NICE advice

CytoSorb therapy for sepsis

Medtech innovation briefing
Published: 29 November 2016

www.nice.org.uk/guidance/mib87

Summary

- The **technology** described in this briefing is CytoSorb therapy. It is an extracorporeal blood purification device that can be used to lower cytokine levels in the blood.
- The **innovative aspects** are that it is the only CE-marked device designed to lower excessive cytokines, which has the potential to control the excessive inflammatory response and reduce complications.
- The intended **place in therapy** would be as an addition to standard treatments, which may include renal replacement therapy, for people with sepsis or septic shock.
- The **key points from the evidence** summarised in this briefing are from 5 studies (1 randomised controlled trial and 4 case series, n=92 in total). The trial reported no differences in mortality between CytoSorb therapy and standard care; but it was not powered to detect this. The quality of this evidence is unclear because the 5 studies were published as abstracts only.
- **Key uncertainties** are that there is little evidence on key outcomes for CytoSorb therapy compared with standard care. Also the generalisability of the available evidence to NHS clinical practice is unclear.

- The **cost** of the CytoSorb device is £920 per single-use unit (excluding VAT). The main **resource impact on the NHS** would be the costs of the technology in addition to standard care.

The technology

CytoSorb (LINC Medical) therapy is designed to reduce the levels of cytokines in the blood. The body can produce excessive levels of cytokines as part of the inflammatory response to severe infection (sometimes referred to as a 'cytokine storm') and this can contribute to toxicity, sepsis and septic shock.

CytoSorb consists of a single-use haemadsorption cartridge for use with standard blood pumps, such as dialysis machines. The CytoSorb cartridge, or adsorber, is filled with sorbent beads made from a porous polymer, which adsorb and capture cytokines as blood passes through the device. The adsorption of cytokines is concentration-dependent and so the higher the levels of cytokines in the blood, the faster the levels are reduced.

Blood is continuously recirculated between the adsorber and the patient for up to 24 hours before the cartridge is replaced. CytoSorb adsorbers can be replaced daily for up to 7 days of continuous use. Patients typically have CytoSorb therapy for 48 to 72 hours.

CytoSorb therapy is designed for treating sepsis and septic shock. It can be used for other indications in which cytokine levels are raised, such as during or after cardiac surgery, during extracorporeal membrane oxygenation procedures, in liver failure, and in people with burns, but these indications are outside the scope for this briefing.

The innovation

Although the principle is not new, CytoSorb is the only currently available CE-marked device to lower excessive cytokines in people with sepsis. Standard therapy does not directly target raised cytokine levels, which are associated with severe sepsis. Elevated cytokine levels can lead to several pathophysiologic changes that increase morbidity and mortality (Kellum 2007), such as peripheral vasodilation, hypotension, tachycardia, restriction of blood flow, and disseminated intravascular coagulation. Reducing cytokine levels may help to control the excessive inflammatory response and possibly avoid complications.

Current NHS pathway

Each year, about 123,000 people in England are diagnosed with sepsis and there are around 37,000 deaths (NHS England 2015). Severe sepsis can develop within hours and close monitoring and therapeutic support are needed to improve the chance of survival.

NICE's guideline on sepsis makes recommendations on the recognition, diagnosis and early management of the condition. Early treatments include intravenous fluids, oxygen therapy, antibiotics, steroids, vasopressors (to increase blood pressure) and inotropic therapy (to support cardiac function). Additional treatments may include sedation, mechanical ventilation and renal replacement therapy or blood purification, such as dialysis (Zhou 2013). Severe sepsis is usually managed in an intensive care setting where organ function can be monitored and supported (Dellinger 2013).

NHS England's action plan (2015) also summarises essential actions that health and care organisations need to take to improve the outcomes for people with sepsis. These actions aim to prevent avoidable cases of sepsis, increase awareness of sepsis, improve identification, treatment, and consistency in reporting of sepsis, and maintain the appropriate use of antibiotics.

NICE is not aware of other CE-marked devices that appear to fulfil a similar function to CytoSorb.

Population, setting and intended user

CytoSorb therapy could be used to treat severe sepsis and excessive levels of cytokines, and would be used alongside standard care, which may include renal replacement therapy in intensive care settings. The therapy would be given by anaesthetists, intensivists and nursing staff who have been trained in its use.

The UK distributor (LINC Medical) provides training in the form of set-up demonstrations, dummy devices on which to practise set up, booklets, videos, and telephone support. A representative from LINC Medical can be present when CytoSorb therapy is given to the first patient (and others after this if needed), depending on the where the patient is in relation to the distributor and the urgency of the treatment.

