CytoSorbents™

CytoSorb Therapy

Indications & Practical Aspects

Literature / Disclaimer

* Brouwer et al., Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study, Crit Care 2019; 317
* Hawchar et al., Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study, JCC 2019; 49: 172 - 8
* Friesecke et al., Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study, J Artif Organs 2017; 20(3): 252-9
* Kogelmann et al., Hemoadsorption by CytoSorb in septic patients - a case series, Crit Care 2017; 21:74
* Garau et al., Hemadsorption during cardiopulmonary bypass reduces interleukin 8 and tumor necrosis factor α serum levels in cardiac surgery: an RCT, Min Anesth 2019; 85(7): 715 - 23
* Calabro et al., Blood Purification With CytoSorb in Critically Ill Patients: Single-Center Preliminary Experience, Artif Organs 2019; 43(2): 289 - 94
* Traeger et al., Hemodasorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - a case series, Int J Art Organs 2017; 40(5):240-9,
* Buttner et al., Application of Hemoadsorption in a Case of Liver Cirrhosis and Alcohol-Related Steatohepatitis with Preexisting Hepatitis C Infection, Blood Purif 2017; 44(1): 30-1
* Friesecke et al., International registry on the use of the CytoSorb adsorber in ICU patients: Study protocol and preliminary results, Med Klein Intens Not 2019; 114(8): 699- 707
[1] Napp et al., Rationale of Hemoadsorption during Extracorporeal Membrane Oxygenation Support, Blood Purif. 2019; 48(3): 203-214

The statements in this document do not constitute diagnostic or therapeutic recommendations. 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 the responsibility of the treating physician.
The Quick Setup Guide does not replace the instructions for use of any components used in the setup.

Visit **cyto.zone/literature** for an overview of all references

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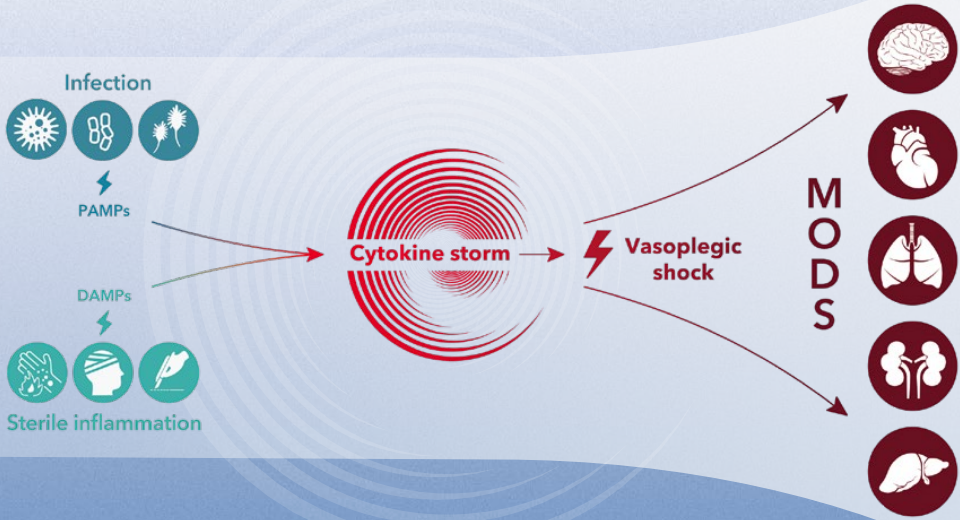
CytoSorb Therapy – REGAIN CONTROL



CytoSorb®
Registry

Join the global CytoSorb scientific network!

1,000 patients
46 hospitals
9 countries

Reasons why you should join the CytoSorb Registry…

- You want to learn more about extracorporeal adsorption methods
- You want to optimize your therapy
- You want to share your experiences with and learn from colleagues all over the world
- It requires little effort: no intervention or randomization
- It's easy, fast and secure using OpenClinica®
- The highest quality standards with independent scientific supervision

