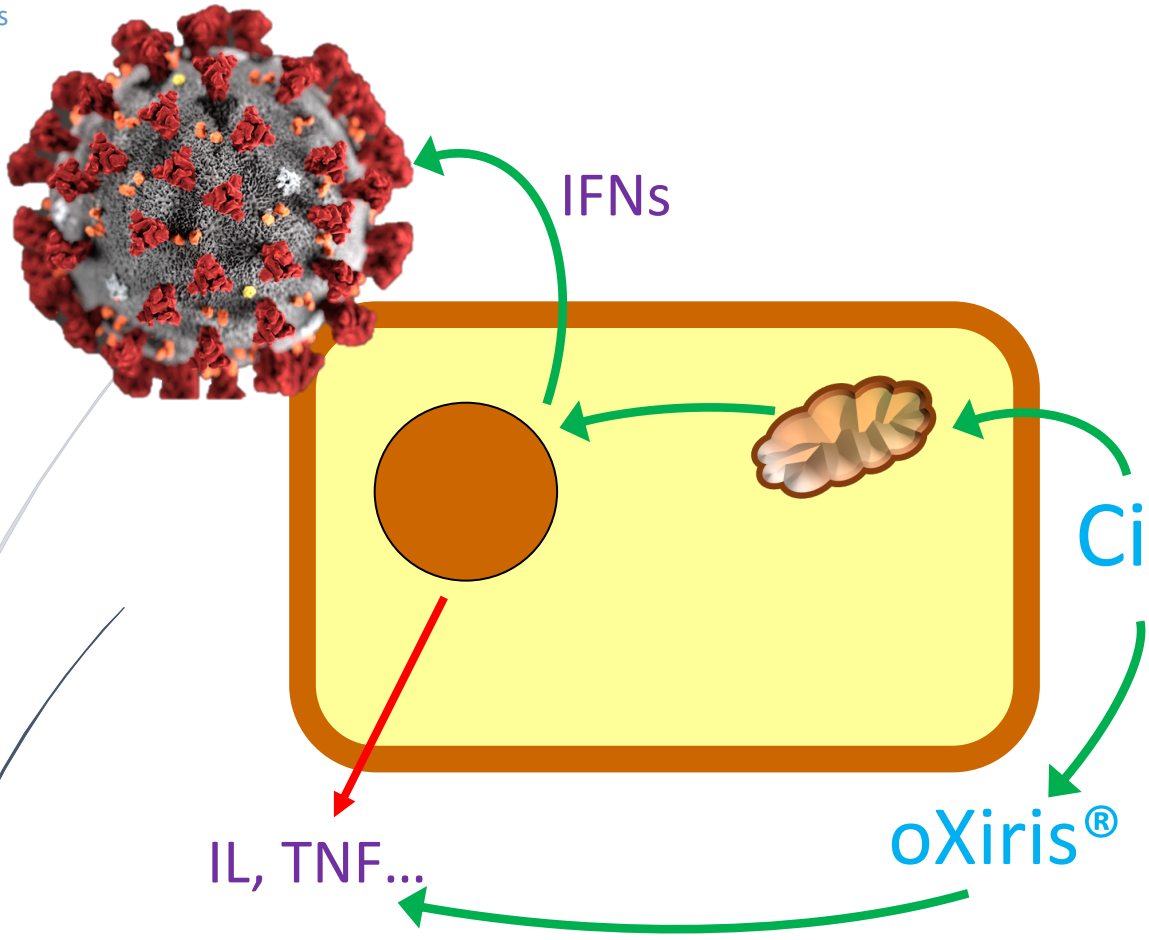
PROTOCOL CONVEHY® COVID19 V1.6

CONTINUOUS VENOUS HYPERFILTRATION: CVHD with oXiris® + citrate + multimodal monitoring

AUTHOR:
Rafael García Hernández

COLLABORATORS:
Isidoro Jiménez Pérez
María Isabel Espigares López
Reyes Gámiz Sánchez
Francisco Miralles Aguiar
Francisco Javier Arroyo Fernández
Miguel Moguel González
Enrique Calderón Seoane
Antonio Pernia Romero
Luis Miguel Torres



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PROTOCOLO CONVEHY®

- CONTINUOUS VENOSA HYPERFILTRATION® (CONVEHY®) is a hemofiltration protocol with an unspecified adsorption membrane oXiris® + regional anticoagulation with citrate.
- It is indicated in the severe DESREGULATED INFLAMATORY RESPONSE either by SEPSIS or by Reperfusion Ischemia Damage with or without renal injury. IN THE CASE OF COVID19 IT IS INTENDED TO CONTROL CYTOKINE STORM AND MITOCHONDRIAL DYSFUNCTION CAUSED BY RNA VIRUSES IN PEOPLE WITH HIGH RISK OF WORST EVOLUTION BEFORE IRREVERSIBLE LUNG DAMAGE IS ESTABLISHED. IT IS ALSO INTENDED TO CONTROL ITS EVOLUTION TOWARDS SDMO.
- **Indications are maintained in patients NOT COVID19 and can be applied in any critical scenario as we have done in the BACTERIAL septic shock.**
- **CONVEHY® has two clinical phases delimited by criteria that relate to the severity of the patient:** PHASE 1: "ANTI-inflammatory". No negative balance is initially made. The oXiris® membrane is periodically change according to defined criteria and a convection is made at 35-40 ml/kg/h (adding up the volume of substitution and citrate). PHASE 2: "Dehydration". Guided and controlled elimination phase of excess fluids of the patient. The convection dose drops to a dose of renal purification if needed and the dose of citrate therefore as well.

⇒ - It is necessary to know various points or aspects of this protocol:

- Theoretical aspects of Anticoagulation with Citrate.

When? Start time.

Who? Indications.

- Frame the CLASSIC SCENARIO.
- Follow the INDICATION ALGORITHM.
- Set the PROTOCOL PHASE.

How much? Dose.

- Follow the DOSIFICATION ALGORITHM according to: the clinical phase, the presence of acidosis and the concetration of postfilter citrate.

How? Controls.

- Analytical controls of ion calcium.
  - General scheduled controls.
  - General unscheduled controls.
- 5X3 adjustment table.
- Alerts of the patient's calcium and potassium.
- Periodic monitoring of clinical variables of the technique.
- Daily Checklist (FACULTATIVES).
- Daily Checklist (NURSE).

Theoretical aspects of Citrate Anticoagulation

Anticoagulation of hemofilter is one of the most important aspects. Regional Anticoagulation with Citrate (ARC) is recommended for choice in our surgical environment as it has been shown to extend the life of the filter and decrease the incidence of bleeding. It does not produce thrombocytopenia. As side effects can cause acidosis or alkalosis, and alterations of calcium, magnesium, phosphorus, potassium... Therefore, good control of therapy is necessary to be able to avoid or diagnose them and treat them.

Citrate

It is a molecule present in the Krebs cycle with the ability to bind to ion calcium. Complex calcium-citrate (Ca-Ci) form that are eliminated (60%) pass through the filter or pass to the body (40%). Ca-Ci complexes are separated in the liver and metabolized by three bicarbonates. Therefore, its only relative contraindication is severe liver failure.

THE REGIOCIT® liquid contains 18 mmol/l of trisodium citrate. If there is no citrate: THERE IS NO THERAPY. It is the anticoagulant of the circuit, the more citrate-> the less calcium -> the greater anticoagulation and vice versa.

Calcium

Ionic calcium is the physiologically active fraction. It is essential for muscle contraction, nerve conduction, and BLOOD COAGULATION among other functions. Normal values: 1-1,2 mmol/l. When it reacts with citrate it becomes inactive, and lowering its concentration prevents blood clotting in the filter.

To check that Ca-Ci dissociates well, the total calcium/ionic calcium ratio is made. If total calcium is expressed in mg/dl: total calcium x 0.25/ion calcium, for conversion to mmol/l. A normal ratio is <2.4. This is because if Ca-Ci is not well separated, laboratory measures the Ca-Ci complex as total calcium and in that case the numerator increases so the ratio is >2,4.

