CytoSorb®

CytoSorbents Corporation

CytoSorb® este un dispozitiv medical de hemoadsorbție folosit ca *cartuș de purificare a sângelui* în tratamentele extracorporale. Practic, este un filtru cu *mărgele polimerice biocompatibile* care captează și elimină din sânge moleculele de dimensiuni medii ce pot provoca *inflamație severă* și dezechilibre în organism, inclusiv citokinele din sindromul de „furtună citokinică", bilirubină (în bolile hepatice) și mioglobină (în rhabdomioliză) etc.

Cum funcționează?

- CytoSorb este amplasat în circuitul extracorporel al echipamentului (de exemplu *B. Braun OMNI*®) și—pe măsură ce sângele trece prin cartuș—moleculele nedorite sunt reținute prin *adsorbție pe suprafața poroasă a polimerului*.
- Tehnologia are o selectivitate pentru molecule hidrofobe de până la ~60 kDa, ceea ce înseamnă că elimină preferențial substanțele care, la niveluri ridicate, sunt dăunătoare sau indică inflamație severă.

De ce se folosește cu OMNI® (B. Braun)?
Platforma OMNI® de la B. Braun este un *sistem de purificare continuă a sângelui* (dializă / hemofiltrare) care poate fi folosită pentru susținerea funcției organelor la pacienți critici (de exemplu insuficiență renală acută, suprasarcină de lichide, intoxicații). CytoSorb® poate fi integrat în circuitul acestei platforme pentru a extinde capacitatea sistemului cu o funcție de *adsorbție specifică* a moleculelor inflamatorii – ceea ce ajută la controlul inflamației în terapie critică.

Utilizări clinice frecvente:

- eliminarea citokinelor în *sepsis* și sindrom de răspuns inflamator sistemic sever;
- susținerea în *ARDS* și alte stări critice unde inflamația severă pune pacienții în risc;
- reducerea bilirubinei în insuficiență hepatică;
- îndepărtarea mioglobinei (de exemplu în rhabdomioliză);
- suport în timpul chirurgiei cardiace pentru reducerea mediátorilor inflamatori post-operatorii.

Caracteristici tehnice ale cartușului CytoSorb:

- volum adsorbant ≈ 300 ml, cu extracorporeal rezidual redus;
- captează molecule până până la ~60 kDa;
- poate fi utilizat în diferite circuite extracorporale (CRRT, hemoperfuzie, hemodializă, ECMO, cardio-pulmonar bypass etc.).

Regulatory / distribuție:
CytoSorb® are marcaj CE pentru utilizare în Uniunea Europeană și este distribuit în zeci de țări. Colaborarea cu B. Braun înseamnă că CytoSorb® poate fi promovat și operat compatibil pe platforma OMNI® pentru tratamente critice extracorporale.

CytoSorb®

CytoSorb Therapy

Indications and set-up

CytoSorb Therapy

REGAIN CONTROL

The statements in this document do not constitute a diagnostic or therapeutic recommendation. It is a "best practice" collection, based on the current level of knowledge and expert opinion. The indication, conduction and termination of the CytoSorb Therapy is in the responsibility of the treating physician. The short set-up guide does not replace the instructions for use.

Table of contents

The International CytoSorb Registry

Why joining the Registry?

- You want to optimize your CytoSorb Therapy
- You want to contribute to the improvement of international safety standards
- You want to exchange your results and experiences worldwide
- Little effort: No intervention, no randomization
- Easy, quick and secure electronic data entry
- Highest quality standard and independent scientific supervision by Center for Clinical Studies in Jena/Germany

CytoSorb Registry

Register here, it's done in 30 seconds:

www.cytosorb-registry.org

01 | The Therapy

02 | Sepsis
Septic shock

03 | Cardiac surgery
intraoperative

04 | Cardiac surgery
postoperative

01 | The Therapy

The Therapy

The CytoSorb Therapy is based on an extracorporeal blood purification that effectively reduces excessive level of inflammatory mediators.

In doing so, the goal is to reduce the overshooting systemic inflammatory response while the physiologic immune response is maintained.

Patients with hyperinflammatory infectious and non-infectious conditions should benefit from a CytoSorb therapy.

The life-threatening complications of the so called cytokine storm could potentially be avoided. Stabilization following a hyperinflammatory phase could be improved.