UNIVERSITÄTS KLINIKUM Jena

ClinicalTrials.gov
ID: NCT02312024

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01

The Therapy

The Therapy

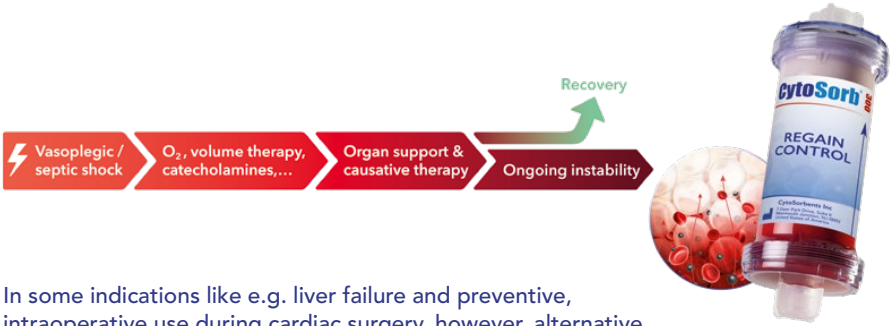
The CytoSorb therapy is based on extracorporeal blood purification that effectively reduces excessive levels of inflammatory mediators. Major therapeutic goals are hemodynamic stabilization, shock control and reduction of vasopressor needs.

In doing so, the overall goal is to reduce the overshooting systemic inflammatory response while while maintaining the physiological immune response.

Evidence shows that patients with hyperinflammatory infectious and non-infections conditions benefit from CytoSorb therapy, particularly if it started early in the clinical course.

The Therapy

In principle CytoSorb therapy should be considered as an adjunctive therapy, if standard therapy based on guidelines fails to give sufficient hemodynamic stabilization (within the first 6 to 24 hrs.).

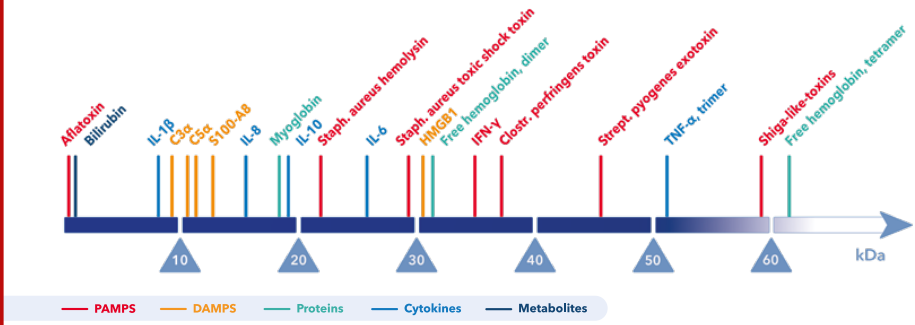


In some indications like e.g. liver failure and preventive, intraoperative use during cardiac surgery, however, alternative criteria and aspects can (additionally) support decision making regarding CytoSorb therapy (please see corresponding pages).

The Therapy

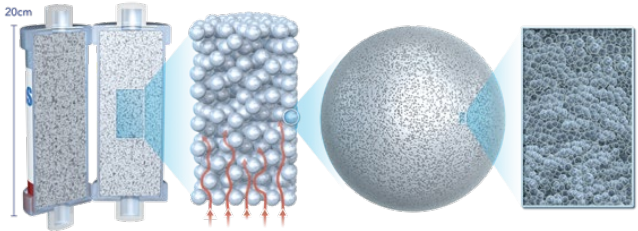
Adsorption spectrum of the CytoSorb adsorber

The CytoSorb adsorber adsorbs hydrophobic substances dependent on their specific molecule size (up to approximately 55 kDa) and concentration.



With high concentrations greater amounts of those substances can be removed very quickly, whereas elimination rates decrease with lower concentrations. **This auto regulation based on physicochemical properties helps to prevent the complete removal of physiologic mediators.**

Proprietary polymer technology



- Unique patent protected biocompatible adsorbent produced by CytoSorbents
- Smart removal of hydrophobic substances based on concentration dependency and size selectivity
- Low flow resistance
- Gamma sterilized, 3 years shelf life
- Technical / recommended blood flow rate 150 - 700 ml/min, with a minimum of 100 ml/min.
- Pre-filled with isotonic saline solution
- Simple priming by gravity:
  Flush with 2 liters saline within 5 min.

