Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Cytokine adsorbers for the treatment of cytokine storm in people with severe coronavirus infection
Topic exploration report number:	TER201

Introduction and aims

Evidence suggests that a subgroup of people with severe coronavirus disease (COVID-19) might have cytokine storm syndrome, where excessive or uncontrolled levels of cytokines are released, resulting in hyperinflammation. Elevated cytokine levels can lead to systemic inflammatory response syndrome and acute respiratory distress syndrome, which can result in refractory hypotension, severe hyperlactatemia, multi-organ failure and mortality. Reducing cytokine levels may help to control the excessive inflammatory response and possibly avoid complications.

The haemoperfusion adsorption device is an extracorporeal technique involving the passage of blood or plasma through a cartridge, where solutes are removed by direct binding to sorbent beads. The cartridges have the ability to remove pro-inflammatory cytokines in cytokine storm, and other cellular inflammatory markers, as blood passes through the device.

We identified three cytokine adsorption devices: D2000 plasma adsorption cartridge and Spectra apheresis system, CytoSorb adsorbent cartridge, and the Jafron HA330 and HA380 haemoperfusion cartridges. The technology developer states that the Jafron haemoadsorption cartridge can be used in:

- patients unresponsive to vasopressor support after fluid resuscitation;
- hyperlactatemia not responding to standard of care;
- COVID-19 rescue therapy;
- patients unresponsive to standard of care who have multiple organ failure;
- patients exhibiting signs of damage-associated molecular patterns (DAMPS) or pathogen-associated molecular patterns (PAMPS);
- intra-operative cardiac surgery where the patient already has significant pre-existing cellular inflammatory activation caused by heart failure or where a ventricular assist device has been implanted, etc.;
- patients requiring long pump procedures such as heart or lung transplant, and other procedures;
- respiratory failure;
- conjunctive therapy with extracorporeal membrane oxygenation.

According to the technology developer, the Jafron haemoadsorption cartridge can be used as a stand-alone device or in conjunction with other extracorporeal therapies, and should be given to COVID-19 patients as a regime of 2+1+1 (two units utilised for 12 hours in the first 24 hours, and one unit per day utilised for 24 hours in the following two days) as opposed to the usual regimen in other conditions of one device per day for one to two days.

Health Technology Wales researchers searched for evidence on the Jafron device or other haemoperfusion adsorption cartridges for the treatment of cytokine storm, particularly in people with COVID-19.

Since original publication of this Topic Exploration Report (TER) in April 2020, the National Institute for Health and Care Excellence (NICE) produced a Medtech Innovation Briefing (MIB) on cytokine adsorption devices for treating respiratory failure in people with COVID-19 (MIB217. 21 May 2020). In July 2020, we updated this TER to include the additional new evidence published in MIB217 and searched for any recently published high-quality evidence on the use of cytokine adsorbers in COVID-19.

Summary of evidence

Secondary evidence

Guidance

We did not identify any national guidelines on the management of cytokine storm with adsorption devices. However, The Brescia Renal COVID Task Force In Italy have specifically recommended use of CytoSorb in severe COVID-19 patients with Stage 3 acute kidney injury requiring continuous renal replacement therapy, and this recommendation was subsequently published by The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) (Alberic et al. 2020). It should be noted that the evidence used to inform these recommendations is not clear. CytoSorb is another CE-mark approved Class IIb medical device, which became available in 2011. It consists of a haemoadsorption cartridge and is an extracorporeal blood purification device that can be used to lower cytokine levels in the blood.

In May 2020, NICE produced a MIB on cytokine adsorption devices for treating respiratory failure in people with COVID-19. The MIB signposted to this TER and included additional evidence made available since publication of the TER (MIB217. 2020).

We identified a NICE MIB for CytoSorb therapy for sepsis, published in 2016. NICE MIB87 states that the intended place in therapy would be as an addition to standard treatments for people with sepsis or septic shock. NICE suggests that, whilst CytoSorb has the potential to control the excessive inflammatory response and reduce complications, there is little evidence on key outcomes for CytoSorb therapy compared with standard of care.

Systematic reviews

We did not identify any systematic reviews specifically for cytokine adsorbers in patients with COVID-19. However, we identified two systematic reviews studying the adsorption of cytokines using these devices in other conditions.

Two systematic reviews and meta-analyses of randomised controlled trials (RCTs) studied the association between various blood purification techniques and mortality in people with sepsis. Both reviews included a range of haemoperfusion and haemofiltration techniques. Only one of the RCTs included in one of the systematic reviews (Zhou et al. 2013), and only seven out of

37 studies in the other systematic review (Putzu et al. 2019) included haemoperfusion cartridges that removed cytokines. Both reviews suggested blood purification techniques may reduce overall mortality from sepsis. However, in both reviews, only haemoperfusion with devices that remove endotoxins was associated with improvements in mortality compared to conventional therapy. The results should be interpreted with caution due to reliability of the evidence (authors of both reviews highlighted the relatively low quality of the included trials), and the unclear generalisability of the evidence to COVID-19.