The total calcium in serum is the sum of the ionized and non-ionized components, their normal values are: 8.2-10.3 mg/dl (2.13-2,15 mmol/l) (they vary somewhat by laboratory). To convert mg/dl to mmol/l, multiply by 0.25. Approximately 50% of total serum calcium is bound to proteins (mainly albumin), 10% is bound to other elements (citrate, phosphate, lactate, heparin, bicarbonate, sulfate) and 40% in ionized form (Ca++, free calcium).

Explanation

Initially by default, 6 liters of patient blood (Red Line) are mixed for each liter of REGIOCIT® 18/0 (White PBP Pump). So we have 18 mmol of citrate diluted in 6 liters of blood (18/6 x 3 mmol of Citrate per liter of blood), when starting the therapy.
This concentration of citrate, when reacting with calcium from the patient's blood, causes the ion calcium concentration to drop in the filter circuit from 1-1'2 mmol/l (normal values for the patient) to 0'25-0'35 mmol/l; values that make it impossible for the blood to clot, just what we want in the filter.

The blood passes through the filter without a choice to clot because without enough ion calcium, all clotting pathways are blocked. On the countercurrent passes the dialysis fluid (Dialysis Pump - Green) which has no calcium. If we administered calcium in the filter, the blood would clot.
As a result of convection and diffusion through the membrane, we obtain the fluid from the effluent (yellow); containing 60% of the Citrate-Calcium complexes that have been formed. The already filtered blood comes out of the blue line, carries little ion calcium and 40% of the Citrate-Calcium complexes that have formed, which go to the liver to become ion calcium + bicarbonate. Post-filter replenishment with replacement liquid, usually PRISMASOL 2® occurs in the blue branch.

To replenish the calcium that citrate steals from the patient, and which is partly removed by the effluent, the Prismaflex system® injects calcium chloride through the syringe pump connected to a special line of calcium (must: if there is no special line: THERE IS NO THERAPY)
This line should go to a central (alone) route to the third light of the Hemofiltration catheter (if any) or to a Y-connection to the venous branch (if there are no other options). NEVER THREE-WAY KEY. NEVER BY PERIPHERAL ROUTE. THE WAYS USED FOR CALCIUM MUST BE PURGED BEFORE STARTING TREATMENT WITH CALCIUM CLORURO (1.5 ml).

Material.

Check compliance.

- ☐ Temperature sensor, preference in order: central by Swan Ganz®, central by bladder probe, peripheral by skin sensor in temples or skin sensor in armpit.
- ☐ Measure the patient's temperature and actively heat in case it is <36 C. Hemofiltration catheter (25, 15, 20 cm depending on insertion place in order: right jugular, left femoral, right femoral, right subclavia). It can vary the place depending on factors such as: contamination of the area, occupation by other routes... . If high blood flows are to be used > 250 ml/min and / or risk of high atrial fibrillation, preferable femorals.
- ☐ Prismax® or Prismaflex® Hemofiltration Monitor® failing that.
- ☐ Set Hemofilter (oXiris®).
- ☐ 2 bags of physiological serum (1000 ml) WITHOUT Heparin (recommended to reserve another).
- ☐ Special original calcium line (Ca++) (no other extension cord or line is valid).
- ☐ 50 ml syringe with luer-lock cone with 5 ampoules of Calcium Chloride. With Model Hemofilter Prismax® must be one of the brands recognized by the machine.
- ☐ Clorhexidine caps (1 strip).
- ☐ Y-connection for calcium (if you don't have enough central pathways).
- ☐ syringe with 10 ml of physiological serum (to purge the "Y").
- ☐ REGIOCIT® bags: anticoagulation.
- ☐ BIPHOZYL® bags: for dialysis fluid initially. It can optionally be used as a replacement liquid in CONVEHY® PHASE 2 under the medical doctor indication.
- ☐ PRISMASOL 2® bags: as a replacement liquid initially. It can optionally be exchanged for BIPHOZYL® in CONVEHY® PHASE 2 under under the medical doctor indication.
- ☐ Records of Hemofiltration and Calcium Controls (Annexes 1 and 2). Important to complete them.
- ☐ Heater with hot air blanket and rescue blanket.
- ☐ Hemodynamic monitor (one of): Vigileo® or EV1000® (with FloTrac® sensor), Vigilance II® (with Swan Ganz catheter®), PICCO ®. Visible IC and SVI minimum or similar.

Assembly, Priming and Connection.

Check compliance.

- ☐ Place the Prismaflex Monitor® in an appropriate place that allows the patient to access and mobilize.
- ☐ Place machine plugs and air heaters.
- ☐ Turn on the machine and check that the date and time are correct.
- ☐ Enter patient name, weight and hematocrit.
- ☐ Choose CRRT and CVVHDF therapy.
- ☐ Perform assembly and priming following instructions from the Prismaflex Monitor®.
- ☐ Maintain maximum sterility in mounting, priming and connection.
- ☐ Assemble the bags on the corresponding scales, following the color code. (DO NOT CHANGE THE DEFECT ORDER EXCEPT FOR ANY WRITTEN INDICATION OF THE SPECIALIST PHYSICIAN) - REGIOCIT® – BIPHOZYL® – PRISMASOL 2®.
- ☐ Line of heparin clamped with stopper.
- ☐ Determination of Ca++ in patient (arterial gasometry), prior to connection. If < or 1.0 mmol/l, warn. It is recommended to administer an ampoule of Calcium Chloride centrally with the knowledge of the responsible physician. IT CAN INCREASE CARDIAC OUTPUT AND BLOOD PRESSURE.
- ☐ Schedule therapy by the responsible physician.
- ☐ Remove heparin seal from hemofiltration catheter, maximum sterility.
- ☐ Connect the patient, following instructions from the Prismaflex monitor®. The responsible physician must be present.
- ☐ If you do not have a specific central route for the Ca++ line place purged "Y" on the blue return path and connect the special Ca++ line on that "Y". THE WAYS USED FOR CALCIUM MUST BE PURGED BEFORE STARTING TREATMENT WITH CALCIUM CHLORIDE (1.5 ml).
- ☐ Cytrate and Ca++ controls and settings according to protocol. Before connecting check all the steps.

In treatment with citrate and COVID patients to decrease the number of box entries:

- Use 9-litre effluent bags.
- or the auto-effluent in PrisMax®.

Special considerations.

Check reading.

- ☐ Original Ca++ line required. Do not use another type of extension cord or interposed keys.
- ☐ Do not reverse the catheter lights. If it is essential to invest, the contribution of Ca++ must go through a central route exclusively. In this case you cannot put the Y on the return line.
- ☐ Do not put three-way keys in the patient connection.
- ☐ By indication of the optional BIPHOZYL® bag could be used for replacement, but keep in mind that it does not carry calcium, although it provides more phosphorus.
- ☐ Keep the Y of the priming sterile for possible recirculation, protect with green plugs.
- ☐ Ion Calcium Controls in Radiometer® according to protocol: Postfilter (blue sampling point) and Patient (arterial catheter).
- ☐ Quickly attend alarms and changes of bags or syringe. Every time you are standing, filter coagulation is favored.
- ☐ Monitor the air chamber level and adjust if necessary.
- ☐ The catheter will remain heparinized, when not in use, with heparin at 1% and the amount indicated by the catheter (venous light is longer than arterial). It is necessary to remove the heparin, before re-establishing the technique.
- ☐ The handling of the catheter and system connections at all times shall be carried out with as high asepsis as possible.