This is how CytoSorb modulates the immune response

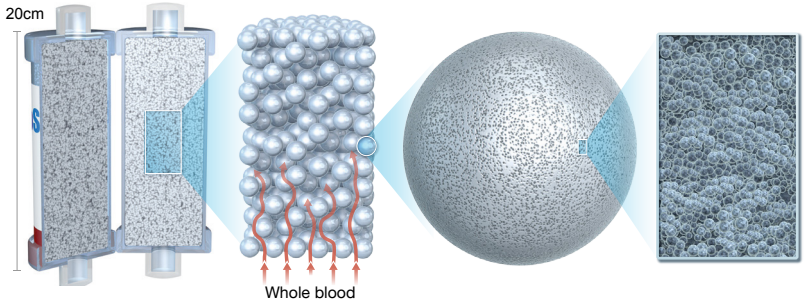
- Effective reduction of excessive cytokine levels
- Decreased de novo synthesis of inflammatory mediators
- Controlled attenuation of the overshooting immune response
- Re-targeting of the cellular immune defense to the focus of infection

Your CytoSorb Therapy goals

- Control the systemic inflammation
- Modulate the immune response
- Stabilize hemodynamics
- Improve the fluid balance
- Prevent and treat organ dysfunction and organ failure

The Therapy

Proprietary polymer technology



Section through adsorber | Adsorber bead | Internal structure

- High-tech polymer
- Size selectivity < 55 kD
- Low flow resistance
- Blood volume 120 ml

- Blood flow 150-500 ml/min
- Pre-filled with isotonic saline solution
- Gamma sterilized, 3 years shelf life

02 | Sepsis
Septic shock

Basic prerequisites

- Onset of or ongoing acute systemic hyperinflammation
- Standard therapy according to sepsis guidelines established (e.g. 6 hr sepsis bundle, focus control)
- APACHE II > 25, platelets > 20.000/µl, no DNR order
- CytoSorb is to be employed as adjunctive, not as causative therapy

- Treatment duration and indication for exchange of adsorber depend on the clinical course, maximum treatment time per adsorber 24 hours
- Continuous treatment is recommended over intermittent one
- Typical blood flow rate 150 – 500 ml/min
- Anticoagulation with heparin or citrate, aPTT of 60 – 80 sec is sufficient for CytoSorb
- With stand-alone mode heparin anticoagulation only
- Contraindications for extracorporeal blood circuits apply

see set-up page 32 ff.

Sepsis / Septic shock

When should the therapy be started?

- Patient cannot be stabilized clinically with standard medical treatment
- Clinical picture of hyperinflammation
  - Onset of shock (Norepinephrine > 0,3 µg/kg/min or rapidly increasing) within the last 24 hrs
  - Signs of capillary leak – e.g. positive fluid balance
- Development of at least one more organ dysfunction
  - Kidney, lung, liver, coagulation, neurologic impairment
- Systemic markers of infection:
  - PCT > 3 ng/l in case of bacterial or fungal sepsis
  - High IL-6 levels (e.g. >500 pg/ml) can, if available, support the treatment decision, but low levels do not preclude reasonableness of treatment

Early start of therapy:
Rather avoid than treat organ failure.

Why start early?

- Pre-clinical data and previous clinical experience hint at survival benefit if CytoSorb Therapy is started early [1- 4]
- The guidelines, that are based on sound clinical evidence, should be followed first
- CytoSorb should be started if patients do not respond sufficiently to guideline therapeutic recommendations
- Insufficient therapeutic efficacy of the sepsis bundle is the recommended indication for start of CytoSorb Therapy in septic shock

References
1. Peng ZY et al, Kidney Int. 2012 Feb;81(4):363-9
2. Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7
3. Hetz H et al, Int J Artif Organs. 2014 May;37(5):422-6
4. Sathe P et al, Critical Care 2015, 19(Suppl 1): P130

Organ dysfunction caused by inflammation is potentially reversible and can be treated, in contrast to irreversible organ cell failure.

Sepsis / Septic shock

Signs of a successful CytoSorb Therapy

- Stabilization of the hemodynamic situation
  - Decreasing vasopressor need
  - Less positive or stabilization of fluid balance
  - No further increase of lactate level

- Decrease of IL-6 level (if measured) and of WBC, PCT, CRP
  - When assessing the course of PCT, be aware of direct, partial PCT removal by CytoSorb

- Stabilization of other organ functions, e.g.
  - No further deterioration of liver function parameters
  - No further increase of ventilatory support necessary
  - Improvement of coagulation situation

When should the therapy be terminated?