02

Vasoplegic / Septic shock

Vasoplegic / Septic shock

Preconditions

- **Acute systemic hyperinflammation in sepsis or non-infectious triggers**

  Normally characterized by

  - Hypotension with vasodilation and need for vasopressors
  - Positive fluid balance / volume need with capillary leakage
  - Over time, additional organ dysfunctions often present

- **Standard therapy according to guidelines (e.g. antibiotic treatment, source control, hemodynamic stabilization etc.) already started**

- **Severe disorder / clinical picture (e.g. SOFA-Score > 10)**

- **No therapy limitations (e.g. infaust prognosis, patient's will)**

Initiation of CytoSorb therapy

The following aspects / parameters can support setting the indication for CytoSorb

Clinical aspects / parameters

- Lactic acidosis persistent or progressive (in the absence of hypovolemia)
- Norepinephrine > 0.3 µg/kg/min or use of two vasopressors
- No indication of stabilization with standard therapy

Laboratory results (if measured)

- PCT > 3 µg/l
  - In the postoperative setting higher threshold values should often be used
- IL-6 > 500-1000 pg/ml
- In cases with a clear clinical picture the use of CytoSorb can be justified even without availability of IL-6 / PCT

Temporal aspect

- Time since diagnosis / start of standard therapy ideally no longer than 6 to 24 hrs. maximum.
- A start later than 48 hrs. after diagnosis / start of standard therapy should be reconsidered individually due to decreasing chances of success

Vasoplegic / Septic shock

Change of adsorber & end of CytoSorb therapy

Change of adsorber can be indicated, if

- After 18 - 24 hrs. insufficient clinical stabilization seen
- After an initial stabilization period a plateau is reached or there is even a clinical deterioration in under 18 - 24 hrs.
- The recommended 24 hrs. as maximum therapy duration per adsorber is reached and therapy should be continued

End of hemoadsorption therapy can be indicated, if

- With the currently used adsorber sufficient clinical stabilization is achieved
- IL-6 < 500 - 1000 pg/ml (depending on the threshold value regarding indication) has been achieved and clinical situation is stable
- Due to the overall situation, further measures seem not to be useful
- Despite the use of a second or third adsorber ongoing deterioration of the clinical situation is seen

Signs of successful CytoSorb therapy

Stabilization of the hemodynamic situation

- Decreasing need for vasopressors
- Stabilization of fluid balance
- No further increase / reductions in lactate levels

Decrease in PCT and IL-6 levels (if measured)

- When assessing the course of PCT, be aware of direct, partial PCT removal by CytoSorb
- Increasing PCT values under CytoSorb therapy might be interpreted as a signal for inadequate source control

Stabilization of other organ functions, e.g.

- No further deterioration/improvement in liver function parameters
- No further increase / reduction of ventilatory support necessary
- Improvement in coagulation situation

