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 by 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 China.
- The Brescia Renal Covid Task Force (Italy) recommends the use of CytoSorb therapy in COVID-19 patients (details see point 4)
- CytoSorb Therapy is also recommended in the recent National Guidelines from Panama for adult COVID-19 patients (details see point 4)

- Additional notes:
  - Risk factors for poor outcome and death include age, prior lung disease, diabetes, cardiac disease, hypertension, and stroke
  - There are no definitive treatments for COVID-19 infection.
    1. There is a small controlled study in 30 patients that supports the use of hydroxychloroquine and azithromycin to speed clearance of the virus. This is being further evaluated in clinical studies
    2. Other anti-viral therapies are under investigation
    3. Tocilizumab, an IL-6 receptor antagonist, has shown initial positive results in a 20 patient Chinese study when given early (90% not intubated). However, data are still limited and a clinical trial will start shortly. Some notes:
       a. Tocilizumab has a molecular weight of 145 kDa and is not expected to be removed by CytoSorb. Concurrent use of CytoSorb should be fine.
       b. Unlike the single-mediator therapy tocilizumab, CytoSorb is a broad spectrum adsorber, designed to reduce high levels of cytokines and many other inflammatory mediators that can cause severe inflammation and capillary leak syndrome

4. Steroids are currently not recommended for the treatment of COVID-19 infection because they may prolong viral infection and may increase the risk of secondary bacterial infections such as pneumonia

2) Basic prerequisites for the use of CytoSorb therapy:

- CytoSorb is to be employed as an adjunctive therapy to lower cytokine storm, not as a primary therapy removing the virus. Due to its concentration dependency CytoSorb does not completely eliminate cytokines from the body but rebalances the immune system on physiologic levels.
- 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. Ideal flow rates using CRRT with systemic heparin anticoagulation seem to be 200-250 mL/min. Flow rates for regional citrate anti-coagulation are normally lower and should adhere to the corresponding protocols. Higher flow rates generally result in higher detoxification.

3) Anticoagulation:

- Clinical experience has shown that critically-ill patients with COVID-19 may be significantly hypercoagulable. This is supported by a recent publication on COVID-19 patients showing elevated D-Dimer levels in the critically ill. This is why adequate anticoagulation seems to be of major importance.
- 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. When using heparin, PTT targets should be at the high end (i.e. PTT 80 sec).
- There are anecdotal verbal reports on individual cases of a successful combination of concomitant heparin and regional citrate anticoagulation, combined with platelet inhibition by acetylsalicylic acid.
- Clinical experiences in regard to clotting have been better with femoral vascular access, probably due to the generally higher possible flow rates.
- Generally, any decision on regimen, 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 from China 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 Italy 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.

c) The recent National Guidelines from Panama for adult COVID-19 patients state that CytoSorb therapy should be considered if one or more of the following criteria occur:

- Profound vasoplegia with elevated lactate levels and high need for vasopressors (e.g. NE > 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, requiring high ventilatory support
- Indication for use of ECMO / ECLS therapy

d) Based on not yet documented experiences in the field, but not specifically related to COVID-19 infection, other reasons to start CytoSorb therapy may include:

- Profound vasoplegia with elevated levels of lactate and high need for vasopressors (e.g. NE > 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 (by applicable guidelines) of extracorporeal membrane oxygenation / extracorporeal life support (ECMO/ECLS) therapy

5) CytoSorb Treatment Recommendations

a) 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). Under no circumstances should air enter the adsorber.

b) 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)

c) Termination of the therapy

- CytoSorb therapy should be re-evaluated 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.

6) Potential drug removal:

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. Removal of hydroxycholoroquine and azithromycin by CytoSorb is possible.

In principle we generally recommend:

- Choosing a dosage for antiviral (and or antibiotic) therapy at the upper end of the recommended range, depending on the drug and therapeutic window of the drug
- Perform therapeutic drug monitoring wherever possible.
- Do not administer the drugs in-line with the dialysis catheter where immediate removal is possible
- Administering the drug during device changes, or before or after treatment, generally reduces the impact of the adsorber on drug levels. If not possible, then an alternative may be to administer an additional dose of the drug 1-2 hours after the start of each new CytoSorb cartridge.

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