CytoSorb Therapy
Indications and set-up
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.
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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

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

- 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
Sepsis / septischer Schock

• Beginnende oder andauernde akute Entzündungsphase

• Standardtherapie gemäß Sepsis-Leitlinien durchgeführt (z. B. 6 Std. Sepsis-Bundle, Fokuskontrolle)

• APACHE II > 25, Thrombozyten > 20.000/μl, keine DNR-Order

• CytoSorb ist als Begleittherapie, nicht als kausale Therapie einzusetzen

• Organversagen eher verhindern als behandeln: irreversible Zellschädigung und Zelltod zuvorkommen

• Kontinuierliche Behandlung gegenüber intermittierender vorzuziehen

• Blutflussrate zwischen 200-400ml/min

• Antikoagulation im extrakorporalen Kreislauf empfohlen mit Heparin oder Zitrat, Ziel aPTT 60 – 80 Sek.

• Im Hämoperfusionsmodus ausschließlich Heparin-Antikoagulation

• Kontraindikationen für extrakorporale Blutkreisläufe beachten

Grundvoraussetzungen

siehe Aufbauschema Seite xx

Organversagen eher verhindern als behandeln: irreversible Zellschädigung und Zelltod zuvorkommen

siehe Aufbauschema Seite xx
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.
Sepsis / Septic shock

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

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
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
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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
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

References

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
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• 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 | Short user guide

06 | CytoSorb as stand-alone therapy

07 | CytoSorb combined with renal replacement therapy

08 | CytoSorb in cardiopulmonary bypass
Set-up:
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 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 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

arterial tubing system
blood from pump

bubble catcher

venous tubing system
blood to patient
07

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

Continued on next page …
Set-up before dialyzer

Additional materials:

- Priming adapter 1
- Red Luer Lock – red DIN Lock
- Color neutral DIN Lock – color neutral DIN Lock
- Blue DIN Lock – blue Luer Lock
- 2l empty bag

Adapter 1
- Color neutral DIN Lock – color neutral DIN Lock

saline solution 2l
CytoSorb combined with renal replacement therapy

Set-up 2 of 2

7. Stop blood pump
8. Clamp all tubes at the dialyzer at \[\text{I}\] by use of scissor clamps
9. Disconnect \(\text{A}\) 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 \(\text{B}\) from \(\text{E}\) and discard \(\text{B}, \text{C}\) and \(\text{D}\)
12. Connect \(\text{E}\) bubble-free with dialyzer blood inlet
13. Remove all scissor clamps at \[\text{J}\]
14. Start patient treatment according to manufacturer‘s instructions
Set-up before dialyzer

Blood pump

Arterial tubing system
Blood from pump

Possible configuration

Dialyzer

Bubble catcher

Venous tubing system
Blood to patient
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

Continued on next page …
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

saline solution 2l
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 \( \Box \) 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 \( \Box \)

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

- Blood pump
- Arterial tubing system
- Blood from pump
- Dialyzer
- Venous bubble catcher
- Venous tubing system
- Blood to patient

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

used

supply tubing system
blood from pump

CytoSorb
08

Set-up:
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 rinse CytoSorb by gravity with 2 liters of saline solution and deaerate it by tapping
6. Close clamps at B and D

Continued on next page …
CytoSorb in cardiopulmonary bypass

Additional materials:
- Adapter 3
- Color neutral Luer Lock – Color neutral DIN Lock with roller clamp
- Color neutral DIN Lock – Color neutral Luer Lock
- 2l empty bag
- High-flow three-way valve

saline solution 2l
CytoSorb in cardiopulmonary bypass

Set-up 2 of 2

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

reservoir

oxygenator

blood pump

blood line

A

B

C

D

E

F

G
Set-up 2 of 2

7. Stop blood pump
8. Clamp blood tubes at the dialyzer blood outlet and before the venous bubble catcher by use of scissor clamps
9. Disconnect saline solution and from and discard it
10. Connect with blood tube from dialyzer blood outlet
11. Connect from CytoSorb blood outlet (top) with line to venous bubble catcher
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.
SIRS and Sepsis

REGAIN CONTROL