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Second update regarding the possible use of CytoSorb as adjuvant therapy in arising complications in patients with Covid-19/Coronavirus (Sars-CoV-2) infections.

This document completes what has already been reported in previous documents and aims to provide useful information on the possible use of CytoSorb as adjuvant therapy against certain complications in patients with severe COVID-19 infection.

It has an exclusively informative and service purpose for clinicians who decide to start this type of therapy on their own.

To date, more than 65 critically ill patients with COVID-19 infection have been treated with CytoSorb as supportive therapy for cytokine cascade remodulation in various centers in China, Germany and, above all, Italy.

Although formal clinical data are not yet available due to the extraordinary circumstances, the experience of many Italian centers in recent weeks has allowed to observe encouraging positive results in more severe COVID-19 patients with severe respiratory syndromes, ARDS and/or multi-organ dysfunction, where the control of the exacerbated inflammatory response seems to have promoted the hemodynamic stabilization of patients and the improvement of respiratory parameters. The role of inflammatory cytokines is known in the pathogenesis of organ damage, also confirmed in COVID-19 [1-4]. Modulation of the "cytokine storm" seems to result in endothelial protection, which can be translated into a reduction of the "capillary leak syndrome" and, consequently, in better control of oedema formation and lung infiltration.

The experience in the most serious cases of COVID-19 complications treated in recent weeks seems to confirm the feasibility and usefulness of combined treatment with Tocilizumab, a monoclonal anti IL-6 drug, as previously highlighted in the treatment of Cytokine Release Syndrome [5], contributing synergistically to cytokine reduction. It should be noted that hemoperfusion with **CytoSorb can be used in combination with monoclonal therapy**, during or after, according to existing protocols in the centers, **without interfering with it**. Tocilizumab has, in fact, a molecular weight of 145 kDa, therefore, removal by CytoSorb is not expected and the above study [5] attests the absence of interference on the clinic.

To support the management of the treatment of COVID-19 patients and the urgent need to deal with the emergency, **the "Brescia Renal Covid Task Force" has drawn up guidelines** for the management of nephropathic patients affected by COVID-19, published by the National Society of Nephrology (SIN) and European (ERA-EDTA) [14]. In particular, given the existing rationale and the first positive findings, **the specific use of CytoSorb was recommended in patients with severe COVID-19 with AKI Stage 3** receiving continuous renal replacement therapy (CRRT) to control the cytokine cascade.

Attention is also drawn to the recent COVID-19 Prevention and Treatment Manual from Zhejiang University School of Medicine, China, which recommends blood purification for the treatment of cytokine storm in critical cases of COVID-19 infection [15].

Criteria / clinical aspects for the use of CytoSorb therapy in patients with 2019 nCoV

After highlighting again, as in previous documents, that in patients with COVID-19, **CytoSorb therapy can only be considered as adjuvant therapy** for cytokine modulation and not as primary therapy for virus removal, and that **it is in any case up to the clinicians to prescribe the treatment,** we invite you review previous documents for specific clinical indications [16,17]; an important aspect that seems to emerge from the findings concerns **the extremely precarious condition of the patients, with rapid inflammatory relapses, which suggest the need to maintain the "Cytokine Storm" containment treatments for a sufficient time**, to ensure a stabilization of the clinical condition and the maintenance of the benefits obtained with the therapy.

We would therefore stress the importance of this:

Duration of therapy

The maximum duration of treatment for each sorbent is 24 hours. In more serious cases where MOF develops, it is generally advisable to replace the first sorbent more frequently after 12 hours.
Subsequently, sorbent substitution and the number of consecutive treatment cycles should be decided by clinicians based on the type of treatment used and the clinical response of the patient (e.g. degree of hemodynamic instability, pulmonary dysfunction). **In general, especially in the most critical patients, therapy should be maintained for at least 3-4 days from the start of treatment** continuously and until the clinical goals of hemodynamic stabilization, inflammatory and respiratory parameters are maintained.