- Treatment should be continued until clinical condition indicates that systemic hyperinflammation is under control
  - No need of catecholamines or rapidly decreasing dosage
  - Reversal of fluid balance, reduction of edema
  - Normalization of lactate level

- Improvement of impaired organ functions, e.g.
  - Marked reduction of ventilatory support
  - Return of spontaneous diuresis
  - Improvement of liver function parameters

- Deterioration after cessation of CytoSorb treatment (e.g. insufficient focus control or second hit) may indicate necessity to recommence CytoSorb Therapy

Sepsis / Septic shock

Possible patient groups

- Post-surgical patients with severe sepsis and onset of AKI
- Patients with severe concomitant diseases and impaired immune competence
  - Often elderly patients
  - Chronic diseases:
    - Chronic dialysis patients
    - Patients with chronic liver disease
- Patients with therapy refractory septic shock and multi-organ failure
- Patients suffering from sepsis boosted by enterotoxins
- Patients with hyperinflammation in viral and fungal sepsis or in tropical diseases

03 | Cardiac surgery intraoperative

Cardiac surgery: Intraoperative use

Basic prerequisites

- Installation never into the mainstream of a cardiopulmonary bypass (CPB)
- Typical blood flow rate 150 – 500 ml/min
- Anticoagulation with heparin, ACT of 160 - 210 sec is sufficient for CytoSorb

see set-up page 52

Cardiac surgery: Intraoperative use

When should the therapy be started?

At the start of CPB

Preemptive use in case of one or more of the following risk factors:

- Age > 75 yrs
- Preoperative activation of the immune system:
  - Endocarditis
  - Cardiac failure with inotropic therapy
  - Preoperative leukocytosis (> 12,000/µl)
  - Organ dysfunctions, e.g. kidney or liver
- Procedures with higher risk for complications and/or SIRS
  - Combination procedures (valve repair/-replacement, CABG)
  - Redo procedures
  - Aortic surgery with hypothermic circulatory arrest
  - LVAD implant
- Long CPB duration expected (>120 min)
- High risk for postoperative need for ECMO

Anytime during CPB

Patients with low primary risk but unexpected course

- Unexpected, significant prolongation of anticipated CPB time
- Intraoperative development of a severe SIRS
- Intraoperative complications with expected development of severe SIRS

Cardiac surgery: Intraoperative use

When should the therapy be terminated?

At the end of CPB in case of preemptive use and

- Uneventful intraoperative course
- No signs of hyperinflammation at end of CPB
- No undue hemodynamic instability at end of CPB

Postoperative continuation on ICU in case of

- Ongoing or beginning SIRS intraoperatively
- Severe SIRS to be expected postoperatively

04 | Cardiac surgery postoperative

Cardiac surgery: Postoperative use

Basic prerequisites

- Onset of or ongoing acute systemic hyperinflammation
- Standard therapy established and optimized
- Platelets > 20.000/µl, no DNR order
- In case of sepsis, CytoSorb is to be employed as adjunctive, not as causative therapy
- Treatment duration and indication for exchange of adsorber depend on the clinical course, maximum treatment time per adsorber 24 hours
- Continuous treatment is recommended over intermittent one
- Typical blood flow rate 150 – 500 ml/min
- Anticoagulation with heparin or citrate, aPTT of 60 – 80 sec is sufficient for CytoSorb
- With stand-alone mode heparin anticoagulation only
- Contraindications for extracorporeal blood circuits apply

Early start of therapy:
Rather avoid than treat organ failure.

See set-up page 32 ff.

Cardiac surgery: Postoperative use

When should the therapy be started?

Immediately upon arrival in ICU

- Postoperative continuation of intraoperative CytoSorb treatment
- Manifest severe SIRS upon arrival

Postoperative (0-48h) development of SIRS with or without proof of infection

- Patient cannot be stabilized clinically with standard medical treatment
- Impaired hemodynamics (shock)
  - Onset of shock (Norepinephrine > 0,3µg/kg/min or rapidly increasing)
  - Signs of capillary leak – e.g. positive fluid balance
- Onset of at least one more organ dysfunction, e.g.
  - Mechanical ventilation
  - Acute kidney failure with need for RRT
- Systemic markers of infection:
  - PCT > 3ng/l in case of bacterial or fungal sepsis
  - High IL-6 levels (e.g. > 500 pg/ml) can, if available, support the treatment decision, but low levels do not preclude reasonableness of treatment

Cardiac surgery: Postoperative use

In case of sepsis - why start early?