Costs

Device costs

The list price of the single-use CytoSorb cartridge is £920 per unit excluding VAT, which includes bloodline sets and standard delivery to the centre. Urgent courier delivery may be arranged at additional cost. There are no additional costs for accessories or consumables.

Pressure monitoring of the bloodline between the blood pump and the CytoSorb device is recommended. This is done with the standard safety equipment of the pump systems, with which CytoSorb is usually used, and which also include air detection and blood detection. If the pump system is not equipped with a pressure-sensing device for this line, use of an accessory pressure monitoring device is recommended.

Costs of standard care

In 2014 to 2015, the NHS reference costs of septic shock were £1,415 to £2,107, and for sepsis with multiple interventions this was £6,424 to £9,673.

Resource consequences

CytoSorb therapy has been used to treat about 20 patients across 7 NHS Trusts.

If adopted, CytoSorb would be used with existing blood pumps and significant changes to current facilities or infrastructure are unlikely to be needed. Therapeutic drug monitoring of certain antibiotics is recommended. This will be an additional cost if it is not part of standard care, but therapeutic drug monitoring may already be done during renal replacement therapy in some trusts. The cost of CytoSorb would be in addition to standard care, but any technology which improves outcomes in severe sepsis could save other NHS resources.

Regulatory information

CytoSorb was CE marked as a class IIb device in March 2011. It is made by CytoSorbents USA and distributed in the UK by Linc Medical.

The Medicines and Healthcare Products Regulatory Agency issued 1 manufacturer Field Safety Notice in 2015, containing advice about a potential incompatibility between the device and nitrous oxide, an inhaled anaesthetic gas. It states that CytoSorb should not be used in combination with nitrous oxide under any circumstances. No Medical Device Alerts were found for this device.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No equality considerations were identified.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant or best publicly-available evidence relating to the clinical and cost effectiveness of the technology. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting mibs@nice.org.uk.

Published evidence

Five studies including a total of 92 patients are summarised in this briefing. These comprise 1 randomised controlled trial (RCT) and 4 case series. The RCT compared CytoSorb therapy with standard care in 43 patients and found no differences in mortality at 28 days or 60 days. In the case series, survival ranged from 21% to 75% and these studies found that survival was better when CytoSorb therapy was started early. No serious device-related adverse events occurred during the RCT. None of the case series reported findings relating to adverse events.

Table 1 summarises the clinical evidence as well as its strengths and limitations. There are several ongoing studies.

Strengths and limitations of the evidence

The evidence from the single RCT comparing CytoSorb therapy with standard care is currently only available in abstract form so the quality of the study could not be assessed. There are limited details of the included patients and the generalisability of the results of the studies is unclear. The RCT was small and was not powered to show differences in mortality. The RCT was funded by the manufacturer; funding for the case series was not reported.

Table 1: Summary of clinical evidence

Study size, design and location	Intervention and comparator	Outcomes	Strengths and limitations
Schadler et al. (2013a); Schadler et al. (2013b) 43 patients Randomised controlled trial Multicentre study Germany	Haemoperfusion treatment for cytokine removal (CytoSorb) and standard care. Standard care (control).	There were no serious device-related adverse events. There were no differences in 28-day or 60-day mortality between CytoSorb and the control. CytoSorb significantly reduced blood concentrations of cytokines.	Unable to assess the trial quality because it has only been published as an abstract in a poster. There was no between-group comparison of reduction in cytokines. Unclear duration of follow-up. Minimal details of the patients. Funded by the manufacturer. The authors noted the limitation that further research is needed to assess the device on clinical outcomes.

Kogelmann et al. (2015) 8 patients Case series Single-centre study Germany	CytoSorb as adjunctive therapy.	Overall survival was 62.5%. Slight decrease in SOFA score and SAPS II.	Small case series only reported as an abstract, so unable to assess study quality. Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported. May include patients from Kogelmann et al. (2016) study.
Kogelmann et al. (2016) 14 patients Case series Single-centre study Germany	CytoSorb as adjunctive therapy.	Overall survival was 35.7%. Survival increased if treatment started within 48 hours.	Small case series only reported as an abstract, so unable to assess study quality. Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported. May include patients from Kogelmann et al. (2015) study.
Laddomada et al. (2016) 8 patients Case series Single-centre study Italy	CytoSorb as adjunctive therapy in combination with continuous renal replacement therapy.	Six of 8 patients survived. In survivors, procalcitonin levels decreased and renal function improved.	Small case series only reported as an abstract, so unable to assess study quality. Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported.