Anticoagulation

Reports of increased aggregative and coagulative activity in these patients, which may be related to high levels of D-dimer reported by work from China, remain confirmed [3]. Therefore, anticoagulation should be effective from the start of treatment for any extracorporeal therapy and can be both systemic with heparin and loco-regional with citrate.

In the most difficult cases, there are preliminary experiences of the successful **combination of regional scoagulation with citrate,** according to standard protocols in use, **and systemic scoagulation with unfractionated heparin** to avoid catheter coagulation after calcium infusion. Calcium infusion should be carried out with an appropriate dosage of anticoagulant (e.g. 15-30/UI/kg/h) to ensure acceptable levels of the reference parameters, such as ACT (200-220 sec), aPTT (>70 sec).

Clinical experiences related to coagulation have led several clinicians to prefer femoral vascular access, for safety reasons but also because of the generally higher flow rates.

Of course, we highlight again that the usual contraindications for extracorporeal blood circuits should be applied and the instructions in the CytoSorb IFUs should be followed.

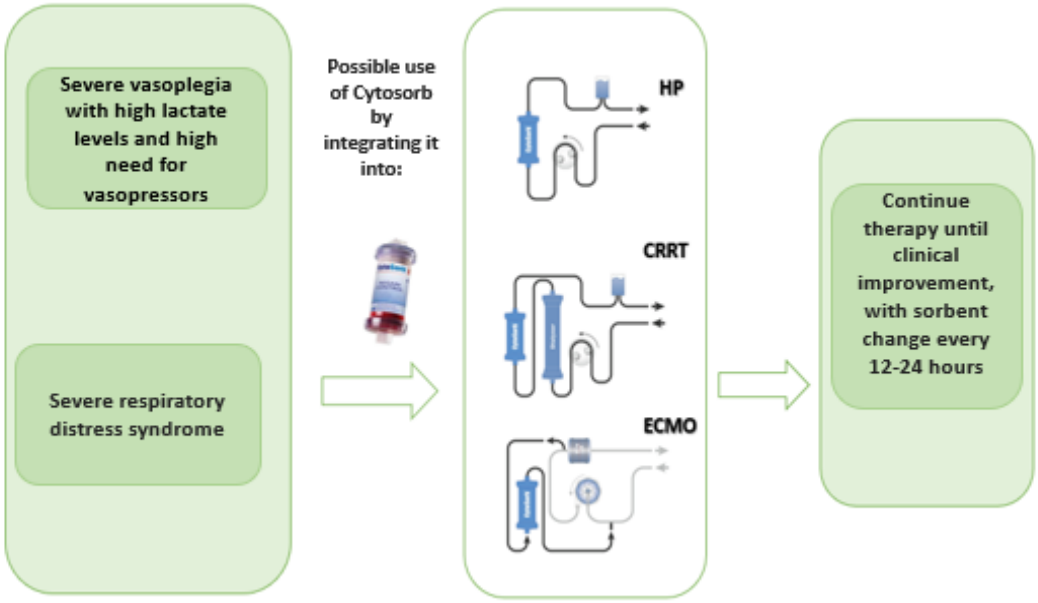
Guidelines for the use of CytoSorb sorbent are available on request from clinicians. In addition, the support service is constantly available to discuss all technical and usage issues.

Drug Interaction

We repeat what has already been reported in previous documents regarding data on the impact of CytoSorb 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, to date, still lacking.

Results from animal studies indicate low removal of Ganciclovir by sorbent and anecdotal reports of CytoSorb therapy in influenza patients treated with Oseltamivir (Tamiflu) have shown no abnormalities indicating its removal.

In principle, however, it is always advisable to choose a dosage for antiviral and/or antibiotic therapy at the upper end of the recommended range and perform therapeutic drug monitoring. If possible, drugs should not be administered directly to the dialysis catheter where direct removal may occur.



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