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, as well as in a recently published expert consensus from Colombia (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 currently no definitive treatments for COVID-19 infection.

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 to more physiologic levels.
- CytoSorb can be integrated into renal replacement therapy circuits or as a bypass in ECMO systems. Alternatively, use in 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 hypercoagulapathic. This is supported by a recent publication on COVID-19 patients showing elevated D-Dimer levels in the critically ill. Standard dosing regimens for therapeutic anticoagulation during CRRT (see e.g. Dickie et al. Critical Care, 2015, 19:376), however, seem to be still sufficient. Close monitoring of anticoagulation is recommended.
- 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).
- Clinical experience of clotting has found to be less of an issue 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 the 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 acute kidney injury (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
- For patients in whom it is planned to receive Tocilizumab but haven't yet 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 the start of standard therapy
- Very severe respiratory distress syndrome, requiring high ventilatory support
- Indication for use of ECMO / ECLS therapy

d) According to a current expert consensus in the Columbia Journal of Nephrology, the initiation of CytoSorb therapy should be considered in severe and complicated cases of COVID-19 with septic shock and increased lactate levels. Furthermore, if renal replacement therapy is necessary or indication for ECMO/ECLS is given.

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 the start of standard therapy

- Moderate ARDS (acute respiratory distress syndrome with100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_20)
- Indication for use (by applicable guidelines) of extracorporeal membrane oxygenation / extracorporeal life support (ECMO/ECLS) therapy

e) Based on positive experiences with CytoSorb therapy in hemophagocytic lymphohistiocytosis (HLH) and the assumption that a considerable portion of critically ill COVID-19 patients might (additionally) suffer from secondary HLH the H-score might be used to detect HLH in COVID-19 patients (and therefore to consider CytoSorb therapy). See H-score calculation table in the Appendix

f) Preliminary anecdotal, verbal reports on individual cases in which CytoSorb therapy was started at an earlier stage of the disease (e.g. prior to the need for intubation), points towards a potentially quite pronounced benefit of CytoSorb therapy in this setting.

5) CytoSorb Treatment Recommendations

a) Initiation of CytoSorb therapy:

- CytoSorb should be flushed with saline and then integrated into the (C)RRT or ECMO system or run as hemoperfusion (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.
- 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:

Hydrophobic drugs may be removed by the device. Data on removal of antiviral medication is unfortunately still scarce. Results from animal studies point to very low removal of Ganciclovir, and anecdotal reports on CytoSorb therapy in influenza patients receiving Oseltamivir did not state any evidence of removal. There is no available data on the removal of Remdesivir. Removal of hydroxycholoroquine and azithromycin by CytoSorb is possible. Relevant removal of corticosteroids by CytoSorb cannot be excluded. Due to the large size of tocilizumab (148 kDa), convalescent plasma antibodies (>150 kDa), and other biologics of a similar size, these

are NOT expected to be removed by CytoSorb. The following modifications to drug dosing are recommended:

- Choosing a dosage for antiviral (or antibiotic) therapy at the upper end of the recommended range, depending on the drug and therapeutic window.
- Perform therapeutic drug monitoring wherever possible.
- Do not administer the drugs in-line with the CytoSorb device where immediate removal is possible.
- Allow time for tissue distribution and cellular uptake following antibiotic administration, where blood purification is less likely to impact on the effect of the antibiotic. This may be accomplished by administering the antibiotic during device changes, or before or after treatment. If not possible, then an alternative is to administer an additional dose of the antibiotic 1-2 hours after the start of each new CytoSorb cartridge.

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Appendix

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The Hscore[11] generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.[11] HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm^3 or less, or platelet count of 110 000 platelets per mm^3 or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

***Table*: HScore for secondary HLH, by clinical parameter**

Mehta P et al., COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 2020; epub

For the HScore calculator see http://saintantoine.aphp.fr/ score/