CYTOKINE ADSORPTION FOR TREATMENT OF COVID-19 DISEASE

An Annotated Bibliography from the Penn Medicine Center for Evidence-based Practice

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Project director: ..... Nikhil Mull, MD (CEP)
Lead analyst: ..... Matthew D. Mitchell, PhD (CEP)
Internal review: ..... Keith Hamilton, MD (Medicine); Judith O'Donnell, MD (Medicine); Naasha Talati, MD (Medicine); William Vernick (Critical Care)

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Summary

- Cytosorb (CytoSorbents, Inc.) is a cytokine adsorption device that can be inserted in an extracorporeal membrane oxygenation (ECMO) or other extracorporeal circulation system. FDA has granted Emergency Use Authorization for this device and for use of the D2000 cytokine adsorption device (Marker Therapeutics) during the COVID-19 pandemic.
- None of the clinical practice guidelines routinely searched for our COVID-19 Rapid Guidance Summary reports made recommendations regarding the use of cytokine adsorption in COVID-19 patients.
- There are two health technology assessment reports on use of cytokine adsorption devices in care of patients with COVID-19 disease. They both concluded there were no published clinical study results or guidelines relating to this indication for the technology.
- We found no published clinical studies of cytokine adsorption in COVID-19 patients and no relevant pre-publication manuscripts posted to the medRxiv server.
- Clinical studies, including open-label randomized trials in COVID-19 patients, are in progress.

** A CEP Annotated Bibliography is an expedited search for evidence and a presentation of selected articles intended to address a particular issue for Penn Medicine stakeholders. Searches are systematic but not necessarily comprehensive, and the results must not be taken as definitive. Additional studies may exist, including studies whose findings may differ from those cited in this report or identify significant limitations in their clinical applicability. Some citations may be to material supplied by drug or device manufacturers, published online, or in "grey literature." Readers should be aware that such material is not peer-reviewed, and CEP does not assess the methodological quality of studies cited in this report. The studies are informative and may provide important perspectives, but their validity and reliability has not been evaluated or confirmed. If you have specific questions about any of the studies cited here, or you wish to commission a full Evidence Review or Evidence Advisory on this or a related topic, please contact CEP.*

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Introduction

CytoSorb is an extracorporeal blood purification device marketed by CytoSorbents, Inc. (Monmouth Jct., NJ). The device is inserted in the circuit of an extracorporeal membrane oxygenation system, heart-lung machine, or other extracorporeal circulation system, where it removes cytokines from the blood. CytoSorb has been approved for sale in Europe, and the FDA granted Emergency Use Authorization on April 10 for its use in adult patients in critical care units who have COVID-19 disease and confirmed or imminent respiratory failure. Detailed indications for use are found in the FDA letter.

The purpose of this report is to identify available evidence and guidance on use of Cytosorb in COVID-19 patients. As this is an emerging technology with very little available guidance, we are reporting on it in the form of an Annotated Bibliography, in order to extend the evidence search beyond the sources usually searched in our COVID-19 Rapid Guidance Summary reports.

The NICE Medtech Information Briefing discussed below in Health technology assessment (HTA) reports identifies similar devices including D2000 Plasma Adsorption Cartridge (Marker Therapeutics AG, Switzerland) and HA330 and HA380 Haemoperfusion Cartridges (Jafron Biomedical, China). The D2000 has FDA Emergency Use Authorization; the Jafron devices do not. We have broadened the scope of this report to include those devices as well.

Previous CEP Reports

CEP has not published any previous reports on this technology.

Methods

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PROTOCOL FOR SYSTEMATIC REVIEW

SPECIFIC AIM:

Identify articles of interest relating to use of the Cytosorb cytokine adsorbent system in patients with COVID-19 disease

METHODS:

Study designs: Guidance documents issued by public health agencies, professional organizations, or hospitals and health systems, health technology assessment reports, all clinical studies.

Inclusion and exclusion criteria:

Participants: Patients with COVID-19 disease

Interventions: Cytosorb cytokine adsorbent system
NOTE: scope was expanded to include other devices of this type

Comparisons: All

Outcomes: All

Other: Published in English; January 1, 2020-present

Data collection

Databases: Medline, EMBASE, medRxiv preprint server, clinicaltrials.gov, Health Technology Assessment database, NICE, CADTH, web sites of relevant professional organizations, hospital web sites.

