Bologna, 15 03 2020

Update regarding the possible use of CytoSorb as adjuvant therapy in patients with Covid-19/ novel Coronavirus (Sars-CoV-2) infections

The purpose of this document is to provide an update regarding the possible use of CytoSorb therapy as an adjuvant therapy in the treatment of some complications in patients with severe COVID-19 infection, considering the experiences that are taking place in these days and the previous information provided.

This document has an exclusively informative purpose for clinicians who decide autonomously to undertake this type of therapy.

The Italian experience of the last days in the fight against the COVID-19 virus is showing more and more patients who need hospitalization in the Intensive Care Unit, patients whose main feature is represented by an interstitial pneumonia with severe hypoxemia, associated to a compliance of the respiratory system higher than that normally typical of severe ARDS. These patients, from the news we are collecting, seem to present an incidence of further organ compromises in a lower percentage than the one expected.

However, patients where further complications occur are still present and the clinical picture could evolve to consequences, such as shock, acute renal failure and MOF (Multiple Organ Failure).

The exacerbated inflammatory response typical of the pathophysiological picture of pneumonia, which is expressed through a "**cytokine storm**", well known in literature, seems to be confirmed also in the context of COVID-19, and seems to lead to a "capillary leak syndrome", leading in the most critical patients to a state of acute respiratory failure, pulmonary edema, and can quickly evolve into a picture of ARDS (Acute Respiratory Distress Syndrome) or sepsis. [1-4]

COVID-19 patients, requiring ICU admission, need ventilatory support, through assisted artificial ventilation, and pronation cycles, while, to date, it seems that the need for extracorporeal oxygenation therapy (VV-ECMO) has rarely occurred, as initially expected.

As a consequence of the above picture, at this moment there are attempts in various Italian centres to use CytoSorb as a support therapy for the modulation of the cytokine cascade, with the aim of controlling the exacerbated inflammatory response, promoting the reversal of septic shock, if present, and hemodynamic stability and trying to accelerate the course of the ARDS.

In this regard, all of you know, thanks to the attention of the press, the experience involving Tocilizumab to reduce inflammatory cytokines in the most serious cases of complications from COVID-19.
We therefore consider useful to underline the recent experience published by Bambin Gesù Pediatric Hospital [5] where it was treated a case of severe CRS (Cytokine Release Syndrome) characterized by a progressive ARDS, following the infusion of CAR-T cells, with the synergic use of Tocilizumab and hemoperfusion with CytoSorb, with excellent results.
Beyond the results, the experience is important because it highlights how **hemoperfusion with CytoSorb does not interfere with monoclonal therapy,** contributing synergistically to the reduction of cytokines.

In addition to the previous considerations, we have received reports of an increased aggregating and coagulating activity in these patients, which could be related to high levels of D-dimer as reported by the

experience in China [3].
Therefore, the indications for the use already presented are confirmed, as shown below, advising to pay particular attention to the coagulation of the extracorporeal circuit.

Criteria / Clinical features for the use of CytoSorb therapy in patients with 2019 nCoV:

In patients with 2019 nCoV, CytoSorb Therapy should be considered in case of:

- 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, with combined indication for /running (continuous) renal replacement therapy (C)RRT or Hemoperfusion (HP), if renal support is not necessary. In this case, CytoSorb therapy should started within the first 6 to maximum 24 hrs after start of standard therapy [7-11].
- Severe respiratory distress syndrome, such as indication for prone positioning to ensure adequate oxygenation under mechanical ventilation with combined indication for /running (continuous) renal replacement therapy (C)RRT or Hemoperfusion (HP), if renal support is not necessary [5, 12].
- Indication for use of ECMO/ECLS therapy [6, 12-13].

- Experiences are ongoing to try to decrease the duration of assisted ventilation through a reduction of the inflammatory state and endothelial damage, but to date there are still no data available that can confirm this possibility.

General Indications for CytoSorb therapy

The guidelines for the use of the CytoSorb Therapy are available on the request of the clinicians, who remain the only responsible for prescribing the treatment. In addition, the support service is constantly available to discuss all the technical and usage problems.