- Pre-clinical data and previous clinical experience hint at survival benefit if CytoSorb Therapy is started early [1 – 4]
- The guidelines, that are based on sound clinical evidence, should be followed first
- CytoSorb should be started if patients do not respond sufficiently to guideline therapeutic recommendations
- Insufficient therapeutic efficacy of the sepsis bundle is the recommended indication for start of CytoSorb Therapy in septic shock

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Organ dysfunction caused by inflammation is potentially reversible and can be treated, in contrast to irreversible organ cell failure.

Cardiac surgery: Postoperative use

Signs of a successful CytoSorb Therapy

- Stabilization of hemodynamic situation
  - Decreasing vasopressor need
  - Less positive or stabilization of fluid balance
  - No further increase of lactate level
- Decrease of IL-6 level (if measured) and of WBC, PCT (in case of sepsis), CRP
  - When assessing the course of PCT, be aware of direct, partial PCT removal by CytoSorb
- Stabilization of other organ functions, e.g.
  - No further deterioration of liver function parameters
  - No further increase of ventilatory support necessary
  - Improvement of coagulation situation

Cardiac surgery: Postoperative use

When should the therapy be terminated?

- Treatment should be continued until clinical condition indicates that systemic hyperinflammation is under control
  - No need of catecholamines or rapidly decreasing dosage
  - Reversal of fluid balance, reduction of edema
  - Normalization of lactate level
- Improvement of impaired organ functions, e.g.
  - Marked reduction of ventilatory support
  - Return of spontaneous diuresis
  - Improvement of liver function parameters
- Deterioration after cessation of CytoSorb treatment (e.g. insufficient focus control or second hit) may indicate necessity to recommence CytoSorb Therapy

05 Set-up: Short user guide

Short user guide

Notes prior to treatment start

- Preparation and use of CytoSorb must always be carried out under hygienic conditions
- Before connecting CytoSorb the supply tubing system must be airlessly pre-filled with sterile isotonic saline solution
- **Under no circumstances must air enter CytoSorb**
- Always pay attention to the prescribed running direction when installing CytoSorb
- The blood flow rate should be 150-500 ml/min
- The maximum duration of usage of a CytoSorb adsorber should not exceed 24 hours
- It may be advisable to change the adsorber sooner if there is evidence of an exhausted elimination capacity
- Check the extracorporeal circuit at regular intervals for signs of blood clots, the secure fit of the connections and air within the circuit

Anticoagulation

- Anticoagulation must be effective at treatment start
- In intensive care patients an aPTT of 60 to 80 sec., when using during heart surgery an ACT of 160 to 210 seconds, is sufficient for CytoSorb. Specifications of the device manufacturer have to be observed
- The aPTT and ACT should be checked regularly during therapy to ensure adequate anticoagulation

General materials required:

- CytoSorb adsorber
- Mounting holder for CytoSorb
- 6 scissor clamps
- Isotonic saline solution with Luer Lock for flushing (2l NaCl 0.9%, sterile)

Your notes

06

Set-up:

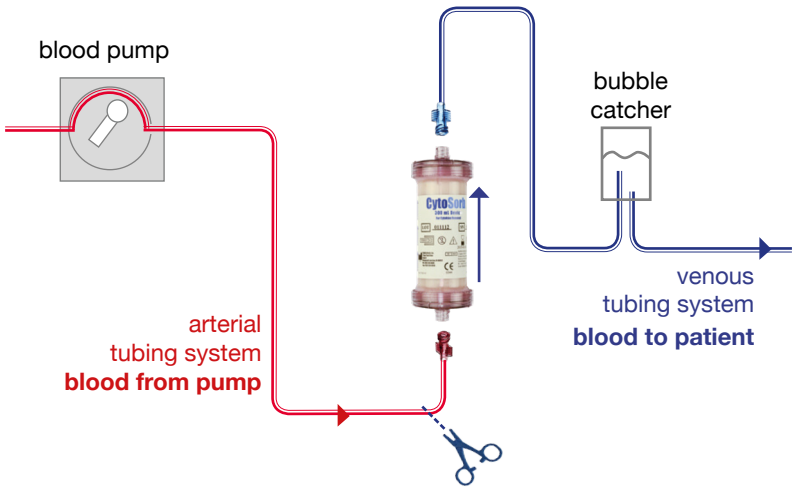
CytoSorb as stand-alone therapy

CytoSorb as stand-alone therapy

Set-up

1. Set-up the device according to the manufacturer's instructions (dry)
2. Mount CytoSorb vertically into holder
3. Start blood pump and deaerate arterial tubing system
4. Stop blood pump and clamp arterial tubing system at ⋮ by using scissors clamp
5. Only remove the port plug on the CytoSorb inlet (bottom)
6. Connect CytoSorb bubble-free with arterial tubing system (observe flow direction)
7. Now remove the blood outlet port plug (top) and connect CytoSorb with venous tubing system
8. Remove scissor clamp from arterial tubing system
9. Start blood pump (approx. 200 ml/min) and rinse system with 2 liters of saline solution
10. Remove CytoSorb from the holder and deaerate it by tapping
11. Start patient treatment according to manufacturer's instructions

Set-up


blood pump
bubble
catcher
CytoSorb
venous
tubing system
blood to patient
arterial
tubing system
blood from pump

Your notes

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Set-up:

CytoSorb combined with renal replacement therapy

CytoSorb combined with renal replacement therapy

Set-up 1 of 2

1. Completely prepare the device according to manufacturer's instructions (incl. flushing). If necessary during ongoing renal replacement therapy first interrupt the treatment (return blood and disconnect patient according to the manufacturer's instructions of each device)
2. Connect saline solution with A, **deaerate** and close red tubing clamp of A
3. Connect bubble-free with CytoSorb blood inlet (bottom) (observe flow direction)
4. Connect CytoSorb blood outlet (top) with E, B, C and D
5. Open red tube clamp of A and rinse CytoSorb by gravity with 2 liters of saline and deaerate it by tapping
6. Close red tube clamp of A and blue tube clamp of C

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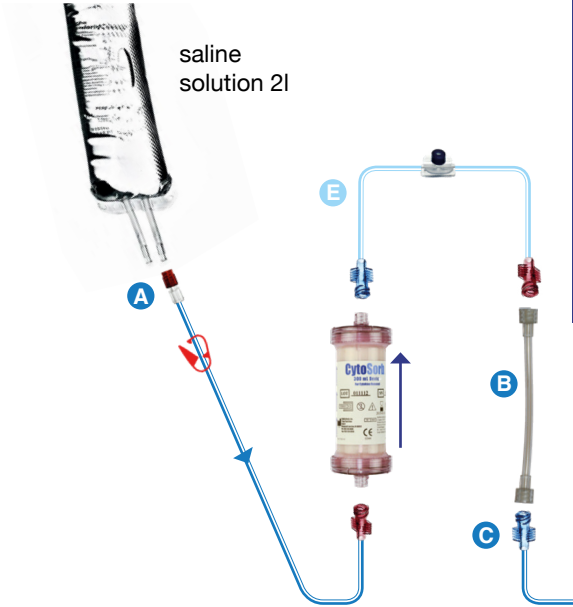
Set-up before dialyzer



Additional materials:

Priming adapter 1

- **A** Red Luer Lock – red DIN Lock
- **B** Color neutral DIN Lock – color neutral DIN Lock
- **C** Blue DIN Lock – blue Luer Lock
- **D** 2l empty bag