Study quality assessment: Not applicable

Data synthesis (calculation of relative risks and confidence intervals, meta-analyses, exploration of heterogeneity): Not applicable

Results

Public health agency and professional society guidance

None of the public health agency and professional society guideline sources routinely searched for our COVID-19 Rapid Guidance Summary reports had any recommendations relating to cytokine adsorption. The guidelines that at least mention this technology are shown in Table 1. A press release from Cytosorbents reports that there are guidelines from Italy and Panama supporting the use of their product in certain critically ill patients.

The current Surviving Sepsis guidelines (issued prior to the pandemic) discuss blood purification techniques but did not make a recommendation for or against their use because of the limited quality and quantity of evidence.

Table 1. Guidelines mentioning cytokine removal

Source	Recommendations
Australia June 4	Cytokine removal is a possible treatment for COVID-19 but there are no recommendations for or against it due to a lack of evidence.

ELSO April 10†	Currently, we lack definite evidence to recommend for or against the use of extracorporeal cytokine hemadsorption devices in COVID-19 patients who develop septic shock. Additionally, the effect of such devices on drug elimination or virus clearance is unknown.
ASAIO April 7†	We also mention emerging early experience to combine ECMO with means of modulating or removing cytokines, as yet a further extension of modalities for the sickest of patients with cytokine storm and severe cardiopulmonary compromise. [CEP note: no recommendations for or against use of the technology]

†–Estimated issue date based on citations included in guideline

Health technology assessment (HTA) reports

The National Institute for Health and Care Excellence has published a short report on cytokine adsorption devices for critical care in patients with COVID-19 (Table 2). It found that none of the published guidelines for treating respiratory failure in COVID-19 patients addressed use of this technology. The COVID-19-specific clinical evidence base is comprised of individual case reports and small cohorts of patients, most of whom have only been reported on in communications from the manufacturers of the adsorbent devices. An earlier report from the Wales HTA center found no relevant guidelines and only one clinical study report, which was still in draft form.

Table 2. Summary of health technology assessment findings

Source	Findings
NICE May 21	The evidence includes a collection of case reports and cohort studies including 56 patients with COVID-19 and respiratory failure. Most of the studies in this briefing were reported through webinars on the company websites. Each of the technologies described in this briefing have been used for alternative indications, primarily sepsis and including pneumonia, acute respiratory distress syndrome (ARDS) and flu. There is a significant amount of published evidence reporting the use of adsorbent technologies, as well as other blood purifying devices, for treating sepsis. A recent systematic review and meta-analysis summarizes the evidence for blood purifying devices for sepsis. This indicates that current evidence is of low quality and further evidence is needed before recommending the devices. An unpublished report summarizing background evidence for the use of the D2000 adsorption cartridge in 9 people with respiratory infections, flu and sepsis was submitted to NICE. The report found there were no adverse events related to using the device. There is an ongoing study using the D2000 adsorption cartridge in people with COVID-19 but currently there are no reported cases Because of the recent emergence of COVID-19 in early 2020, the evidence in this summary has not been peer reviewed and is of low methodological quality, but there are ongoing higher-quality studies. The evidence primarily reports the effect of adsorption devices on blood levels of cytokines and lung function but there are limited data about the effect of the treatment on rates of patient recovery and mortality. Well-designed comparative studies are needed to establish whether adsorption devices decrease mortality rates.
Wales April 2020	Evidence on the use of cytokine adsorbers specifically in COVID-19 is available from a single prospective non-randomized cohort study of 47 patients in China. This trial used the Jafron device and we are not aware of evidence on the use of any other similar devices in COVID-19 cases. Results of this study suggest that in critically ill patients with COVID-19, hemoadsorption-type hemoperfusion can improve outcomes including cytokine clearance, oxygen supply, mortality and requirement for ventilation/ICU treatment. We identified one ongoing randomized trial on cytokine adsorption in people with COVID-19, which is due to complete in October 2020. The effectiveness of cytokine adsorbers compared to existing treatment options has been most widely studied in people with sepsis, along with some evidence on their effectiveness in acute lung injury and cardiac surgery. The generalizability of this evidence to COVID-19 is not known.

Additional health technology assessment reports on the Cytosorb system and similar devices were published prior to the COVID-19 pandemic. Please see citations below.

1. Hawlik K, Wild C. Extracorporeal cytokine haemadsorption therapy in patients with sepsis or SIRS, Decision Support Document No.106; 2017. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment. http://eprints.aihta.at/1129/

2. National Institute for Health and Care Excellence. Medtech innovation briefing 87: CytoSorb therapy for sepsis. November 2016. http://nice.org.uk/guidance/mib87

Hospital and health system guidance

The only hospital or health system guidance document to mention cytokine adsorption was from Yale-New Haven Health System. It did not provide any guidance on when or how to use the technology.