When? Start time. **"As soon as possible".**

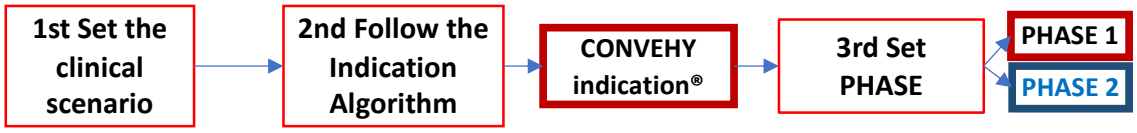
- ☐ You should not delay the taking of cultures and the administration of the pauted antibiotics.
- ☐ It is not a cardiorespiratory stop and there is no emerging complication at that time that requires a vital maneuver.
- ☐ There is indication according to the protocol. See below figure.
- ☐ Review the objectives to be achieved according to the type of indication. See below figure.
- ☐ In doubtful cases or limits:
  - Identify hemodynamic shock.
  - Assess the trend of support.
  - A > systemic involvement, < renal injury required.
- ☐ The list of "Material, assembly, priming and connection and special considerations" has been checked.

To Whom? Indications.

- **Indication of CRRT (Continuous Renal Replacement Technique):** Uremic syndrome or water balance management in patients refractory to diuretics.
- **Indication of EDT (CONVEHY® extracorporeal depuration technique):** SDMO in the context of a deregulated Inflammatory Response. See decision tree.
- **Indication of EIT (CONVEHY® Early Immunomodulation Technique):** patients or with manifest clinic, or with poor oxygenation, which has an affected Rx or Pulmonary Echo by COVID. Special attention in the subgroup with risk factors. See decision tree.

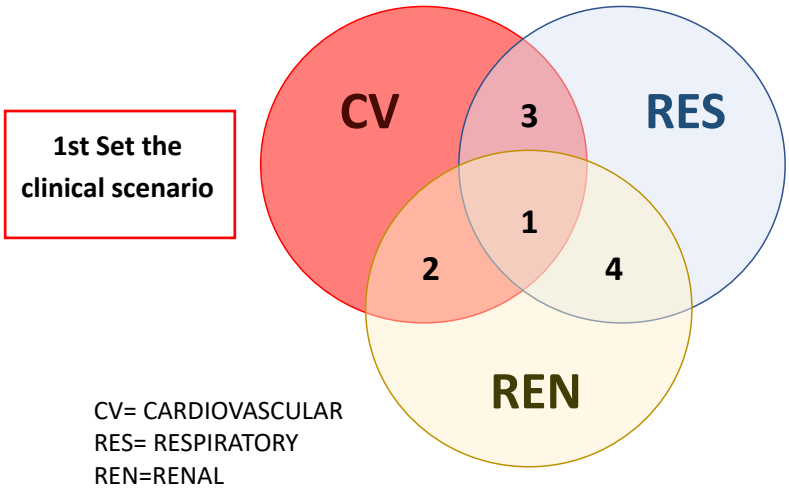
• **CONVEHY®** is indicated in clinical scenarios with a Deregulated Systemic Inflammatory Response (RID), inadequate or altered by infectious cause (SEPSIS) or by Reperfusion Ischemia Damage (RID).

• **The global systemic involvement is the one that should alert us to its possible indication EVEN IF there is no renal or anuria failure.**



CONVEHY INDICATION ®

CLINICAL SCENARIOS OF SYSTEMIC AFFECTATION IN WHICH BLOOD PURIFICATION CAN BE APPLIED.



CLINICS SCENARIOS:

1 CV+RES+REN

2 CV+REN

3 LOW CARDIAC OUTPUT+CV+RES

4 RES+REN

CV= CARDIOVASCULAR
RES= RESPIRATORY
REN=RENAL

• If you have all the objectives of PHASE 1 fulfilled, consider entering PHASE 2.

• DEFINITIONS:

- CV: cardiovascular involvement at any degree based on the SOFA scale.
- RES: respiratory involvement at any degree based on the SOFA scale.
- REN: renal involvement to any degree according to the KDIGO scale.
- LOW CARDIAC OUTPUT: LOW cardiac contractility.
- SHOCK: use of norepinephrine to maintain TAM of 60 mmHg despite adequate replacement of volume plus high lactate according to laboratory reference value.

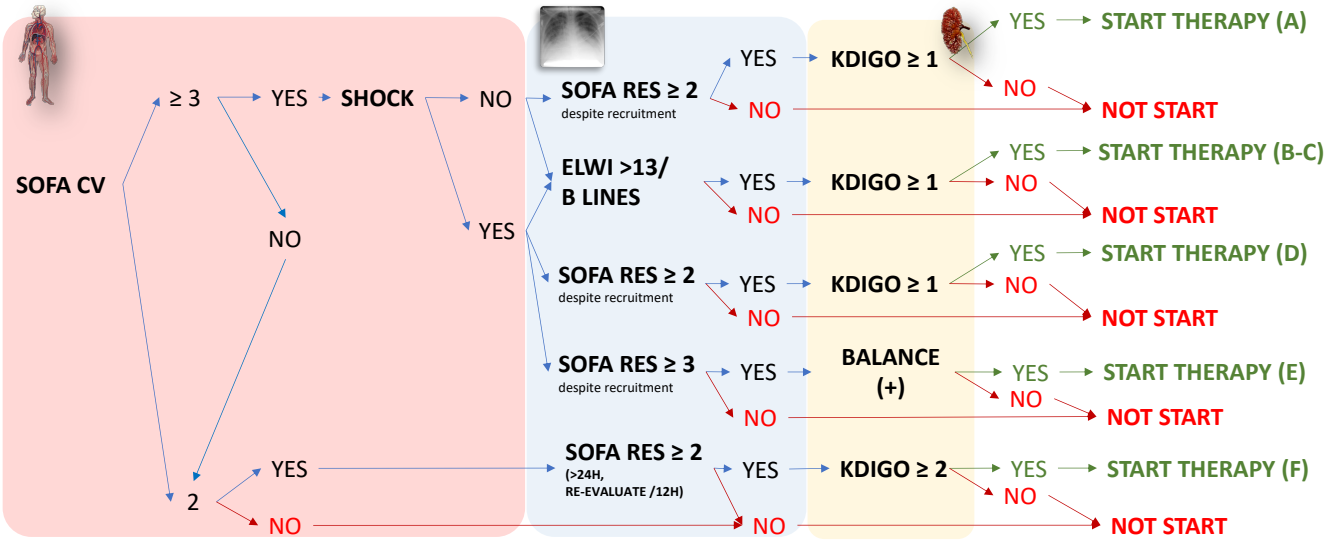
• GENERAL RECOMMENDATIONS:

- Identify hemodynamic shock: most likely has an indication.
- Assess the trend of support: in doubtful cases assess a progressive negative trend and maintained as an indication criterion.
- A > systemic involvement, < renal injury required to decide the start of the technique.

Indication of EDT (CONVEHY® Extracorporeal Depuration Technique):

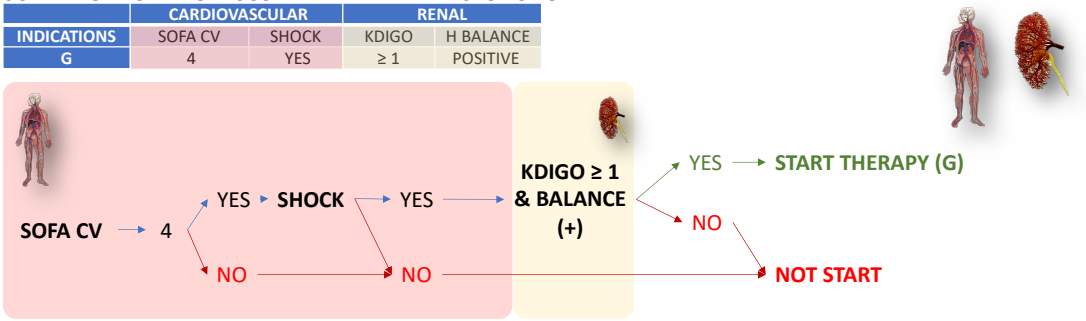
SCENARIO 1. CARDIOVASCULAR, RESPIRATORY AND RENAL DYSFUNCTION.