Primary evidence

The technology developer provided an unpublished draft manuscript: a Chinese prospective cohort study investigating extracorporeal blood purification therapy using haemoadsorption-type haemoperfusion in critically ill people with COVID-19. A total of 47 patients with severe COVID-19 were included: 26 people (55·3%) received haemoadsorption treatment. At 72 hours, serum cytokines were decreased. The oxygen supply in the haemoadsorption group improved, with a significant increase in the ratio of arterial oxygen partial pressure to fractional inspired oxygen compared with that in the control group (who received conventional treatment). The mortality at day 28 in the haemoadsorption group was significantly lower than that in the control group (15·38% and 47·62%, respectively; $p < 0·05$) and was concurrent with significantly longer intensive care unit (ICU)-free days compared with that in the control group (6·5 days and 2.0 days, respectively; $p < 0·01$) (Liang et al. 2020). At the time of updating the TER, we were not able to find a published version of this study.

We also identified two randomised trials on haemoadsorption devices published more recently than the systematic reviews described above, and a further two trials in other conditions: one in acute lung injury and one in people having cardiac surgery. These are described in the Brief Literature Results section.

Most of the evidence in NICE MIB217 comes from a collection of unpublished, non-peer-reviewed case reports and cohort studies including 56 patients with COVID-19 and respiratory failure who were treated with either the CytoSorb adsorption cartridge, or Jafron HA330 and HA380 haemoperfusion adsorption cartridges. Most of the studies were reported through webinars on the company websites. One of these studies was a non-randomised, comparative, single-arm, observational study where CytoSorb was used in 10 patients with COVID-19 and severe acute respiratory distress syndrome in China. Levels of IL-6 and lactate were reduced, and lung function improved, after CytoSorb therapy compared with pre-treatment levels (Peng 2020. Evidence summary in CytoSorb webinar).

Economic evaluations

No studies were identified that measured the economic impact of using cytokine adsorbers in any condition. NICE MIB217 (2020) states that the cost of a Jafron HA330 and HA380 cartridge is £450 (excluding VAT), the cost of a CytoSorb cartridge is £920 (excluding VAT), and the cost of a D2000 cartridge is £1,785 (excluding VAT). Extracorporeal machines cost between £10,000 to £40,000, and the cost of the Spectra Optia Apheresis System (used with the D2000 cartridge) is £58,338.31 per unit (excluding VAT), with an additional £4,083 annual service charge. The MIB states that it is expected that most hospitals will already have access to the appropriate machines. In their briefing, NICE concluded that the resource impact would be greater than standard care because the technology is intended to be used in addition to standard care.

Ongoing evidence collection

We identified three relevant ongoing trials. One of these studies is a RCT investigating the influence of extracorporeal cytokine adsorption, using a cytokine adsorber, on humoral inflammation parameters and patient survival in people with severe COVID-19 pneumonia. (ClinicalTrials.gov Identifier: NCT04324528). One of the studies is an observational trial to determine the specific population of critically ill septic patients who benefit most from cytokine adsorption therapy with the HA-380 cartridge (ClinicalTrials.gov Identifier: NCT04306419). The other is patient registry study in Germany, Austria and Switzerland to record the use of CytoSorb under real life conditions in as many different clinical cases as possible (ClinicalTrials.gov identifier: NCT02312024).

Areas of uncertainty

Although systematic reviews of RCTs have been published on the use of cytokine adsorbers in certain conditions, evidence for their use in the treatment of cytokine storm in patients with COVID-19 is much more limited and it is unclear whether existing evidence from other conditions is generalisable to COVID-19. We did not identify any RCTs on the use of cytokine adsorbers specifically in children. Limited evidence on the economic impact of using cytokine adsorbers was identified.