Table 3. Hospital and health system guidance mentioning cytokine removal

Source	Recommendations
Yale May 27	Cytokine adsorption via ECMO circuit is a potential adjunctive therapy in patients with refractory respiratory failure requiring ECMO. Specific device, patient selection criteria, and methods not specified.

Peer-reviewed literature

We found 4 review/commentary articles regarding cytokine adsorption in COVID-19 patients, and no articles reporting results of clinical studies.

1. Al Shareef K, Bakouri M. Cytokine Blood Filtration Responses in COVID-19. Blood Purif. 2020:1-9. https://doi.org/10.1159/000508278

Abstract: The real issue with the COVID-19 pandemic is that a rapidly increasing number of patients with life-threatening complications are admitted in hospitals and are not well-administered. Although a limited number of patients use the intensive care unit (ICU), they consume medical resources, safety equipment, and enormous equipment with little possibility of rapid recovery and ICU discharge. This work reviews effective methods of using filtration devices in treatment to reduce the level of various inflammatory mediators and discharge patients from the ICU faster. Extracorporeal technologies have been reviewed as a medical approach to absorb cytokines. Although these devices do not kill or remove the virus, they are a promising solution for treating patients and their faster removal from the ICU, thus relieving the bottleneck

2. Berhes M, Fabian A, Laszlo I, Vegh T, Molnar C, Fulesdi B, et al. [Organ replacement therapy and life-supporting treatment modalities in critically ill COVID-19 patients]. Orv Hetil. 2020;161(17):704-9. [published in Hungarian] https://doi.org/10.1556/650.2020.31813

Abstract: In critically ill COVID-19 patients, the failure of the cardiorespiratory system can be due to one of the following: (1) cytokine storm, haemophagocytosis - septic shock, (2) unmanageable hypoxemia, (3) isolated organ failure or as part of multi-organ failure. Herein we give an overview of the therapeutic options for treating or preventing these disease states. In recent years, CytoSorb-haemoperfusion to remove cytokines has shown promising results in the treatment of septic shock. Inhalational nitric oxide (iNO), inhalational epoprostenol and veno-venous extracorporeal membrane oxygenation (ECMO) are options in severe hypoxemia that is unresponsive to conventional mechanical ventilation. Renal failure is a frequent component of the multi-organ failure usually seen with disease progression and necessitates starting one of the available continuous renal replacement modalities.

3. Chen G, Zhou Y, Ma J, Xia P, Qin Y, Li X. Is there a role for blood purification therapies targeting cytokine storm syndrome in critically severe COVID-19 patients? Ren Fail. 2020;42(1):483-8 https://dx.doi.org/10.1080/0886022X.2020.1764369

Abstract: The coronavirus disease-19 (COVID-19) has spread over many countries and regions since the end of 2019, becoming the most severe public health event at present. Most of the critical cases developed multiple organ dysfunction, including acute kidney injury (AKI). Cytokine storm syndrome (CSS) may complicate the process of severe COVID-19 patients. This manuscript reviews the different aspects of blood purification in critically ill patients with AKI and increased inflammatory factors, and examines its potential role in severe COVID-19 treatment. Continuous renal replacement therapy (CRRT) has been practiced in many sepsis patients with AKI. Still, the timing and dosing need further robust evidence. In addition to the traditional CRRT, the high-throughput membrane with adsorption function and cytokine adsorption column are two representatives of recently emerging novel membrane technologies. Their potential in removing inflammatory factors and other toxins prospects for the treatment of severe COVID-19.

4. Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. COVID-19 in the heart and the lungs: could we "notch" the inflammatory storm? [editorial] Basic Res Cardiol. 2020;115(3). https://doi.org/10.1007/s00395-020-0791-5

Abstract: From January 2020, coronavirus disease (COVID-19) originated in China has spread around the world. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The presence of myocarditis, cardiac arrest, and acute heart failure in COVID-19 patients suggests the existence of a relationship between SARS-CoV-2 infection and cardiac disease. The Notch signalling is a major regulator of cardiovascular function and it is also implicated in several biological processes mediating viral infections. In this report we discuss the possibility to target Notch signalling to prevent SARS-CoV-2 infection and interfere with the progression of COVID-19- associated heart and lungs disease.