Vasoplegic / Septic shock

CytoSorb Therapy – Initiation

MAP normal

MAP low
< 65 mmHg
Vasopressors
start

Vasopressors
continue
Lactate
> 2 mmol/l

Vasopressors
NE > 0.3 µg/kg/min
Capillary leak

Lactate further
elevated/increasing

IL-6 (> 500 pg/ml)
PCT (> 3µg/l)
if measured

*Extracorp. circuit
available / indicated*

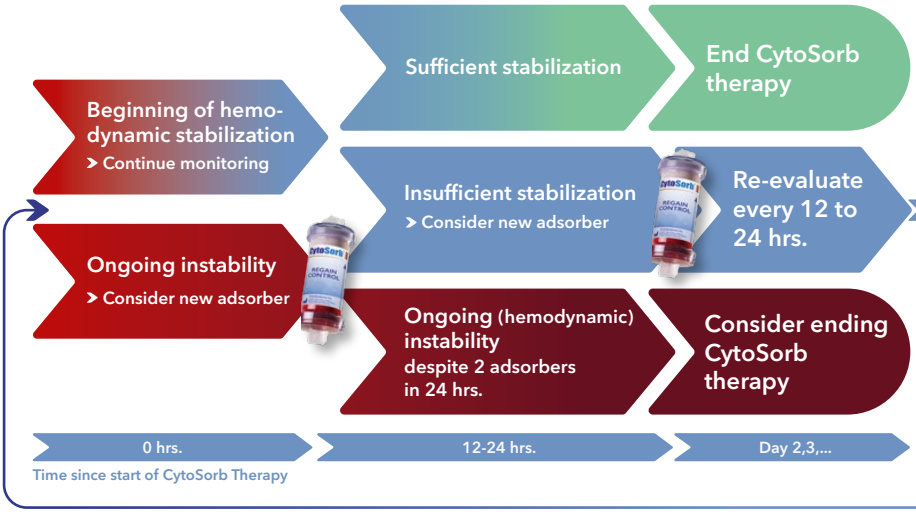
Start CytoSorb

Diagnosis

Stable → Unstable → Shock → Refractory septic / vasoplegic shock

Early start within 6-24 hrs. is recommended for best results

CytoSorb Therapy – Continuation



Vasoplegic / Septic shock

Potential Indications

The following clinical conditions are characterized or aggravated by hyperinflammation, often with deterioration and shock. CytoSorb therapy may therefore be considered in addition to standard of care and treatment of the underlying cause in:

- Refractory septic shock
- Vasoplegic shock e.g. postoperatively, with ECMO therapy
- Toxic shock syndrome
- Necrotizing fasciitis
- Meningococcal sepsis
- Hemophagocytic Lymphohistiocytosis (HLH)
- Cytokine Release Syndrome (CRS) after e.g. CAR T-cell therapy
- Pancreatitis
- Burns, Trauma

Other potential therapeutic goals might include

- Liver failure (removal of bilirubin)
- Rhabdomyolysis (removal of myoglobin)

03

Cardiac surgery

- **For postoperative use: Preconditions, indication setting, signs of therapeutic success, change of adsorber and end of therapy are in principle very similar to use in septic / vasoplegic shock** (see p.14-17)

Cardiac surgery – Intraoperative use

Intraoperative Initiation

Goal: Reduce risk of inflammatory activation

The intraoperative use of CytoSorb therapy should be considered if one or more of the following aspects is given:

- Complex intervention with expected long CPB time (> 120 min.)
  - Combination procedure
  - Redo procedure
- Acute, infective endocarditis requiring valve replacement
- Heart transplant surgery
- Aortic surgery with prolonged hypothermic circulatory arrest time (> 20 min.)
- High patient comorbidity and / or pre-existing liver / renal dysfunction
- Increased risk for the development of intra- & postoperative, hyperinflammatory based complications

Cardiac surgery – Intraoperative use

When should the therapy be terminated?

At the end of CPB in cases of preemptive use

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

Postoperative continuation in ICU in cases of

- Ongoing or beginning severe hemodynamic instability with high vasopressor need
- Severe hemodynamic instability with high vasopressor need expected postoperatively
- A fresh adsorber should be used if therapy is to be continued on the ICU due to reasons of hygiene and the risk of clotting inside of the adsorber during stopped flow, which could impair the adsorption capability.

Cardiac surgery – Postoperative use

CytoSorb Therapy – Postoperative Initiation

Postoperative hemodynamic instability

Vasopressors
NE > 0.3 µg/kg/min
Capillary leak

Lactate further elevated/increasing

IL-6 (> 500 pg/ml)
PCT (> 3µg/l)

Differentiated volume-/ Catecholamine therapy

Advanced hemodynamic monitoring

Organ support (Ventilation, CRRT)

CytoSorb?
(early use in anticipation of ongoing deterioration or as continuation of intraoperative use)