Adapter 1

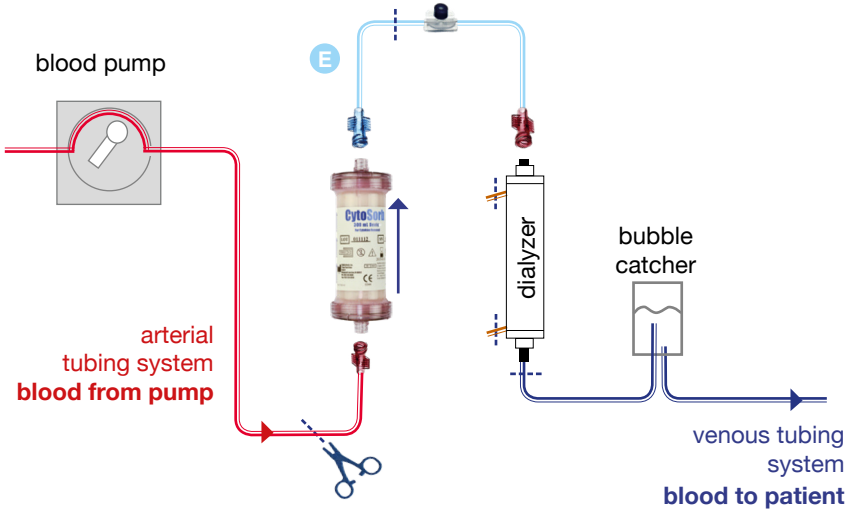
- **E** Color neutral DIN Lock – color neutral DIN Lock

CytoSorb combined with renal replacement therapy

Set-up 2 of 2

7. Stop blood pump
8. Clamp all tubes at the dialyzer at ¦ by use of scissor clamps
9. Disconnect A from CytoSorb blood inlet (bottom) and discard it
10. Disconnect arterial blood tube from dialyzer blood inlet and connect bubble-free with CytoSorb blood inlet (bottom)
11. Disconnect B from E and discard B, C and D
12. Connect E bubble-free with dialyzer blood inlet
13. Remove all scissor clamps at ¦
14. Start patient treatment according to manufacturer‘s instructions

Set-up before dialyzer



possible configuration

CytoSorb combined with renal replacement therapy

Set-up 1 of 2

1. Completely prepare the device according to manufacturer‘s instructions (incl. flushing). If necessary during ongoing renal replacement therapy first interrupt the treatment (return blood and disconnect patient according to the manufacturer‘s instructions of each device)
2. Connect saline solution with A and B, **deaerate** and close red tubing clamp of A
3. Connect B bubble-free with CytoSorb blood inlet (bottom) (observe flow direction)
4. Connect CytoSorb blood outlet (top) with C, D and E
5. Open red tube clamp of A and rinse CytoSorb by gravity with 2 liters of saline and deaerate it by tapping
6. Close red tube clamp of A and blue tube clamp of B. Clamp B before and C after CytoSorb at ⋮ by using scissor clamps

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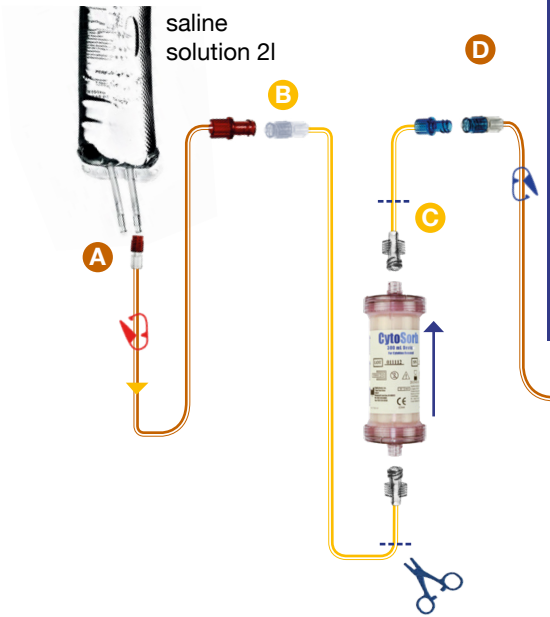
Set-up after dialyzer



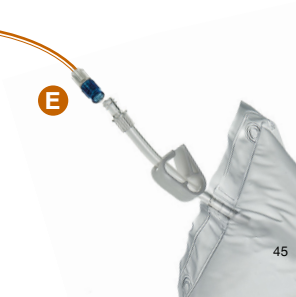
Additional materials:

Priming adapter 2

- **A** Red Luer Lock – red Luer Lock
- **D** Blue Luer Lock – blue Luer Lock
- **E** 2l empty bag

Adapter 2

- **B** Color neutral Luer Lock – color neutral DIN Lock
- **C** Color neutral DIN Lock – blue Luer Lock