	CARDIOVASCULAR		RESPIRATORY		RENAL	
INDICATIONS	SOFA CV	SHOCK	SOFA RES	ELWI>13/B LINES	KDIGO	H BALANCE
A	≥ 3		≥ 2 despite recruitment		≥ 1	
B	≥ 3			YES	≥ 1	
C	≥ 3	YES		YES	≥ 1	
D	≥ 3	YES	≥ 2 despite recruitment		≥ 1	
E	≥ 3	YES	≥ 3 despite recruitment			POSITIVE
F	2		≥ 2 (>24H) Re-evaluate every 12H		≥ 2	



SCENARIO 2. CARDIOVASCULAR AND RENAL DYSFUNCTION

	CARDIOVASCULAR		RENAL	
INDICATIONS	SOFA CV	SHOCK	KDIGO	H BALANCE
G	4	YES	≥ 1	POSITIVE



SCENARIO 3. MULTIORGANIC SYSTEMIC DYSFUNCTION: LOW CARDIAC OUTPUT, CARDIOVASCULAR AND RESPIRATORY

	CARDIOVASCULAR		RESPIRATORIO	
INDICATIONS	FE% ≤ 40%*	SOFA CV	SOFA RES	ELWI >13/B LINES
H	YES	≥ 2	≥ 2 despite recruitment	
I	YES	≥ 2		YES

* It requires discarding other causes that justify a low EF%.

SCENARIO 4. RESPIRATORY AND RENAL DYSFUNCTION

	RESPIRATORY		RENAL	
INDICATIONS	SOFA RES	ELWI >13/B LINES	KDIGO	BALANCE H
J	≥ 3			POSITIVE

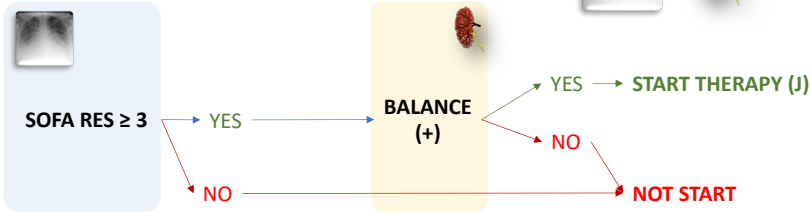


Table 1. Indication algorithm. First you have to choose the clinical scenario and then check the parameters of organic dysfunction. **KDIGO** - classification of the "Kidney Disease: Improving Global Outcomes" of acute kidney injury (AKI); **SOFA** -; **ELWI** - Extra Lung Water Index, extra pulmonary water indexed; **B LINES** in pulmonary ultrasound, presence of B-lines indicating the presence of interstitial water; **PICCO** - transpulmonary thermodilution with PiCCO™ system; **ECO-CARDIO** - echocardiography performed by anesthesiologists and/or cardiologists as appropriate; **EF** - ejection fraction.

SOFA SCALE

	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Hepatic system					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular system					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Coagulation					
Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Central nervous system					
Glasgow coma scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)				<500	<200

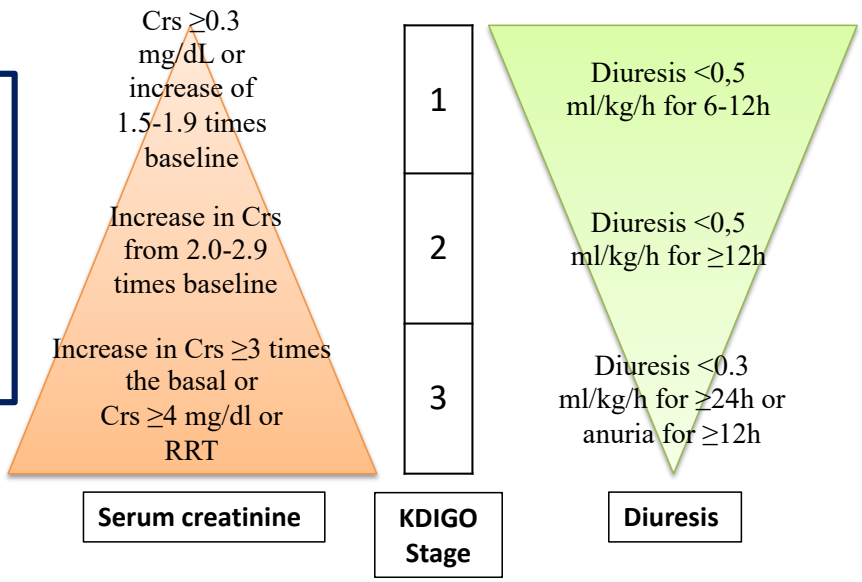
Notes: [a]All catecholamine doses represent μg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. *Intensive Care Med.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707–710, Vincent JL, Moreno R, Takala J, et al. With permission of Springer.[17]

Abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

KDIGO CLASSIFICATION

ARI diagnostic criteria:

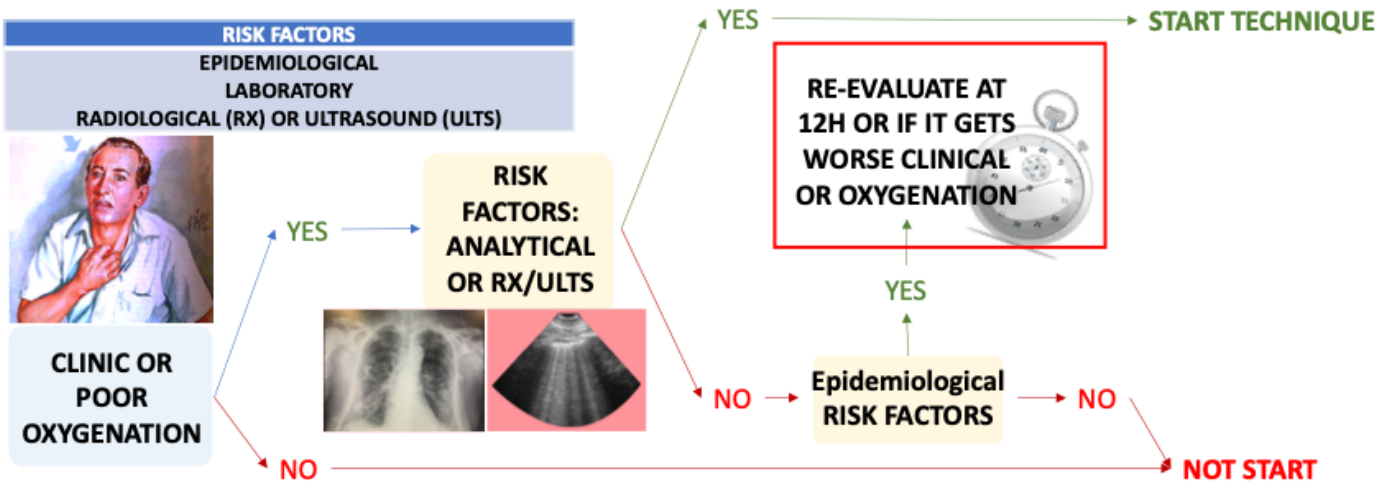
- Increased creatinine - 0.3 mg/dl in 48 hours **OR**
- Increased creatinine 1.5 times basal serum creatinine, which is known or presumed to have occurred in the last 7 days **OR**
- Diuresis < 0.5 ml/kg for 6 h



EIT Indication (CONVEHY® Early Immunomodulation Technique):

COVID SCENARIO. CRITERIA OF EARLY IMMUNOMODULATION.

CLINICAL (one of)					SATURATION OR GASOMETRY (one of)		
RESP. FREC.	DYSPNEA	BREATHING WORK	INTERCOSTAL RETRACTIONS	CONFUSION DISORIENTATION	<94%	PaO_2/FiO_2	pH or pCO2
≥ 25	Moderate	Moderate	Any severity	Any severity	with FiO_2 >0,4	< 250 o < 275 if strong slope	<7,35 or >45mmHg.