Rapid stabilization → Recovery

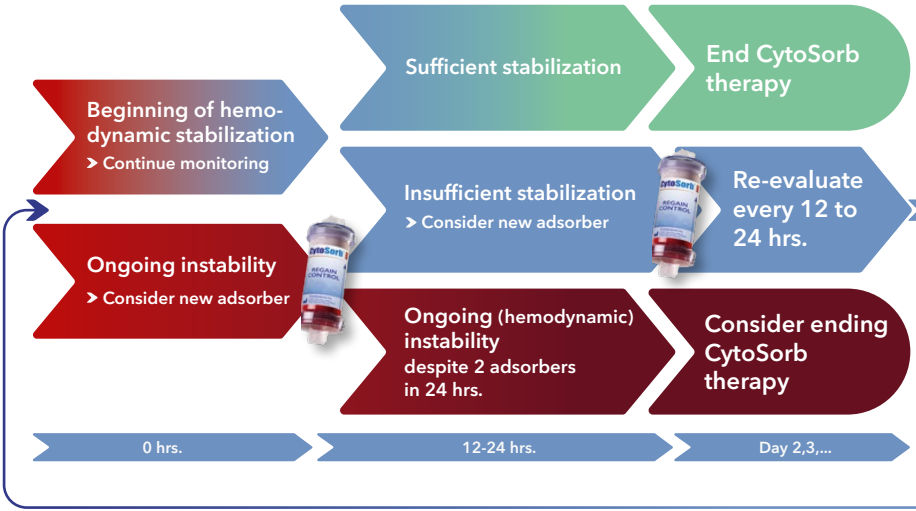
Refractory septic / vasoplegic shock → Start CytoSorb

0 hrs. → 6-24 hrs.

Early start within 6-24 hrs. is recommended for best results

Cardiac surgery – Postoperative use

CytoSorb Therapy – Postoperative Continuation



04

Liver failure

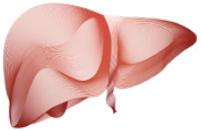
Liver failure

When should the therapy be started?

- **CytoSorb therapy should be considered if one or more of the following aspects is given:**
  - Bilirubin > 10mg/dl
  - Hepatic encephalopathy III - IV
  - Intractable pruritus
  - ACLF grade 2-3
  - Liver failure with concomitant vasoplegic shock
  - Bridge to transplant

- **CytoSorb therapy is NOT a primary treatment for liver failure itself, but is a support system for excretory liver function.**
- **Other beneficial effects can result from the modulation of the systemic hyperinflammation usually present in liver failure patients.**

Signs of successful CytoSorb therapy



Stabilization of liver function

- Reduction of bilirubin levels
- Reduction of ammonia and bile acid levels
- Improvement in coagulation function

Stabilization of the hemodynamic situation

- Decreasing need for vasopressors
- Stabilization of fluid balance
- No further increases or even reductions in lactate level

05

ECMO patients

ECMO patients

General aspects [1, see p.2]

- The primary therapeutic goal of CytoSorb treatment is shock reversal and/or a reduction in catecholamine dosages, with the intention of preventing or limiting organ failure.
- The decision for or against CytoSorb should be made independent of the indication and start of CRRT, or other extracorporeal therapies. CytoSorb treatment should be considered as complementary and autonomous.
- If there is an inadequate response to standard therapy after an observation period of a maximum of 6 hrs, clinical and laboratory re-evaluation should be performed when considering CytoSorb treatment.
- In selected cases, it might be reasonable to start CytoSorb treatment immediately and in parallel to standard therapy, e.g. in patients in fulminant septic shock.

ECMO patients

When should the therapy be started? (1, see p.2)

Proposed clinical and laboratory criteria for considering CytoSorb use

- Consistently increased vasopressor requirements >0.3 µg/kg/min
  - Or use of 2 vasopressors
  - Or additional need for inotropes
- IL-6 >300–500 pg/mL as a laboratory sign of systemic hyperinflammation
- Metabolic acidosis (pH <7.20)
- Poor lactate clearance

ECMO patients

CytoSorb Therapy – Initiation

Start of ECMO therapy as indicated

Consider early use of CytoSorb in anticipation of ongoing deterioration as well as use of CytoSorbents ECMO connectors during setup to allow for the safe integration of CytoSorb

