CytoSorb® Therapy
Indications and Set-up
CytoSorb therapy

REGAIN CONTROL

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 short set-up guide does not replace the instructions for use.
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The International CytoSorb Registry

Why join 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

Register here, it’s done in 30 seconds: www.cytosorb-registry.org
01 | The Therapy

02 | Sepsis
    Septic shock

03 | Cardiac surgery
    intraoperative

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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.

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

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

The life-threatening complications of the so called cytokine storm can potentially be avoided. Stabilization following the hyperinflammatory phase can be improved.
Attenuated Inflammatory Response

Overshooting Inflammatory Response

Pro-inflammatory Cytokines

Anti-inflammatory Cytokines

Dysregulated toxic level

Insult

Organ failure

Recovery

MOF / Death

without CytoSorb

with CytoSorb

The Therapy
The Therapy

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 therapeutic goals

• Control the systemic inflammation
• Modulate the immune response
• Stabilize hemodynamics
• Improve the fluid balance
• Prevent and treat organ dysfunction and organ failure
Adsorption spectrum of the CytoSorb adsorber

The CytoSorb adsorber adsorbs hydrophobic low and middle molecular substances dependent on their concentrations.

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 mechanisms protects against the complete, unphysiological removal of mediators.
Proprietary polymer technology

- High-tech polymer
- Size selectivity < 55 kD
- Low flow resistance
- Gamma sterilized, 3 years shelf life

- Recommended blood flow 150-500 ml/min
- Pre-filled with isotonic saline solution
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 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 hours
- Continuous treatment is recommended over intermittent
- Recommended blood flow rate 150 - 500 ml/min
- Anticoagulation with heparin or citrate, aPTT of 60 – 80 sec is sufficient for CytoSorb
- In stand-alone mode use heparin anticoagulation only
- Contraindications for extracorporeal blood circuits apply

See set-up page 34
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 within the last 24 hrs
    (Norepinephrine > 0.3 μg/kg/min or rapidly increasing)
  - 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 μg/l in cases of bacterial or fungal sepsis dysfunctions
  - High IL-6 levels (e.g. > 500 pg/ml) can, if available, support the treatment decision, however low levels do not preclude reasonableness of treatment

Early start of therapy:
Better to avoid than have to treat organ failure
Why start early?

- Pre-clinical data and previous clinical experience point towards a 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 therapeutic guideline recommendations.
- Insufficient therapeutic efficacy of the sepsis bundle is the recommended indication for start of CytoSorb therapy in septic shock.

References
1. Kogelmann K et al., Critical Care 2016 20(Suppl 2):94
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 successful CytoSorb therapy

- Stabilization of the hemodynamic situation
  - Decreasing need for vasopressors
  - Stabilization of fluid balance
  - No further increase in lactate level

- Decrease in 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 the clinical condition indicates that systemic hyperinflammation is under control
  - No need for catecholamines or rapidly decreasing dosage
  - Reversal of fluid balance, reduction in edema
  - Normalization of lactate level

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

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

- Post-surgical patients with 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 caused by enterotoxins
- Patients with hyperinflammation caused by viral and fungal sepsis or by tropical diseases
03 Cardiac surgery intraoperative
Cardiac surgery: Intraoperative use

Basic prerequisites

• Installation must never be into the main-stream of a cardiopulmonary bypass (CPB)
• CytoSorb placement should be in a shunt off the main flow as is the current practice with hemoconcentrators
• Pressure or flow monitoring of CytoSorb line is recommended
• Recommended blow flow rate 150 - 500 ml/min
• Anticoagulation with heparin, ACT of 160 - 210 sec is sufficient for CytoSorb

See set-up page 54
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 cases 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 in ICU in cases of

• Ongoing or beginning SIRS intraoperatively
• Severe SIRS 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 be employed as an adjunctive, and not a causative therapy.
- Treatment duration and indication for exchange of adsorber depends on the clinical course. The maximum treatment time per adsorber is 24 hours
- Continuous treatment is recommended over intermittent
- Recommended blood flow rate 150 – 500 ml/min
- Anticoagulation with heparin or citrate, aPTT of 60 – 80 sec is sufficient for CytoSorb
- In stand-alone mode use heparin anticoagulation only
- Contraindications for extracorporeal blood circuits apply

Early start of therapy:
Better to avoid than have to treat organ failure.