RISK FACTORS FOR SEVERE ILLNESS		
Epidemiological	**Laboratory**	**Radiological or Ultrasound**
>55 years	D-dimer >1000 ng/ml	Multilobular infiltrators
Previous lung disease	CPK >2 times baseline	• B lines ("Bertical") wide diffuse fixed fused (move with pleura) • Sign of the waterfall • "White" lung • Thickened, irregular pleura • Healthy and sick lung patches • Subpleural consolidation
Chronic kidney disease	C-Reactive Protein >100	
DM HbA1c >7,6%	LDH >254 U/L	
Arterial hypertension	Elevated troponin	
Cardiovascular disease	Ferritin >300 ug/L	
Transplanted or other immunosuppression	Lynphopenia <800/mm^3 o Leukopenia <4000/mm^3	
HIV independent of CD4	Neutrophil/Lymphocyte Ratio >3	
	Thrombocytopenia <100000/mm^3	

CLINICAL PHASES, OBJECTIVES AND GOALS OF THE PROTOCOL

PHASE 1 : **ANTI-inflamatoria**

General goals

-Reperfusion of tissues and shock recovery
-Avoid dialitrauma: hypothermia, inadequate negative balance, ions, antibiotics
- Liquid removal: zero

PHASE 1 : **monitoring**

Physiological and multimodal.
Measure SVI, $SatO_2$% c/mix, lactate, CO_2 GAP, echocardiography, pulmonary ultrasound

Goals:
-Decrease in vasoactive drugs (75%)
-Normalization of arterial lactate
-Acidosis correction
-Metabolic purification

PHASE 2 **: DEHYDRATION**

General goals

-Guided negative balance
-Avoid dialitrauma
-Kidney support if required

PHASE 2 : **same monitoring**

Goals:
-Set the maximum tolerable negative balance
-"Permissible" reduction of the SVI
-$SatO_2$% central >70%
-Lactate <19.8 mg/dl
-CO2 GAP <6 mmHg

How much? Dosage.

- ☐ **CHECK THE DOSING ALGORITHM. (See figure below)**
- ☐ **The doctor responsible will establish the therapy by adapting it TO THE patient DAILY.**
- ☐ **Make an individualized pattern manually according to the "Dosing Algorithm".**
- ☐ **Patient fluid removal: INITIALLY ZERO. Modifiable according to clinical situation.**
- ☐ **initial post-filter [citrate]: 3 mmol/l.**
- ☐ **Initial calcium compensation: 100%.**

a) **Dialysis liquid as deemed necessary:** in PHASE 1, to LIMIT the MAXIMUM "citrate load" to 25 mmol/h;
b) to increase the purification of small molecules (K, urea, creatinine...).

Met the objectives of PHASE 1, move to the dose of PHASE 2 of dehydration with knowledge and optional supervision.

MAKE A PROGRAMMED REPLACEMENT OF THE ox iris® MEMBRANE every 6 hours if:

a) There is insufficient improvement at the discretion of the practitioner.
b) The same severity continues at the discretion of the doctor.

GENERAL GUIDELINES FOR MANUAL DOSING OF THE TREATMENT DOSE.

The doctor responsible will establish the therapy by adapting it TO THE patient DAILY.

- ☐ **Follow the "Manual Dosage Algorithm" to guide an individualized dose manually.**
- ☐ **Modify the blood flow to modify the volume of citrate.**
- ☐ **Check the citrate load in mmol/h.**
- ☐ **Modify the volume (substitution + elimination) to: not exceed the maximum citrate load (25 mmol/h) and not exceed the maximum convection dose.**
- ☐ **Check the citrate load and convection volume (Citrate Volume + Substitution + Removal) finally.**
- ☐ **Patient fluid removal: INITIALLY ZERO. Modifiable at optional criteria.**
- ☐ **initial post-filter [citrate]: 3 mmol/l.**
- ☐ **Initial calcium compensation: 100%.**
- ☐ **DOSAGE of DIALYSIS LIQUID as deemed necessary:** in PHASE 1, to limit the MAXIMUM "citrate load" to 25 mmol/h;
- ☐ To increase the purification of small molecules (K, urea, creatinine...).

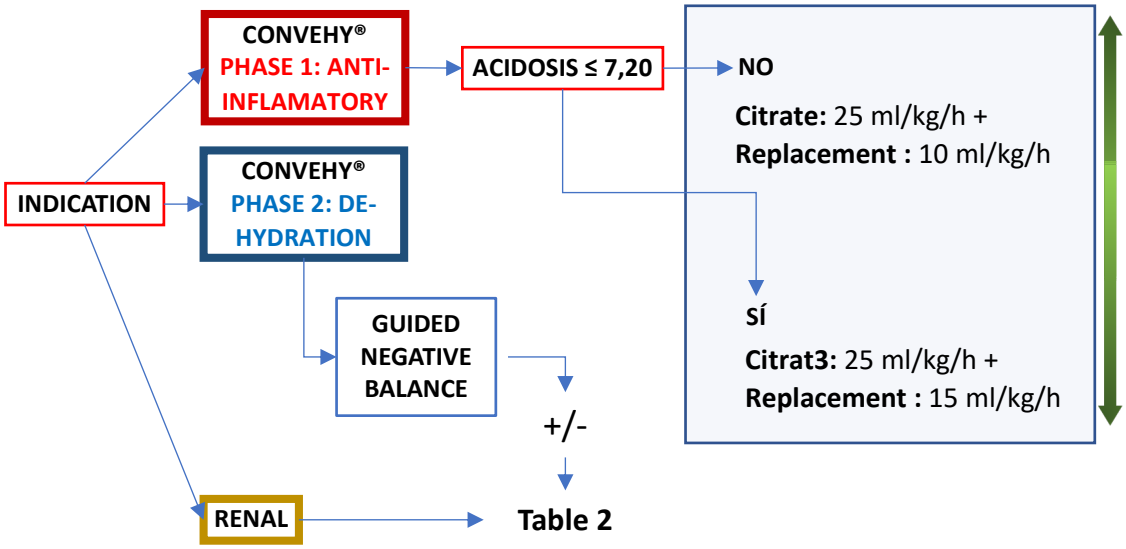
Met the objectives of PHASE 1, move to the dose of PHASE 2 of dehydration with knowledge and optional supervision. The convection dose drops to a dose of renal purification if needed and the dose of citrate therefore as well.

MAKE A PROGRAMMED REPLACEMENT OF THE oXiris® MEMBRANE every 6 hours if:

a) There is insufficient improvement at the discretion of the practitioner.

b) The same severity continues at the discretion of the doctor.

CONVEHY® "Manual" Dosing Algorithm



Clarifications: With a post-filter [citrate] of 3.0 mmol/l, for every 6000 ml/h of blood, 1000 ml/h of "citrate 18/0" is administered (ratio 6:1). This is 100 ml/min of blood per 1000 ml/h of "citrate 18/0". When the

postfilter [citrate] changes, for example to 3.5 mmol/l, it also changes the blood/citrate ratio (ratio 6:1,33) so that without changing blood flow, the machine increases the total volume of citrate administered.

Table 2

Renal indication.
HDFVVC protocol with CITRATO.

Weight (Kg)	Blood ml/min	Citrate ml/h	Sustitución ml/h	Dialysis liquid ml/h
50	100	1000	200	1000
60	110	1100	400	1100
70	**120**	**1200**	**500**	**1200**
80	130	1300	500	1300
90	140	1400	500	1400
100	150	1500	600	1500
110	160	1600	700	1600
120	170	1700	800	1700
130	180	1800	1000	1800

- **Fluid removal:** according to patient needs.
- **Citrate initiation dose:** 3 mmol/l.
- **Calcium compensation initiation dose:** 100%

GUIDED NEGATIVE BALANCE. PHASE 2 OBJETIVES: DEHYDRATION.

☐ Check that the current SVI provides sufficient O2 to the patient. Otherwise, it is not recommended to start.