Stabilization of clinical and hemodynamic situation

Recovery

No control of shock parameters / ongoing shock

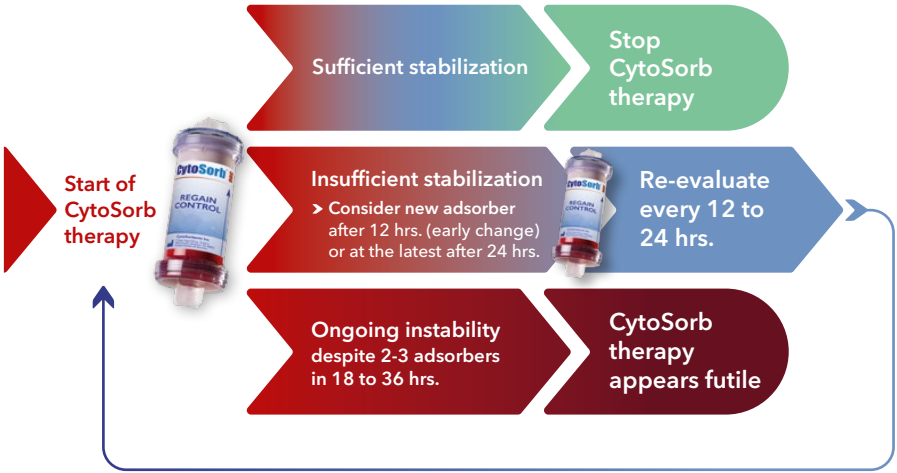
Consider elevated levels of bilirubin and myoglobin as additional rationale for CytoSorb therapy

› Start CytoSorb

(integrated into ECMO/ separate extra-corporeal circuit)

Observation period ideally not longer than 6 hrs. before considering CytoSorb as an adjunctive therapy

CytoSorb Therapy – Continuation



Adequate causative therapy and technical conditions of ECMO therapy (catheter position, flow rate etc.) are the prerequisite for therapeutic success

ECMO patients

Potential Indications

The following clinical conditions are characterized or aggravated by hyperinflammation, often with deterioration and shock. CytoSorb therapy may therefore be considered in addition to standard of care and treatment of the underlying cause in:

- Cardiogenic shock
- ECPR
- Bridge to VAD surgery
- ARDS with high vasopressor demand
- Post cardiotomy syndrome
- Infective endocarditis
- Septic shock
- *Liver failure (removal of bilirubin)*
- *Rhabdomyolysis (removal of myoglobin)*

06

Basic prerequisites / Anticoagulation

Basic prerequisites / Anticoagulation

Basic prerequisites

- CytoSorb should be installed in a shunt off the main flow as is the current practice with hemoconcentrators
- Installation must never be into the main stream of a CPB or ECMO
- Pressure or flow monitoring of the CytoSorb line is recommended
- The recommended blood flow rate should be between 150 - 700 ml/min, with a minimum of 100 ml/min.
- CytoSorb is to be employed as an adjunctive, not as a causative therapy
- Treatment duration and indication for exchange of adsorber depends on the clinical course. The maximum treatment time per adsorber is 24 hrs.
- Continuous treatment is recommended rather than intermittent
- Contraindications for extracorporeal blood circuits apply

Anticoagulation

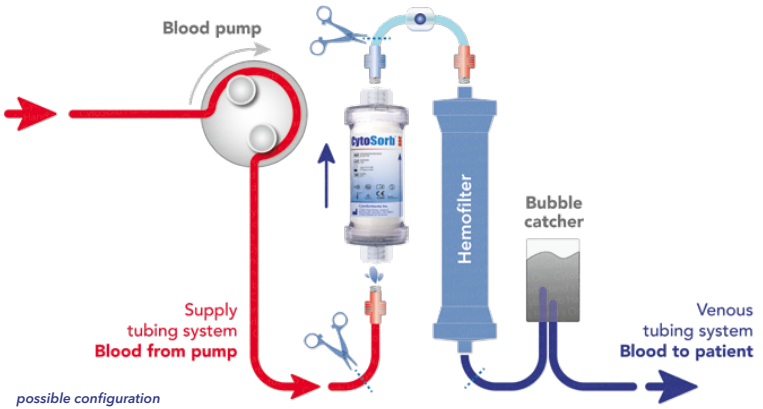
- Anticoagulation must be effective at the start of treatment.
- In general, no special adaptations of the protocols for CytoSorb are necessary. The specifications of the device manufacturer must be observed.
- Systemic heparinization
    - An aPTT of 60-80 sec or an ACT of 160-210 sec is usually sufficient for CytoSorb. The aPTT or ACT should be checked regularly.
- Regional anticoagulation with citrate
    - Initial dose, blood flow rate, control and adjustment of calcium and citrate according to protocol used. Citrate and calcium additions are made at the usual sites of the CRRT.
    - The control of ionized calcium (CRRT circuit & patient) a few minutes after the start of treatment and at regular intervals of 2-4 hrs. is recommended.
- Any decision on dosage and target values is the responsibility of the treating physician.
- In hemoperfusion (stand alone mode without hemofilter) use heparin anticoagulation only.