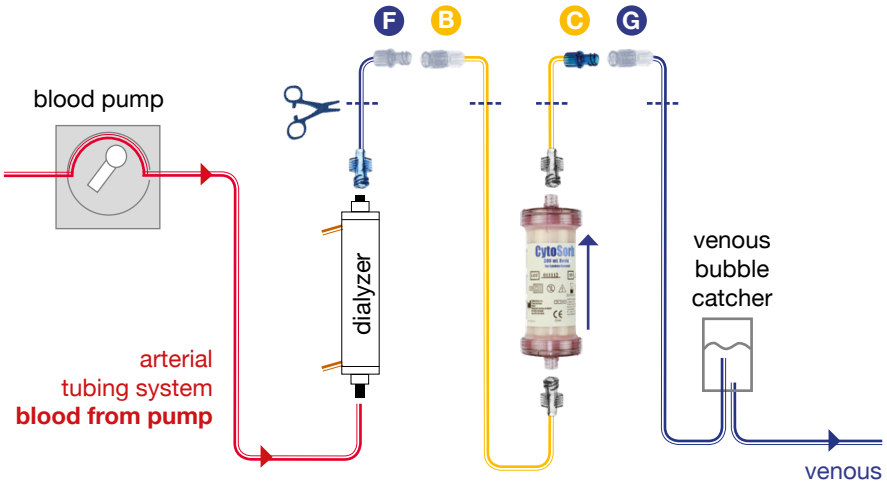
CytoSorb combined with renal replacement therapy

Set-up 2 of 2

7. Stop blood pump
8. Clamp blood tubes at the dialyzer blood outlet F and before the venous bubble catcher G at ⋮ by use of scissor clamps
9. Disconnect saline solution and A from B and discard it
10. Connect B with blood tube from dialyzer blood outlet F
11. Connect C from CytoSorb blood outlet (top) with line to venous bubble catcher G
12. Remove all scissor clamps at ⋮
13. Start patient treatment according to manufacturer‘s instructions

Cave: If CytoSorb gets integrated after a dialyzer, postdilution in combination with a low blood flow may lead to clotting. Predilution configuration is recommended in this setting.

Set-up after dialyzer



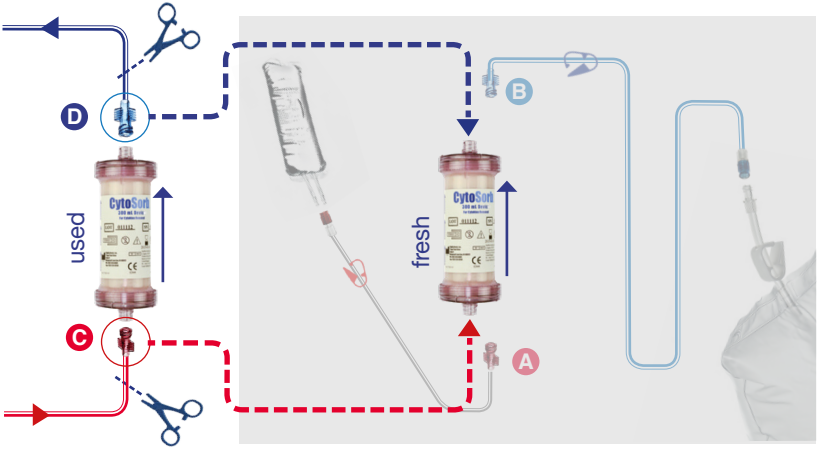
possible configuration

CytoSorb exchange

1. Prepare CytoSorb according to instructions for installation before or after dialyzer
2. Interrupt ongoing treatment (return blood and disconnect patient according to manufacturer`s instructions of each device)
3. Stop blood pump
4. Clamp blood tubes directly before and after the used CytoSorb by using scissor clamps at ⋮
5. Disconnect flushing tube A from blood inlet of the fresh CytoSorb (bottom) and discard it
6. Remove the supply tubing system C from the blood inlet of the **used** CytoSorb (bottom) and connect it to the blood inlet of the **fresh** CytoSorb (bottom)
7. Close the blood inlet of the used CytoSorb with the port plug of the fresh CytoSorb
8. Disconnect the flushing tube B from the blood outlet of the fresh CytoSorb (top) and discard it
9. Disconnect the return tubing system D from the used CytoSorb (top) and connect it to the blood outlet of the fresh CytoSorb (top)
10. Close the blood outlet of the used CytoSorb with the port plug of the fresh CytoSorb
11. Remove scissor clamps at ⋮
12. Continue patient treatment according to manufacturer`s instructions