☐ Evaluate the SVI trend after initiating a liquid removal with 100 ml/h:

IVS

NEGATIVE BALANCE TREND	LIMITING FACTOR TENDENCY PERFUSION STATUS*			CHOICE
Start 100 ml/h.	SatO2% cen/mix	GAP CO2	LACTATO	Slow increments. Wait 10 min and evaluate response
a) NO CHANGES				
b) DOWNWARDS	↓	↑	↑	Stop o lower extraction
	N	N	↓	Increase or maintain extraction according to clinical objective.
c) UPWARD				Rapid extraction increments. Effective ventricular decongestion. Highest extractions require constant re-evaluation.

GAP CO2: Arteriovenous difference of CO2; SVI: systolic volume index; N: normal; SatO2% cen/mix: venous oxygen saturation measured at the central level or pulmonary artery, respectively.

How? Controls.

PATIENT's CALCIUM and POTASSIUM Alerts

***Ca < 0,90:**

1. Notify the doctor and administer with their knowledge 1 ampoule of ClCa.
2. Repeat extra calcium control every hour until trend normalizes.

****Ca < 0,95:**

1. Notify the doctor.
2. Consider the administration of 1 ampoule of ClCa.
3. Consider performing new extra checks.

K^+ < 3 mmol/l:

1. Notify the doctor.
2. We recommend a load of 0.5 mEq of ClK/kg body weight, centrally, in one hour by controlled infusion pump.
3. New control in one hour and repeat load, if necessary, until reaching > 3.5 mmol/l.

IONIC CALCIUM ANALYTICAL CONTROLS

The checks are performed with an arterial sample of the patient and another postfilter at the blue point of taking samples.

a) **General scheduled controls: Before starting therapy.**

Arterial sample for patient ion calcium measurement.

1. If <1 mmol/l administer 1 ampoule calcium chloride in 50 ml in 10 min. Confirm with responsible physician first.
2. If <0.9 mmol/l we recommend administering 2 ampoules of calcium chloride in 50 ml in 10 min.

NOTE: MAY INCREASE CARDIAC OUTPUT AND BLOOD PRESSURE.

b) **Therapy started: point** to the start time as zero hour.

1	15 minutes after the start	Measurement in arterial sample and post-filter sample
2	45 minutes after the start	
3	At 2 hours after the start	
4	At 6 hours after the start	
5	Then every 12 hours	
(If a recirculation is needed, after connecting perform control at 15 min. If there are no changes, re-measure according to your scheduled overall control)		

Try to do the first two checks without leaving the box. Attempt to overlap interventions with the schedule of other nursing tasks.

- **Make precise adjustments as "Table adjustment [Citrate] and Calcium %" of the protocol.**

General controls NOT scheduled:

If changes are made to therapy

1	**[CITRATO] by change of Ca++ POSTFILTRO: control in 2 hours. E.g. 3.0 mmol/l is changed to 3.5 mmol/l.**
2	Dialysis liquid, replacement or elimination: scheduled control.

If there is a filter change

1	Start with the latest parameters and control at 15 min and 45 min from the start of the new filter.
2	**If there are no modifications:** Continue with the scheduled controls prior to filter change.
3	**If there are changes:** Follow the instructions in the table above.

Special considerations

In the values of postfilter calcium and patients we will consider the EXACT VALUE that we have obtained, no deviations are accepted.

→ Make precise adjustments as "Table adjustment [Citrate] and Calcium %" of the protocol.

NOTE: THE INFUSION LINES USED FOR CALCIUM MUST BE PURGED BEFORE STARTING TREATMENT WITH CALCIC CHLORIDE (1,5 ml).

5x3 Adjustment Table

Adjustment table [Citrate] and Calcium %		**CALCIUM POSTFILTRO**		
		< 0,25	***NORMAL 0,25 - 0,35***	***> 0,35***
PATIENT CALCIUM	***< 0,90**** *WARN And Manage 1 ClCa ampoule*	**REDUCE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%	**INCREASE** Calcium 20%	**INCREASE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%
	< 0,95* *WARN And CONSIDER administering 1 ClCa amp.*	**REDUCE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%	**INCREASE** Calcium 20%	**INCREASE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%
	< 1,00	**REDUCE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%	**INCREASE** Calcium 20%	**INCREASE** [Citrate] 0.5 mmol/l and **INCREASE** Calcium 20%
	NORMAL 1,00 – 1,20	**REDUCE** [Citrate] 0.5 mmol/l	**OK**	**INCREASE** [Citrate] 0.5 mmol/l
	> 1,20	**REDUCE** [Citrate] 0.5 mmol/l and **REDUCE** Calcium 10%	**REDUCE** Calcium 10%	**REDUCE** Calcium 10% and **INCREASE** [Citrate] 0.5 mmol/l

- **CONSIDER THE EXACT VALUES.** If you have any questions, consult the SPECIALIST PHYSICIAN. We recommend valuing the trend of previously obtained records. For example, an upward trend of postfilter calcium, i.e. 0.25, 0.30, 0.36 (in three last checks) can make you consider 0.36 as a high value and force you to take action and pose an extra measurement if the next scheduled exceeds one hour. Another example, a downward trend of the patient's calcium, i.e. 1.2, 1.1, 0.99, can make 0.99 as a low value, and force action and provide extra control if the next scheduled exceeds the hour. If stability has been achieved with the initial controls, follow the protocol guideline.

Periodic monitoring of clinical variables of the technique

- **Ionic calcium analytical control according to protocol** (See 5x3 Adjustment Table and assigned times for controls).
- **Acidosis or alkalosis** (in the analytical controls of Ionic calcium).
- **Sodium and Potassium:** C/ 12 h minimum.
- **Total Ca, Magnesium, Phosphorus and liver function:** C/ 24 h minimum.
- **Water balance:** C/ 24h.
- **Time temperature control:** peripheral 36.5ºC. Do not exceed 37ºC or fall below 36ºC. The central reference is: 37.5ºC.

Fluid balance

Prismaflex® and Prismax® monitors record all liquid inputs and outlets and show a timely water balance. To view this information, press the History key. The monitor performs a cumulative 24-hour balance measured from 7:00 a.m. to 7:00 p.m.

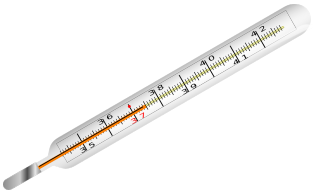
Records

- Record all therapy parameters in the Hemofiltration Log Sheet. Fundamental to analyze the results and improve the protocol.
- It will be completed at the beginning of treatment, and then at 9:00, 16:00 and 23:00; as well as when there are any changes to the treatment parameters.
- Calcium controls shall be recorded on the specific sheet, according to the timetables set out in the protocol.
- Data regarding liquid loss will be recorded in the URP Chart to be incorporated into the daily balance.

DAILY Checklist (SPECIALIST PHYSICIAN).

The following aspects should be assessed by the **RESPONSIBLE MEDICAL** on a daily basis and when clinical changes occur in the patient.

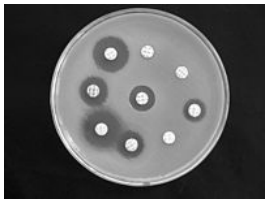
- ☐ **Indication:** start or withdrawal. (See Indications algorithm).
- ☐ **Modality:** according to the indication and the CONVEHY® phase (See figure).
- ☐ **Dosage:** dependent on the indication and phase CONVEHY®(See figure).
- ☐ **Composition of solutions:** dependent on the indication, THE PHASE of CONVEHY® and the patient (See dialytruma control: phosphorus and pH control).
- ☐ **Anticoagulation:** from the indication and the patient.
- ☐ **DIALYTRAUMA CONTROL:**



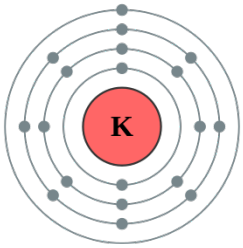
☐ **TEMPERATURE:**
(see "Periodic Monitoring")

- Add air heater (1 or 2)
- Rescue blanket.
- head insulation.