The treatment duration of each sorbent is 24 hours. In severe cases where MOF develops, it is generally advisable to replace the first sorbent more frequently after 12 hours.
Subsequently, the replacement of the sorbent and the number of consecutive treatment cycles should be decided on the basis of the treatment type and the clinical response of the patient (e.g. degree of hemodynamic instability, lung dysfunction). In general, the treatment should continue until the clinical goals of hemodynamic stabilization, inflammatory and respiratory parameters are reached.

Anticoagulation should be effective from the start of treatment for any extracorporeal therapy. Critical patients affected by COVID-19 seem to present alterations in the coagulation status, with an increase in the coagulation activity (eg: increase D-dimer) [3], therefore, it is necessary to define an appropriate dosage of anticoagulant, to ensure acceptable levels of the main parameters, such as ACT, aPTT.

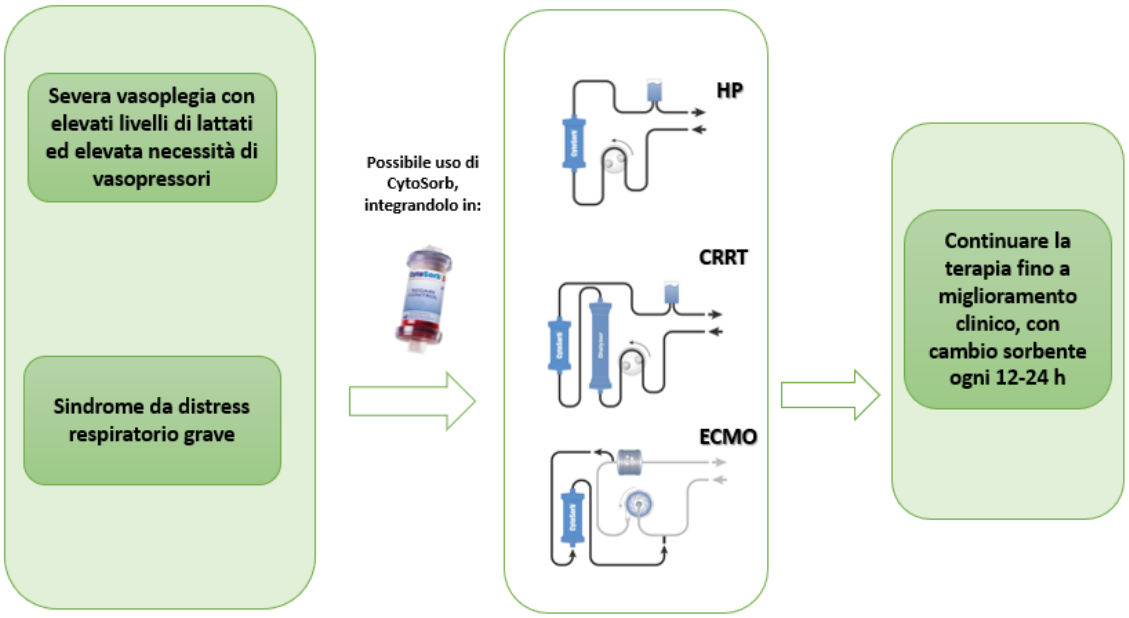
Vanno applicate le consuete controindicazioni per i circuiti ematici extracorporei e seguite le istruzioni contenute nelle IFU di CytoSorb.

The usual contraindications for extracorporeal blood circuits should be applied and the instructions contained in the CytoSorb IFU followed.

Remarks:

A further remark on the use of CytoSorb concerns data on the impact of this sorbent therapy on antibiotics and antiviral drugs. While studies on the adsorption of various types of antibiotics are available, data on plasma levels of antiviral drugs are still scarce to date. The results of animal studies indicate a low sorbent removal of Ganciclovir and anecdotal reports on CytoSorb therapy in patients with influenza treated with Oseltamivir (Tamiflu) did not state any abnormalities indicating relevant removal by CytoSorb.

In principle, however, it is always advisable to choose a dosage for antiviral and / or antibiotic therapy at the upper limit of the recommended range and to perform therapeutic drug monitoring.



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