5. Adapa, S, Aeddula, N, Konala, V, Chenna, A, Naramala, S, Madhira, B, Gayam, V, Balla, M, Muppidi, V, Bose, S. 2020 May 8. COVID-19 and renal failure: challenges in the delivery of renal replacement therapy. J Clin Med Res. [Online] 12:5 https://doi.org/10.14740/jocmr4160

Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first officially reported in December 2019 in Wuhan City, Hubei province, China, and has since lead to a pandemic. Most cases result in minor symptoms such as cough, fever, sore throat, myalgia, fatigue, nausea, diarrhea, loss of smell, and abdominal pain. As of April 8, 2020, more than 1,485,000 cases of COVID-19 have been reported in more than 200 countries and territories, resulting in over 90,000 deaths. Outcomes are worse in elderly patients, particularly males, and those with comorbidities, but can affect any age group. The incidence of acute kidney injury in patients with COVID-19 infection is about 3-15%; and in patients with severe infection requiring care in the intensive care unit, the rates of acute kidney injury increased significantly from 15% to 50%. Acute kidney injury is an independent risk factor for mortality in COVID-19 patients. The nephrologists, as well as intensivists, are facing immense daily challenges while providing care for these patients in the inpatient setting as well as end-stage renal disease patients on chronic dialysis in both inpatient and outpatient settings. In the current review article, we discussed the epidemiology and etiology of acute kidney injury, management of acute kidney injury including renal replacement therapy options (both hemodialysis and peritoneal dialysis) for inpatient floor, as well as intensive care unit settings. We also discussed the challenges faced by the outpatient dialysis units with COVID-19 infection. We discussed measures required to limit the spread of infection, as well as summarized the guidance as

per the Centers for Disease Control and Prevention (CDC), American Society of Nephrology (ASN), American Society of Diagnostic and Interventional Nephrology (ASDIN) and the Vascular Access Society of the Americas (VASA).

6. Alberici F, Delbarba E, Manenti C, et al., on behalf of the Brescia Renal COVID Task Force. Management of patients on dialysis and with kidney transplantation during the SARS-CoV-2 (COVID-19) pandemic in Brescia, Italy. KI Reports 2020, 5(5)580-85 https://doi.org/10.1016/j.ekir.2020.04.001

Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease (COVID-19), is a major pandemic challenging health care systems around the world. The optimal management of patients infected with COVID-19 is still unclear, although the consensus is moving toward the need of a biphasic approach. During the first phase of the disease (from onset of the symptoms up to 7–10 days) viral-induced effects are prominent, with the opportunity to institute antiviral therapy. In the second inflammatory phase of the disease, immunosuppressive strategies (for example with glucocorticoids or anticytokine drugs) may be considered. This latter stage is characterized by the development of progressive lung involvement with increasing oxygen requirements and occasionally signs of the hemophagocytic syndrome. The management of the disease in patients with kidney disease is even more challenging, especially in those who are immunosuppressed or with severe comorbidities. Here we present the therapeutic approach used in Brescia (Italy) for managing patients infected with COVID-19 who underwent kidney transplantation and are receiving hemodialysis. Furthermore, we provide some clinical and physiopathological background, as well as preliminary outcome data of our cohort, to better clarify the pathogenesis of the disease and clinical management.

CEP NOTE: This may represent the guideline referred to by the manufacturer of Cytosorb. The authors present a proposed management plan including Cytosorb for dialysis and transplant patients with COVID-19 disease.

7. Ronco C, Navalesi P, Vincent JL. Coronavirus epidemic: preparing for extracorporeal organ support in intensive care. Lancet Respir Med 2020, 8(3);240-41. https://doi.org/10.1016/S2213-2600(20)30060-6

No abstract.

CEP NOTE: Authors suggest that new extracorporeal support therapies including haemoadsorption and haemoperfusion, with new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered in patients with sepsis-like syndrome.