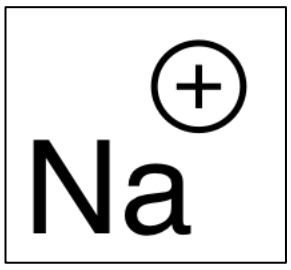
PRIORITY



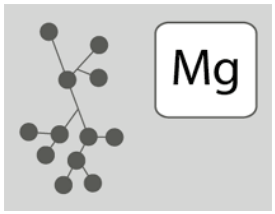
☐ **ANTIBIOTICS and other drugs:**
Use App RenalCalc®
OR similar.
PRIORITY.



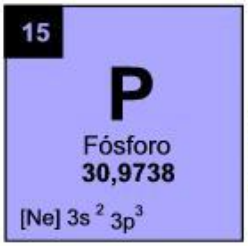
☐ **POTASSIUM (K):**
1. Measure c/12h minimum and use loads to have > 3 mmo/l.
2. See "Patient Calcium and Potassium Alerts".
PRIORITY.



☐ **SODIUM (Na):**
Avoid hypernatremia.
Provide more free water (SUEROTERAPIA/PNT) and moderate the elimination.



☐ **MAGNESIUM (Mg):**
necessary for muscle strength.
1. Measure c/12 h.
2. Administer 2-4 g/d iv.



☐ **PHOSPHORUS (P):**
essential for energy transfer.
See dose below.

☐ **PHOSPHORUS (P): essential for energy transfer.**

1. Measure c/24h. Replenish daily at NTP 20 mEq. (1 mEq x 0.5 mmol).
2. Administer as independent infusion according to technical label:

   If P serum >0.5 mg/dl → 0.25 mmol/kg in perf. 4h.

   If P <0.5 mg/dl → 0.5 mmol/kg in perf. 4h.

   If there is hypercalcemia: reduce from 25% to 50%.

   (0.5 mmol= 1 mEq). E.g. 75 kg: 18.75-37.5 mmol (37.5-75 mEq) in perf. 4h.
3. Consider using BIPHOZYL® instead of PRISMASOL® 2 as REPLACEMENT LIQUID.

Note: **Biphozyl®** contains MORE P: 2 mEq/L, Na: 140 mEq/l, MORE K: 4 mEq/L, MORE Mg: 1.5 mEq/L, MORE Cl: 122 mEq/L and Bicarbonate at lower limit: 22 mEq/l than **Prismasol® 2** that has no P, Na: equal, minus K: 2 mEq/L, LESS Mg:, 1 mEq/L, LESS Cl: 111 mEq/L and MORE Bicarbonate: 32 mEq/l.

☐ **pH CONTROL: METABOLIC ALCALOSIS**

METABOLIC ALCALOSIS

(most common at the end of CONVEHY® PHASE 1):

a) Consider whether there are criteria to move to PHASE 2 and reduce the load/dose of citrate.
b) Correct hypokalaemia.
c) Reduce lactate and acetate intake administered by serum therapy and parenteral nutrition.
d) Add replacement doses, and/or dialysis according to the objectives.
e) Rating using **BIPHOZYL®** as REPLACEMENT LIQUID instead of **PRISMASOL 2®.**

Note: **Biphozyl®** contains MORE P: 2 mEq/L, Na: 140 mEq/l, MORE K: 4 mEq/L, MORE Mg: 1.5 mEq/L, MORE Cl: 122 mEq/L and Bicarbonate at lower limit: 22 mEq/l than **Prismasol® 2** that has no P, Na: equal, minus K: 2 mEq/L, LESS Mg:, 1 mEq/L, LESS Cl: 111 mEq/L and MORE Bicarbonate: 32 mEq/l.

pH

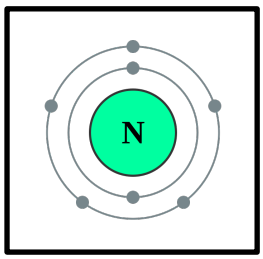
☐ • **pH CONTROL: METABOLIC ACIDOSIS**

a) **METABOLIC ACIDOSIS** (common in the pre-CONVEHY® patient and in cases of mala metabolization of the Ca-Ci complex):
b) a) Check **ion calcium** and follow the replenishment pattern. View calcium and POTASSIUM alerts of the patient.
c) b) Check **total calcium/ionic calcium ratio**. First, the total calcium of mg/dl must be converted to mmol/l: Total calcium (mg/dl) X 0.25= total calcium (mmol/l). The ion calcium is shown by the gasometer in mmo/l. **IF THE RATIO IS ≥2.4**, the net contribution of citrate should be lowered at the hour: lowering blood flow. We can also increase substitution and dialysis liquid based on our goals.
d) Correct hyperkalaemia if any.
e) Consider changing BIPHOZYL® to PRISMASOL 2® (MORE Bicarbonate: 32 mEq/l).

Note: **Biphozyl®** contains MORE P: 2 mEq/L, Na: 140 mEq/l, MORE K: 4 mEq/L, MORE Mg: 1.5 mEq/L, MORE Cl: 122 mEq/L and Bicarbonate at lower limit: 22 mEq/l than **Prismasol® 2** that has no P, Na: equal, minus K: 2 mEq/L, LESS Mg:, 1 mEq/L, LESS Cl: 111 mEq/L and MORE Bicarbonate: 32 mEq/l.

☐ **ADJUSTMENT OF THE Nutrition:**

☐ **BLOOD SUGAR LEVELS:**
Diabetics: approximately 160 mg/dl.
Non-diabetic: > 120 mg/dl.



☐ **NITROGEN (N):**
Increase N/day g by 20%.

Note: N requirements in critics of 0.25 g of N/kg ideal weight at 0.45 g of N/kg ideal weight in patients with polytrauma or burnt. (g of N= g of proteins/6.25).

Glutamine

☐ **Glutamine (Dipeptiven®):**

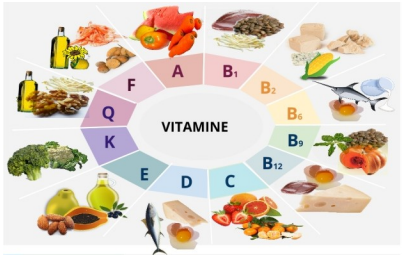
MAXIMUM DOSAGE:

a) CONVEHY® PHASE 1: 2 ml/kg body weight. E.g. pat. 80 kg body weight 160 ml.

b) CONVEHY® PHASE 2: 1.5 ml/kg body weight.

E.g. pat. 80 kg body weight 120 ml.

Note: The pharmacologist must be notified, if necessary, that he is with hemofiltration and MODS. This means a high consumption and a high loss by the technique. One hundred ml provide 4 g of N approx. Dipeptiven® should be administered with caution and controls to patients with severe renal impairment (creatinine clearance <25 ml/min), with severe hepatic impairment or with severe metabolic acidosis. The maximum dose is 2.5 ml/kg body weight.



☐ **SOLUBLE VITAMINS: there is a high loss by CVHF.**

a) CONVEHY® PHASE 1:

Cernevit®: 2 vials daily in PNT. In case of high needs (e.g. severe burns), Cernevit can be administered at daily doses 2-3 times higher than recommended.

b) CONVEHY® PHASE 2:

Cernevit®: 1 vial daily at PNT.

☐ **OLIGOELEMENTOS:** existe una alta pérdida por CVHF.

a) CONVEHY® PHASE 1:

I. Addamel®: 2 vials daily in PNT.

ADDAMEL® should be used with caution in patients with biliary impairment where and in patients with biochemical or clinical evidence of hepatic impairment (especially cholestasis).

II. Oligo-zinc: 20 ml equivalent to 20 mg.

Normal daily need 11 mg/d in adult male without CVHF.

b) CONVEHY® PHASE 2:

I. Addamel®: 1 vial daily at NTP.

II. Oligo-zinc: 10 ml equivalent to 10 mg.

Normal daily need 11 mg/d in adult male without CVHF.