CytoSorb exchange

return tubing system
blood to the patient



supply tubing system
blood from pump

Your notes

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Set-up:

CytoSorb in cardiopulmonary bypass

CytoSorb in cardiopulmonary bypass

Set-up 1 of 2

1. Completely prepare the device according to manufacturer's instructions (incl. flushing)
2. Connect saline solution with A, **deaerate** and clamp with roller clamp B
3. Connect bubble-free with CytoSorb blood inlet (bottom) (observe flow direction)
4. Connect CytoSorb blood outlet (top) with C and D
5. Open roller clamp B and and rinse CytoSorb by gravity with 2 liters of saline solution and deaerate it by tapping
6. Close clamps at B and D

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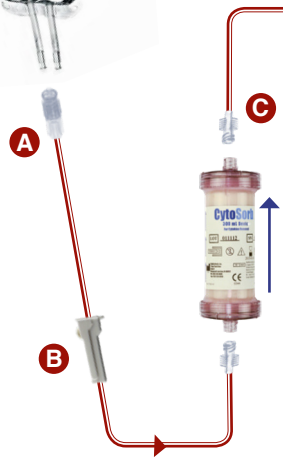
CytoSorb in cardiopulmonary bypass

saline
solution 2l



Additional materials:
Adapter 3

- A Color neutral Luer Lock – Color neutral DIN Lock with roller clamp B
- C Color neutral DIN Lock – Color neutral Luer Lock
- D 2l empty bag
- E High-flow three-way valve

CytoSorb in cardiopulmonary bypass

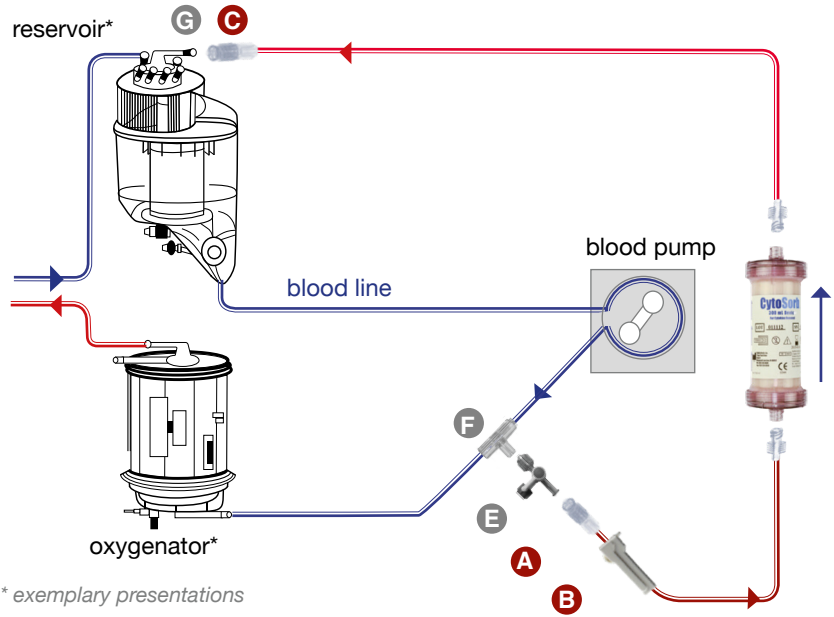
Set-up 2 of 2

7. Vertically install CytoSorb at the heart-lung-machine by using the holder
8. Disconnect A from the saline bag and connect it bubble-free to a Luer Lock F on the blood line after the pump by use of a three-way high flow valve E.
9. Connect C via a Luer Lock connection to the reservoir G
10. If necessary, regulate the flow via roller clamp B

NOTES

- For safety reasons, the installation of CytoSorb in cardiopulmonary bypass is always carried out via a Luer lock branch between the pump and oxygenator, forming a reflux to the reservoir
- Due to the diameter of the Luer lock connection the blood flow through CytoSorb is limited to 400 to 500 ml/min
- In order to avoid clotting, a continuous blood flow has to be ensured after start of the CytoSorb therapy

CytoSorb in cardiopulmonary bypass



** exemplary presentations*

Your notes

CytoSorb®

SIRS and Sepsis

REGAIN CONTROL

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