See set-up page 34
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 > 0.3 μg/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 > 3 μg/l in cases of bacterial or fungal sepsis
  - High IL-6 levels (e.g. > 500 pg/ml) can, if available, support the treatment decision, however 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 point to a 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 therapeutic guideline recommendations
• Insufficient therapeutic efficacy of the sepsis bundle is the recommended indication for start of CytoSorb therapy in septic shock

References
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  - Return of spontaneous diuresis
  - Improvement in liver function parameters

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05 | Short user guide

06 | CytoSorb as stand-alone therapy

07 | CytoSorb combined with renal replacement therapy

08 | CytoSorb in cardiopulmonary bypass
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 primed with sterile isotonic saline solution
• **Under no circumstances must air enter the CytoSorb**
• Always pay attention to the prescribed running direction when installing CytoSorb
• The blood flow rate should be between 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 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., and when used during heart surgery an ACT of 160 to 210 seconds, is sufficient for CytoSorb. Specifications of the device manufacturer have to be observed
- The aPTTT 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)
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 \( \text{clamp} \) by using scissors
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. 100 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
Stand-alone set-up

blood pump

arterial tubing system

blood from pump

bubble catcher

venous tubing system

blood to patient
Your notes
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 for each device)

2. Connect saline solution with A, deaerate and close red pinch clamp of A

3. Connect A bubble-free with CytoSorb blood inlet (bottom) (observe flow direction)

4. Connect CytoSorb blood outlet (top) with B, C, D and E

5. Open red pinch clamp of A and rinse CytoSorb by gravity with 2 liters of saline and deaerate it by tapping

6. Close red pinch clamp of A and blue pinch clamp of D

Continued on next page …
Set-up before dialyzer

saline solution
2 liters

Additional materials:

Priming Adapter 1

A Red Luer Lock – Red DIN Lock
C Color neutral DIN Lock – Color neutral DIN Lock
D Blue DIN Lock – Blue Luer Lock
E 2 liter disposal bag

Adapter 1

B Color blue DIN Lock – Color red 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 \textit{scissor clamps}.
9. Disconnect \( A \) from CytoSorb blood inlet (bottom) and discard it.
10. Disconnect \textit{arterial blood tube} from dialyzer blood inlet and connect bubble-free with CytoSorb blood inlet (bottom).
11. Disconnect \( C \) from \( B \) and discard \( C, D, \) and \( E \).
12. Connect \( B \) bubble-free with dialyzer blood inlet.
13. Remove all \textit{scissor clamps} at \( \) and start blood pump.
14. Start patient treatment as prescribed.
Set-up before dialyzer

blood pump

arterial tubing system

blood from pump

dialyzer

bubble catcher

venous tubing system

blood to patient

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 pinch 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 pinch clamp of A and rinse CytoSorb by gravity with 2 liters of saline and deaerate it by tapping

6. Close red pinch clamp of A and blue pinch clamp of B. Clamp B before and C after CytoSorb at by using scissor clamps

Continued on next page …
Set-up after dialyzer

Saline solution
2 liters

Additional materials:

**Priming Adapter 2**
- A Red Luer Lock – Red Luer Lock
- D Blue Luer Lock – Blue Luer Lock
- E 2 liter disposal 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 and start blood pump
13. Start patient treatment as prescribed.

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

blood pump

arterial tubing system

blood from pump

dialyzer

possible configuration

F B

C G

bubble catcher

venous tubing system

blood to patient
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 for each device)
3. Stop blood pump
4. Clamp blood tubes directly before and after the used CytoSorb by using scissor clamps at [a]
5. Disconnect flushing tube [C] from blood inlet of the fresh CytoSorb (bottom) and discard it
6. Remove the supply tubing system [A] 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 [D] from the blood outlet of the fresh CytoSorb (top) and discard it
9. Disconnect the return tubing system [B] 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 [a] and start blood pump
12. Continue patient treatment as prescribed
CytoSorb exchange

return tubing system
blood to the patient

supply tubing system
blood from pump

used

fresh

A

B

C

D
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 on **A**
3. Connect **A** bubble-free with CytoSorb blood inlet (bottom) (observe flow direction)
4. Connect CytoSorb blood outlet (top) with **B** and **C**
5. Open roller clamp on **A** and and rinse CytoSorb by gravity with 2 liters of saline solution and deaerate it by tapping
6. Close roller clamp on **A**. Clamp line **B** with **scissor clamp at**
7. Close pinch clamp on **C**
CytoSorb in cardiopulmonary bypass

Additional materials:
- **Adapter 3**
  - **A** Color neutral Luer Lock – Color neutral DIN Lock with roller clamp
  - **B** Color neutral DIN Lock – Color neutral Luer Lock
  - **C** 2 liter disposal bag
  - **D** High-flow three-way valve
  - **F** Luer Lock adapter for main tubing

saline solution 2 liters
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 D on the blood line after the pump by use of a three-way high flow valve F.

9. Connect B via a Luer Lock connection to the reservoir E.

10. If necessary, regulate the flow via roller clamp on A.

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

reservoir*

oxygenator*

blood pump

* exemplary presentations
Your notes
Your local CytoSorbents contact
SIRS and Sepsis

REGAIN CONTROL