07

Learn more about CytoSorb Integration options
cyto.zone/setup

Setup

RRT with CytoSorb – Pre Filter



possible configuration

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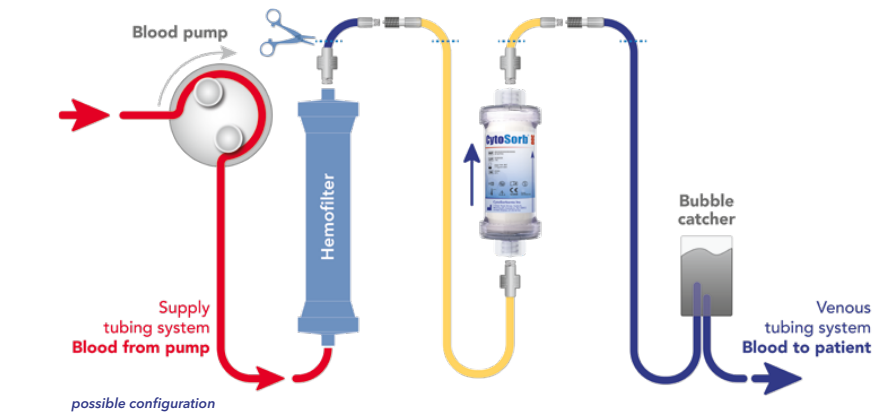
RRT with CytoSorb – Post Filter



possible configuration

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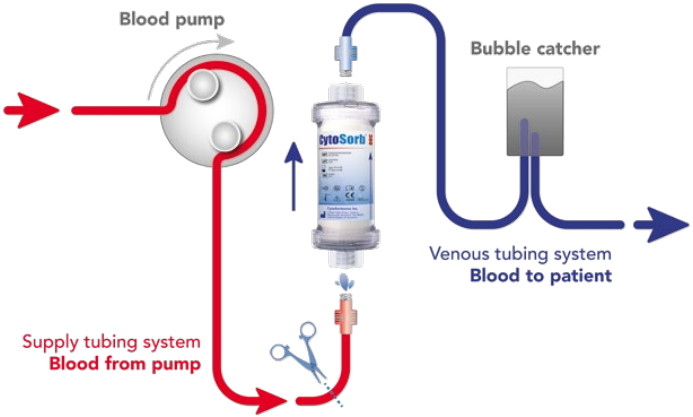
Setup

Hemoperfusion with CytoSorb



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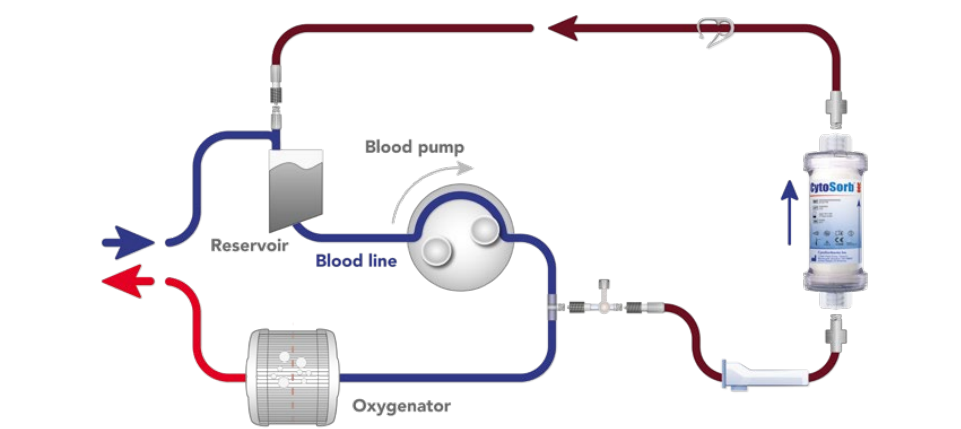
CPB with CytoSorb – Intraoperative Use