Conclusions

The majority of the evidence on the use of cytokine adsorbers specifically in COVID-19 is available from a number of small cohort studies and case reports. Results of these studies suggest that in critically ill patients with COVID-19, haemoadsorption-type haemoperfusion can improve outcomes including cytokine clearance, oxygen supply, mortality and requirement for ventilation/ICU treatment. We identified one ongoing randomised 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 generalisability of this evidence to COVID-19 is not known.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant publications from this source
Health Technology Assessment Group	We did not identify any relevant evidence from this source
Health Information and Quality Authority	We did not identify any relevant evidence from this source
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source
NICE	We identified the following advice for use in COVID-19: • Medtech Innovation briefing (MIB 217). Cytokine adsorption devices for treating respiratory failure in people with COVID-19. Published May 2020: https://www.nice.org.uk/advice/mib217 We identified the following advice on the cytokine adsorber for the treatment of people with sepsis: • MIB87: CytoSorb therapy for sepsis. Published November 2016. https://www.nice.org.uk/advice/mib87
European guidelines and guidance	
ERA-EDTA	Alberici F, Delbarba E , Manenti C, Econimo L, et al. (2020). Management of patients on dialysis and with kidney transplant during COVID-19 coronavirus infection. https://www.era-edta.org/en/wp-content/uploads/2020/03/COVID_guidelines_finale_eng-GB.pdf
Secondary literature and economic evaluations	
ECRI	We did not identify any relevant evidence from this source
EUnetHTA	We did not identify any relevant publications from this source
Cochrane library	We did not identify any relevant evidence from this source
Medline (Ovid)	Putzu A; Schorer R; Lopez-Delgado JC; Cassina T; Landoni G.(2019). Blood Purification and Mortality in Sepsis and Septic Shock: A Systematic Review and Meta-analysis of Randomized Trials. Anesthesiology. 131(3):580-593. doi: 10.1097/aln.0000000000002820 Zhou F, Peng Z, Murugan R, et al. (2013). Blood Purification and Mortality in sepsis: A Meta-analysis of Randomized Trials. Critical Care Medicine. 41(9): 2209-2220. doi: 10.1097/CCM.0b013e31828cf412

Primary studies	
Cochrane library	We did not identify any additional relevant evidence from this source
Medline	Hawchar F, Laszlo I, Oveges N, et al. (2019). Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study. Journal of Critical Care. 49:172-178. https://doi.org/10.1016/j.jcrc.2018.11.003 *Used the CytoSorb device compared to control treatment. Significant improvement in clinical outcomes, norepinephrine requirements, procalcitonin and Big-endothelin-1 concentrations compared to controls.* Poli EC, Alberio L, Bauer-Doerries A, et al. (2019). Cytokine clearance with CytoSorb R during cardiac surgery: a pilot randomized controlled trial. Critical Care (London, England). 23(1):108. doi: https://doi.org/10.1186/s13054-019-2399-4 *Used the CytoSorb device compared to control treatment. Did not show a reduction in inflammatory cytokines or relevant clinical outcomes.* Schadler D, Pausch C, Heise D, et al. (2017). The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. PLoS ONE [Electronic Resource]. 12(10):e0187015. doi: 10.1371/journal.pone.0187015 *Used the CytoSorb device compared to control treatment. Measured IL-6 plasma levels as primary outcome, but did find any significant difference between groups for this, or for secondary outcomes.*
Other (CytoSorb website)	Peng. 2020. Evidence summary in CytoSorb webinar: https://cytosorb-therapy.com/en/covid-19/
Ongoing primary or secondary research	
PROSPERO database	We did not identify any relevant evidence from this source
Clinicaltrials.gov	Cytokine adsorption in severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV_ECMO). Randomised controlled trial of 30 participants investigating the influence of extracorporeal cytokine adsorption, using a CytoSorb adsorber, on humoral inflammation parameters and patient survival. Not yet recruiting. Estimated primary completion date: 1 October 2020. ClinicalTrials.gov Identifier: NCT04324528 Observational Trial on Cytokine Adsorption in Sepsis. A study of 100 participants to determine the specific population of critically ill septic patients who benefit most from cytokine adsorption therapy with the HA-380 cartridge. Not yet recruiting. Estimated primary completion date: February 28, 2022. ClinicalTrials.gov Identifier: NCT04306419 International registry on the use of the CytoSorb Adsorber in ICU patients. Observational patient registry study of 3,000 patients with the aim of recording the use of CytoSorb under real life conditions in as many cases as possible. All CytoSorb applications in different clinical settings and in all patients who are treated with this

	technology in Germany, Austria and Switzerland are planned to be included. Currently recruiting. Estimated primary completion date: December 2020. ClinicalTrials.gov identifier: NCT02312024
Other	
Evidence provided by the technology developer	Huang Z, Wang SR, Yang ZL, Liu JY. Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. (2013) Therapeutic Apheresis and Dialysis. 17(4):454–61. doi: https://doi.org/10.1111/j.1744-9987.2012.01083.x *Compared the Jafron device to standard therapy. Duration of mechanical ventilation, duration of continuous renal replacement therapy, mortality and length of ICU stay were all improved in those who received haemoperfusion treatment.* Liang Y, Zhu M, Zhang Y, et al. (2020). Draft Manuscript. Extracorporeal blood purification therapy using haemoadsorption type haemoperfusion improves ICU outcomes in critically ill patients with SARS-CoV-2 infection: a prospective cohort study

Date of search:	March 2020 (updated July 2020)
Concepts used:	Haemoperfusion; hemoperfusion; haemoadsorption; haemoadsorption; blood purification; cytokine adsorber; CytoSorb; HA330; HA380; cytokine storm; COVID-19; coronavirus; systemic inflammatory response syndrome; respiratory distress syndrome; hypotension; hyperlactatemia