Sathe et al. (2015) 19 patients Case series Single-centre study India	Cytosorb as an adjuvant therapy with standard care.	Four of 19 patients with predicted high mortality survived. Three of the 4 survivors had CytoSorb in less than 24 hours of admission. Almost half of those who died were given CytoSorb more than 24 hours after admission.	Small retrospective case series only reported as an abstract, so unable to assess study quality. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported.
Abbreviations: SOFA, Sepsis-related Organ Failure Assessment; SAPS, Simplified Acute Physiology Score.			

Recent and ongoing studies

- Multi-center, efficacy study of the MedaSorb CytoSorb Hemoperfusion device as an adjunctive therapy in subjects with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) in the setting of sepsis. ClinicalTrials.gov identifier: NCT00559130. Status: completed. Indications: acute respiratory distress syndrome, acute lung injury, sepsis. Devices: CytoSorb.
- The effect of early cytokine absorption on the systemic inflammatory response syndrome and organ dysfunction in the first 48 hours of septic shock. ClinicalTrials.gov identifier: NCT02288975. Status: currently recruiting. Indications: sepsis, septic shock. Devices: CytoSorb.

- Cytokine adsorption in sepsis and acute kidney injury. ClinicalTrials.gov identifier: NCT02588794. Status: currently recruiting. Indications: renal insufficiency or renal failure or end-stage renal disease with severe sepsis or septic shock. Devices: CytoSorb.
- Case-observation and compassionate use: use of extracorporeal treatment with the Cytosorb-Adsorber for the reduction of postoperative hyperinflammation and SIRS after heart-surgery with the use of a heart-lung-machine. ClinicalTrials.gov identifier: NCT02265419. Status: currently recruiting. Indications: multiple organ failure. Devices: CytoSorb.
- International registry on the use of the CytoSorb Adsorber in ICU patients. ClinicalTrials.gov identifier: NCT02312024. Status: currently recruiting. Indications: sepsis, need for cardiac surgery. Devices: CytoSorb.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Two of 3 specialist commentators were aware of the technology. One has used CytoSorb therapy about 4 to 5 times a year over the past few years.

Level of innovation

One specialist commentator felt that CytoSorb therapy was reasonably innovative, noting that previous attempts to remove or block cytokines have not been very successful. Another noted that CytoSorb therapy is based on well-known principles of haemoadsorption but that the design and components of CytoSorb are original. The specialist commentators believed that some training would be needed to use this technology.

Potential patient impact

Two of the commentators noted that the current evidence does not show that using CytoSorb therapy results in any improvements in outcomes, such as mortality. They felt

that the technology was promising but further studies are needed. One noted the need for evidence to show the impact on outcomes, such as length of stay in the intensive therapy unit, and the need for vasopressors or renal replacement therapy. One commentator felt that people with severe sepsis may particularly benefit from this therapy, especially those needing high doses of vasopressor drugs to maintain adequate organ perfusion. They pointed out that it is still unclear whether removing cytokines can affect mortality and outcomes in a beneficial way, although they felt it was clear that it can reduce the dose of vasopressor drugs needed, which is beneficial because these drugs can have harmful effects. The commentator noted that the optimal length of treatment with CytoSorb therapy is still unknown and further research is needed to determine this.

Potential system impact

One specialist commentator stated that any potential effect on NHS services would be specific to critical care. Two commentators felt that there would not be any need for changes in facilities or infrastructure if CytoSorb therapy was adopted.

All 3 commentators stated that the cost of the device would be the only impact on services, 1 of whom noted that the costs would be significant if CytoSorb therapy was used for several days. All of the commentators found it difficult to identify potential cost savings associated with using CytoSorb therapy, because there is no clear evidence to show where savings could be made. However, 1 commentator thought that savings might be made if CytoSorb reduced length of stay and another believed that savings could result from reducing the use of vasopressor drugs.

General comments

One specialist commentator believed the technology would be used in a small and specialised service for people with significantly elevated cytokine levels (particularly IL-6) but that it is unlikely to be routinely used.

Specialist commentators

The following clinicians contributed to this briefing:

- Ms Jacqui Jones, Sepsis Specialist Nurse and Chair of the UK Sepsis Practitioner Forum, South Tees NHS Hospitals Foundation Trust. No conflicts of interest declared.

- Dr Nicholas Lees, Consultant in Anaesthesia and Critical Care, Royal Brompton and Harefield NHS Foundation Trust. No conflicts of interest declared.
- Dr Patrick Lillie, Consultant in Acute Medicine and Infectious Diseases, University Hospital Southampton NHS Foundation Trust. No conflicts of interest declared.

Development of this briefing

This briefing was developed for NICE by Birmingham and Brunel Consortium. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2178-2