Options for actions regarding the use of CytoSorb therapy in COVID-19 patients

1) General aspects:

- The virus infects the respiratory epithelium of the lower airways, causing widespread damage via cytopathic effects, resulting in severe inflammation and pneumonitis.
- High local and circulating levels of cytokines, or cytokine storm, can lead to capillary leak syndrome, progressive lung injury, respiratory failure and acute respiratory distress syndrome (ARDS).
- In addition to ARDS, further complications in the critically-ill include shock and acute kidney injury (AKI).
- Patients with severe COVID-19 also seem to have higher rates of liver dysfunction.
- Blood purification has been recommended in the 7th edition of "Diagnosis and Treatment Guidance on COVID-19" for severe and critically ill patients with cytokine storm by the National Health Commission of the People's Republic of China.
- The Brescia Renal Covid Task Force recommends the use of CytoSorb therapy in COVID-19 patients (details see point 4)

2) Basic prerequisites for the use of CytoSorb therapy:

- CytoSorb is to be employed as an adjunctive, not as a primary therapy
- CytoSorb can be integrated into renal replacement therapy circuits or as a bypass in ECMO systems. Alternatively, usage as stand-alone hemoperfusion is possible.
- Treatment duration and indication for exchange of adsorber depends on the clinical course. The maximum treatment time per adsorber is 24 hours.
- Usual contraindications for extracorporeal blood circuits apply.
- Installation must never be into the main-stream of an ECMO circuit, pressure or flow monitoring of CytoSorb line is recommended
- Recommended blood flow rate 150 - 700 ml/min with a minimal flow of 100ml/min. Higher flow rates result in higher detoxification.

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3) Anticoagulation:

- Therapeutic anticoagulation for CytoSorb is possible with heparin and citrate (if an additional hemofilter is present in the circuit) and must be fully effective at the start of treatment.
- A recent publication on COVID-19 patients showed elevated D-Dimer levels in the critically ill. This could point to a potential hypercoagulability, which is why adequate anticoagulation seems to be of major importance.
- Generally, any decision on dosage, target values and monitoring intervals is the responsibility of the treating physician.

4) Clinical criteria for the use of CytoSorb therapy in critically ill COVID-19 patients

a) The recent Handbook of COVID-19 Prevention and Treatment states the following:
   - Critical cases are divided into early, middle and late stages according to the oxygenation index and compliance of respiratory system

     - Early stage: 100 mmHg <oxygenation index ≤ 150 mmHg; compliance of respiratory system ≥ 30 mL/ cmH_2O; without organ failure other than the lungs. The patient has a great chance of recovery through active antiviral, *ANTI-CYTOKINE STORM*, and supportive *TREATMENT*.

b) The recent recommendations for the management of patients on dialysis and kidney transplant in the course of COVID-19 infection from the Brescia Renal Covid Task Force (endorsed by the Italian Society of Nephrology and ERA-EDTA) state the following for patients with AKI stage 3:

   - Patients with AKI stage 3 hospitalized in ICU should receive Continuous Veno-Venous Hemofiltration (CVVH)
   - CytoSorb therapy is recommended for 48 hrs. (with change of the adsorber after 24 hrs.) in patients for which Tocilizumab is not indicated or not available
   - In patients who are planned to receive Tocilizumab but haven't been given it at the time of CVVH start, CytoSorb therapy should be continued for 24 to 48 hrs. after the beginning of the Tocilizumab treatment.

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c) Recent not yet documented experiences with CytoSorb therapy in this field point towards the following additional criteria being helpful when considering the use of the adsorber:

- Profound vasoplegia with elevated levels of lactate and high need for vasopressors (e.g. Norepinephrine > 0.3 µg/kg/min) not responding to standard therapy. CytoSorb therapy should be started within the first 6 to maximum 24 hrs after start of standard therapy

- Very severe respiratory distress syndrome, such as indication for prone positioning to ensure adequate oxygenation under mechanical ventilation

- Indication for use of extracorporeal membrane oxygenation / extracorporeal life support (ECMO/ECLS) therapy

5) Initiation of CytoSorb therapy:

- CytoSorb should be flushed with saline and then be integrated into the (C)RRT or ECMO system (see detailed instructions in the quick setup guides/instructions for use - IFU)

6) Follow up / change of the adsorber

- After initiation of CytoSorb therapy the first adsorber should be changed after 12 hrs (to 24 hrs. at the latest).
- Thereafter, the adsorber should be changed every 12-24 hrs. depending on the clinical course (e.g. degree of hemodynamic instability, pulmonary dysfunction)

7) Termination of the therapy

- CytoSorb therapy should be terminated after 2-3 days in cases of primarily respiratory problems
- In cases of profound vasoplegia as the leading clinical problem, CytoSorb therapy should be continued (with new adsorbers every 12-24 hrs) until shock reversal and reduction of vasopressor need is down to <10% of baseline need.

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8) Remarks:

Data on the impact of CytoSorb therapy on plasma levels of antiviral medication is unfortunately still scarce. Results from animal studies point to the very low removal of Ganciclovir by the CytoSorb adsorber and anecdotal reports on CytoSorb therapy in influenza patients receiving Oseltamivir (Tamiflu) did not state any abnormalities that indicated relevant removal by CytoSorb. Anecdotal experience points towards the possible impact of CytoSorb on Chloroquine levels.

In principle we generally recommend choosing a dosage for antiviral (and or antibiotic) therapy at the upper end of the recommended range and to perform therapeutic drug monitoring wherever possible.

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