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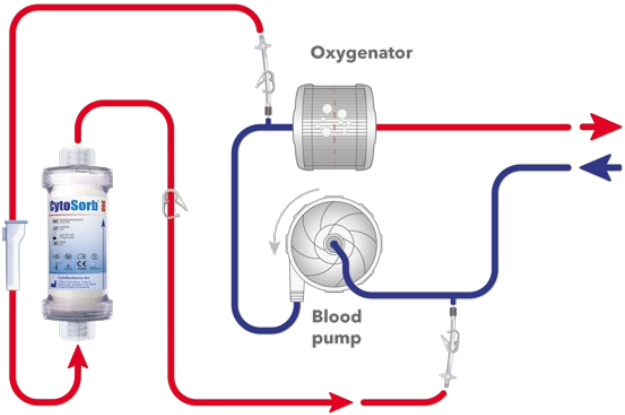
Setup

ECMO with CytoSorb



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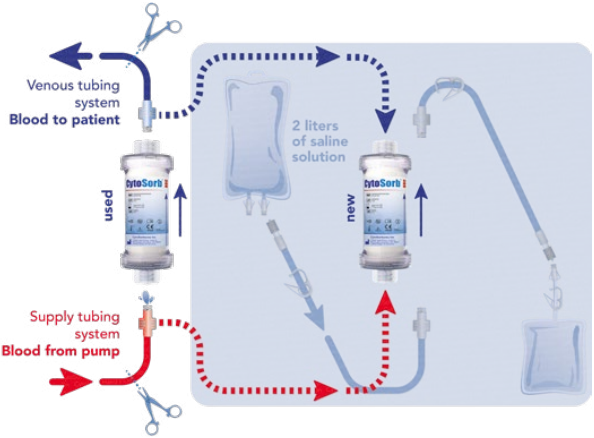
Exchange of the CytoSorb Adsorber



cyto.zone/setup-xchg1

Order-Nr.	Article	Description	Quantity
30-0011	CytoSorb® 300 Adsorber 300ml	12 box of whole-blood-adsorbers for application in patients with increased cytokine / bilirubin / myoglobin levels	12
30-0021	CytoSorb® 300 Adsorber 300ml	6 box of whole-blood-adsorbers for application in patients with increased cytokine / bilirubin / myoglobin levels	6
40-001a-01	CytoSorb® Adapter 1	1 x DIN-Lock female red - DIN-Lock female blue	6
40-001b-01	CytoSorb® Priming Adapter 1	1x DINLock female blue - LuerLock male blue 1x DINLock female red - LuerLock male red 1x DINLock male - DINLock male 1x Disposal-bag, 2-liters	6
40-002a-01	CytoSorb® Adapter 2	1x LuerLock female - DINLock female 1x LuerLock male - DINLock female	6
40-002b-01	CytoSorb® Priming Adapter 2	1x LuerLock male blue - LuerLock male blue 1x LuerLock female red - LuerLock male red 1x Disposal-bag, 2-liters	6
41-0003-01	CytoSorb® Adapter 3	2x LuerLock male - DINLock female	6
42-0001-01	CytoSorb® EC Connector Set	2x ECMO Connector 2x LuerLock syringe 10ml	6
42-0002-01	CytoSorb® EC Priming Set Adapter 4	1x DINLock female - LuerLock male, roller clamp 1x DINLock female - LuerLock male, pinch clamp 1x Disposal-bag, 2-liters 1x Adapter LuerLock female - spike 1x Adapter DINLock male - LuerLock female 1x DINLock female- DINLock female with sample port	6
30-0041	CytoSorb® Clamp	Adsorber holder (short, rotatable) for rigid attachment to rods or handles	1
90-5011	CytoSorb® FLEX-Arm	Adsorber bracket (long, bendable) for flexible attachment to poles, handles or rails	1

For orders or questions please contact us at support@cytosorbents.com or T +49 30 65 49 91 45

Notes

The clinical and preclinical data and results obtained with the CytoSorb adsorber are not transferable to other products. CytoSorb should only be administered by personnel who have been properly trained in administration of extracorporeal therapies. CytoSorb is not available for commercial sale in the USA.
Only indications listed by the CytoSorb 300 IFU represent on-label indications.

Your local CytoSorbents contact

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