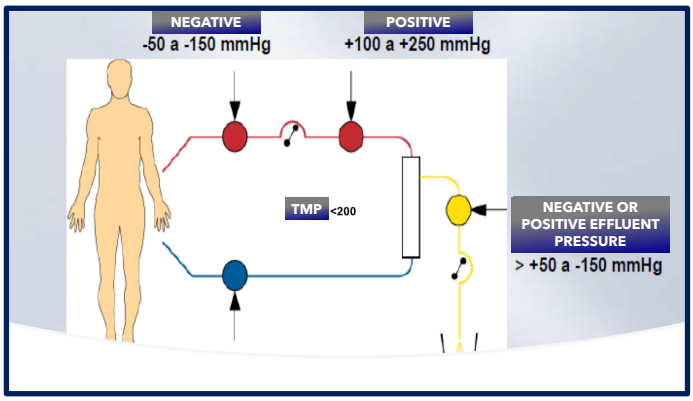
DAILY Checklist (NURSE).

- ☐ Catheter evaluation: dressing and position.
- ☐ Verification of the composition of the liquids used.
- ☐ Valuation of line placement and protection of PRESSURE ULCERS/ burns.
- ☐ Verification of analytical controls and that they are in the correct range.
- ☐ Air chamber level.
- ☐ Patient temperature and heating systems.
- ☐ Hemofilter records: therapy programming and pressures.
- ☐ Alert data.

Information about PRESSURES.

Pressures

The objective when monitoring pressures is to avoid incidences in therapy and prevent the possibility of change of the circuit by clotting the filter, thus being able to recover the blood.



Pressing History - Press; we can look at the trends

Input pressure

It should always be negative (-50/-150 mmHg). Ideal value -100 mmHg.

It is the pressure with which the pump sucks to draw the patient's blood and depends on the state of the catheter's arterial light, the arterial line segment and the speed of the blood pump.

If the inlet pressure to the hemofilter shows a positive value may be due to a disconnection on the line or the patient having an excess of circulating volume, causes that is not usual.

If you have a more negative value it may be due to a problem in the arterial line (cloggings and grips), catheter obstruction (clots or catheter adhesion to the wall), or excessive blood pump speed.

Filter pressure

The filter pressure is always positive (it is the most positive pressure of the entire circuit) and its values range from +100/+250 mmHg.

If the pressure increases it may be due to the filter presenting clotted capillaries or an increase in membrane resistances, as well as kinks of the lines or catheter coagulation.

Effluent pressure

This corresponds to the ultrafiltering. It can be positive when the filter works properly, or negative when coagulated capillaries exist. At first it is positive, it can gradually decrease until it becomes negative which will indicate that the filter is clotting. This pressure depends on the default ultrafilter flow, blood pump speed and number of working capillaries of the filter.

Transmembrane Pressure (TMP)

TMP can be positive or negative. It is the result of the pressure difference between the dialysis fluid compartment (EXTRACAPILAR SPACE) and the blood (INTRACAPILAR SPACE) (hydrostatic gradient).

For its calculation, the following formula is used: TMP (P filter + P return)/2 – P effluent.

When this value starts to increase, the performance of the filter decreases.

Its value must be less than 200 mmHg. Communicate if this value is exceeded. As it approaches 250 mmHg increases the possibility of filter clotting, and the inability to recover blood.

Return pressure

The return pressure is positive (+ 50/+150 mmHg) and measures the pressure that exists when blood returns to the patient. Ideal value +100 mmHg.

It depends on blood flow, the condition of the venous line (access or grip) and the catheter (clots or catheter adhesion to the wall).

Pressure drop

Pressure drop in the filter is a calculated value that is used to determine pressure conditions in the filter's hollow fibers. The pressure drop in the filter is calculated by the Prismaflex program® as follows:

Filter socket pressure – Return sensor pressure - Pressure drop in the filter

During treatment microcoagulations may occur in the hollow fibers of the filter, eventually producing massive coagulation and the need to switch to a new set. Coagulation generates resistance as blood passes through hollow fibers and causes pressure drop in the filter to increase.

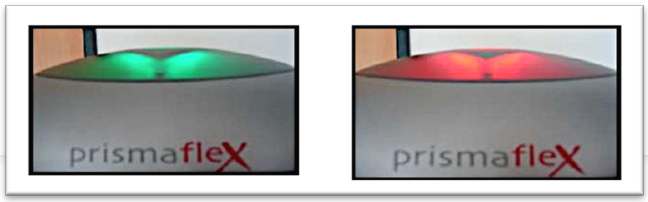
Information about ALARMS.

In the instruction manual (located in the Shared Folder of the Unit), you can find additional information in Chapter 6 (Alarm System) and Chapter 7 (Troubleshooting)

During some types of alarms the treatment is paused, so filter coagulation is favored. They must be taken care of as soon as possible.

There are four types of alarm, each of which has a different function and behavior

They can be muted for 2 minutes, after which the audible alarm resumes if the alarm situation has not been resolved.



Status lights indicate working conditions.

Green. Indicates that all monitored parameters are normal during treatment.

Yellow. Indicates that a precautionary or warning alarm has occurred, or that an alarm is canceled. The user needs to detect the cause.

Red. Indicates that a warning or malfunction alarm has occurred due to a potential risk condition for the patient. Immediate operator intervention is required.

Alarm	Cause	Action
Warning Red Light Quick Beep	They occur if there are situations of **possible risk to the patie**nt that require rapid intervention from the operator; for example, air bubbles on the return line or extreme positive pressure on the return line or very negative on the input line.	The Prismaflex control unit® introduces a "safe situation" by **stopping all pumps and closing the return line clamp**. Treatment is discontinued. The patient's blood does not circulate through the blood circuit.
Malfunctioning Red Light Quick Beep	They occur if patient safety cannot be monitored due to **system failure**; for example, a self-diagnosis failure, program errors, or hardware failures.	
Precautionary Yellow Light Moderate Beep	They occur if there is a situation where the correct action is to stop treatment, but it **is safe to continue with the flow of the syringe or blood pump**; for example, the replacement solution bag, dialysis liquid or PBP is empty or the effluent bag is full.	PBP pumps, substitution, dialysis liquid and effluent stop. Blood and syringe pumps continue to work and the return line clamp remains open. **The patient's blood continues to circulate** through the blood circuit, even if treatment is discontinued.
On notice Yellow Light Slow Beep	They occur if there is a situation that the operator should be aware of, but which does not pose an immediate risk to the patient; for example, when preventive maintenance is needed. Patient treatment continues during a Warning alarm.	The pumps don't stop and the treatment continues.
Power Loss Alarm	Continuous beeping for at least 2 minutes	

All alarms have priorities. This means that if multiple problems occur, only the alarm with the highest priority is displayed. If the alarm with higher priority is cleared, the screen with the next high priority alarm, etc. is displayed.

As each alarm appears on the screen, the operator must follow the on-screen instructions to respond to the alarm.

ABOUT THIS PROTOCOL:

- This protocol is based on the experience of a post-surgical critical care unit as well as the existing literature. To expand the concepts we refer to the article: García-Hernández R, Espigares López M, García-Palacios M, Gámiz Sánchez R, Miralles-Aguiar F, Calderón Seoane E, et al. A pilot study into the use of Continuous Venous Hyperfiltration to manage patients in a critical state with dysregulated inflammation. Rev Esp Anestesiol Reanim. 2019;66(7):370–80.

- Any use of this protocol and its possible consequences will be the responsibility of the person applying them in clinical practice.

- The intellectual property of the CONVEHY® protocol is registered and protected and its use for the conduct of any clinical research based on it without the knowledge and authorization of the author is prohibited.

RAFAEL GARCÍA-HERNÁNDEZ. M.D.
SPECIALIST IN ANESTHESIOLOGY AND REANIMATION
SURGICAL CRITICAL CARE UNIT COORDINATOR
HOSPITAL UNIVERSITARIO PUERTA DEL MAR
CADIZ
SPAIN

Author's email: rafaghernandez@yahoo.es.
Orcid: 0000-0003-1859-601X