8. Ronco C, Reis T, Husain-Syed F. Coronavirus epidemic: preparing for extracorporeal organ support in intensive care. Lancet Respir Med 2020 [online]. https://doi.org/10.1016/S2213-2600(20)30229-0

SUMMARY: The outbreak of coronavirus disease 2019 (COVID-19) has rapidly evolved into a global pandemic. Most patients with COVID-19 have mild symptoms, but about 5% develop severe symptoms, which can include acute respiratory distress syndrome, septic shock, and multiple organ failure. Kidney involvement is frequent, with clinical presentation ranging from mild proteinuria to progressive acute kidney injury (AKI) necessitating renal replacement therapy (RRT). An understanding of the pathophysiology and mechanisms of kidney damage and AKI in the setting of critical illness and COVID-19 is emerging, although further research is needed to identify patients at risk of AKI and to guide management strategies. As no specific treatment options exist for AKI secondary to COVID-19, intensive care is largely supportive. Current approaches to prevention and management of AKI, and

identification of potential indications for use of RRT and sequential extracorporeal therapies, are based mainly on clinical experience, and AKI strategies are adapted empirically to patients with COVID-19. International collaborative and cross-disciplinary research is needed to obtain adequate evidence to support current clinical approaches and to develop new approaches to management.

Unpublished literature

No relevant unpublished manuscripts were found.

Studies in progress

Studies from the National Library of Medicine clinical trials registry are listed in the table below. Additional studies were identified from manufacturer web sites.

Table 4. Registered clinical trials for patients with COVID-19 disease

Trial Design	Patients	Intervention Comparison	Status As of
NCT04324528 RCT (open label) Germany	Patients receiving vv-ECMO therapy	ECMO with CytoSorb ECMO without	Recruiting March 31
NCT04344080 RCT (open label) Germany	Refractory shock, IL6 ≥ 500 ng/l, and indication for ECMO or CRRT	CytoSorb Usual care	Recruiting April 14
NCT04358003 † Cohort	Acute lung injury, ARDS, severe disease, respiratory failure, septic shock, or multiple organ dysfunction	D2000 no control arm	Recruiting June 4
NCT04361526 RCT (open label) Spain	Moderate to severe ARDS with onset in previous 36 hours, inflammatory markers: CRP > 10 mg/l	CytoSorb Usual care	Recruiting April 24
NCT04385771 RCT (open label) Germany	Patients receiving vv-ECMO therapy	ECMO with CytoSorb ECMO without	Not yet recruiting May 14
NCT04391920 † Registry	All COVID-19 patients receiving CytoSorb therapy	CytoSorb no control arm	Not yet recruiting May 18
DRKS00021447 Germany	Age 18-80, in vasoplegic shock, CRP > 100 mg/l, PCT < 2 ng/l	CytoSorb Usual care	Recruiting April 27

If location is not specified, study is multi-center with one or more US centers

†–manufacturer-sponsored trial

Appendix. Literature Searches

Searches were completed on June 6-8 and updated on June 12. Additional literature was identified from manufacturer web sites.

Table 5. Medline search

Search	Syntax	Hits	Retrieved	Included
1	cytosorb.mp.	112	—	—
2	(cytokine* adj3 (adsorb* or absorb*)).mp.	94	—	—
3	1 or 2	194	—	—
4	limit 3 to yr="2020 -Current"	29	—	—
5	(COVID* or SARS* or coronavirus).mp.	42,959	—	—
6	3 and 5	3	—	—
7	4 or 6	30	—	—
	exclude 1 duplicate reference within set	29	3	3

mp: keyword (title, abstract, subject heading)

Table 6. EMBASE search

Search	Syntax	Hits	Retrieved	Included
1	cytosorb	260	—	—
2	cytokine* NEAR/3 (adsorb* OR absorb*)	151	—	—
3	#1 OR #2	374	—	—
4	#3 AND 2020:py	36	—	—
5	covid* OR sars* OR coronavirus	53,878	—	—
6	#3 AND #5	4	—	—
7	#4 OR #6	36	—	—
	exclude 1 duplicate reference within set and 25 references duplicating Medline results	10	1	1

Table 7. medRxiv (unpublished manuscript) search

Database	Keywords or syntax	Hits	Retrieved	Included
medRxiv	cytokine and adsorption	6	0	0
	Cytosorb	4	0	0
	D2000	14	0	0
	HA330 or HA380	2	0	0

Searches limited to post dates 01/01/2020 to present

Table 8. Clinical trial search

Database	Keywords or syntax	Hits	Retrieved	Included
Clinicaltrials.gov	cytokine and adsorption	5	3	3
	Cytosorb	8	3	3
	D2000	1	1	1
	HA330 or HA380	0	0	0

Searches limited to study start 01/01/2020 to present

†-one additional trial duplicated results from previous search

Health technology assessment sources searched

Please contact CEP for details of these searches

- ECRI Institute
- Canadian Agency for Drugs and Technology in Health (CADTH)
- NICE Evidence Search
- International Network of Agencies for Health Technology Assessment (INAHTA, pre-release version)