Extracorporeal Cytokine Haemadsorption Therapy in Patients with Sepsis or SIRS

Update 2020

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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Content

List of Figures

List of tables

List of abbreviations

AE ..... Adverse Event
CG ..... Control Group
CIM ..... Critical Illness Myopathy
CIP ..... Critical Illness Polyneuropathy
CPB ..... Cardiopulmonary Bypass
CRD ..... Centre for Reviews and Dissemination
DARE ..... Database of Abstracts of Reviews of Effects
ECAT ..... Extracorporeal Cytokine Adsorption Therapy
EU ..... European Union
GRADE ..... Grading of Recommendations, Assessment, Development and Evaluation
HTA ..... Health Technology Assessment
ICU ..... Intensive Care Unit
IG ..... Intervention Group, Interventionsgruppe
IL ..... Interleukin
KG ..... Kontrollgruppe
LPS ..... Lipopolysaccharides
MIP ..... Macrophage Inflammatory Protein
MODS ..... Multiple Organ Dysfunction Score
NHS-EED ..... NHS Economic Evaluation Database
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT ..... Randomised Controlled Trial
RoB ..... Risk of Bias
SAE ..... Serious Adverse Event
SUE ..... Schwere Unerwünschte Ereignisse
SIRS ..... Systemic Inflammatory Response Syndrome
SOFA ..... Sepsis-Related Organ Failure Assessment
TNF ..... Tumour Necrosis Factor
UE ..... Unerwünschte Ereignisse
WHO-ICTRP ..... World Health Organisation – International Clinical Trials Registry Platform

Executive summary

Introduction

Health problem

Sepsis, septic shock and systemic inflammatory response syndrome (SIRS) are life-threatening conditions associated with an overreacting immune response. The dysregulated response can lead to multiple organ dysfunction. Whilst sepsis and septic shock have an infectious origin, SIRS may also have non-infectious triggers such as cardiac surgery using the Cardiopulmonary Bypass (CPB). SIRS, sepsis and septic shock have a 28-day mortality of an estimated 7, 16 and 46%, respectively.

sepsis, septic shock and SIRS are life-threatening conditions associated with an overreacting immune response

Sepsis should be considered in the event of an infectious process associated with an increase in the sepsis-related organ failure assessment (SOFA) score of two points or more (Sepsis-3 taskforce). Patients with septic shock would be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater, and a serum lactate level greater than 2 mmol/L (>18 mg/dl) in the absence of hypovolemia. SIRS patients are identified by fulfilling two or more of the four SIRS criteria (temperature >38°C or <36°C, heart rate of more than 90 beats per minute, respiratory rate more than 20 beats per minute or $PaCO_2$ of less than 32 mmHg, abnormal white blood cell count).

differences: sepsis, septic shock and SIRS

Increase in SOFA Score of 2 points or more: sepsis

>2 of the 4 SIRS criteria leads to the diagnosis of SIRS

The two main therapeutic priorities include the early identification of a potential infectious origin and the haemodynamic stabilisation of the patient. Other than the control of the primary site of infection, there is no causal treatment for sepsis, septic shock or SIRS.

priorities: early identification of a potential infectious origin and haemodynamic stabilisation

Description of technology

Extracorporeal cytokine adsorption therapy (ECAT) aims to reduce the levels of cytokines in the blood. Cytokines are signalling molecules produced during an immune response. In sepsis, septic shock and SIRS this response is dysregulated, resulting in an excessive release of cytokines that trigger further immune cascades. ECAT intends to adsorb the cytokines from the blood to restore a balanced immune response. Cytokine adsorption therapy can be regarded as a possible addition to standard care of sepsis or SIRS.

ECAT aims at reducing cytokine levels

addition to standard care

CytoSorb® received CE mark approval in 2011 as the first ECAT device indicated for the treatment of conditions of excessive cytokine levels. The device consists of a single-use cartridge that can be used as stand-alone therapy and in combination with dialysis machines and heart-lung machines. The absorber cartridge is filled with sorbent beads, which adsorb the cytokines as they pass through the blood pump. One further product received CE mark authorisation within the past years: the oXiris® device for critical care. This product is an extracorporeal blood purification set to adsorb endotoxin, cytokines or uremic toxins. The product is marketed to be used in sepsis management.

2 ECAT devices available

Methods

update-SR

In this report, an update assessment was conducted to evaluate the efficacy and safety of extracorporeal cytokine adsorption therapy.

systematic search: 2016-2019

A systematic literature search for relevant publications was carried out in four databases (Medline, Embase, The Cochrane Library, and the University of York Centre for Reviews and Dissemination).

selection, extraction and quality appraisal: conducted by 2 researchers

In addition, a manual search on the internet was performed and information provided by the manufacturer and submitting hospital was screened to identify further relevant studies. The study selection, data extraction and assessment of the methodological quality of the studies were performed by two independent researchers. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was further used and the evidence qualitatively synthesised.

Domain effectiveness

crucial outcomes for effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: reduced mortality, improved clinical outcomes (organ function), days spent in the ICU, and total days of hospitalisation.

Domain safety

and safety

The following safety-related outcomes were used as evidence to derive a recommendation: adverse events (AE) and serious adverse events (SAE).

Results

1 PREVENTIVE USE OF THE TECHNOLOGY IN PATIENTS UNDERGOING CARDIAC SURGERY

Available evidence

ECAT preventive use in pts undergoing cardiac surgery 5 RCTs (n=163)

Five randomised controlled trials with a total of 197 enrolled patients (of whom 163 were analysed) investigated the preventive use of the technology in patients undergoing cardiac surgery.

Quality of evidence

certainty of the evidence: very low

Overall, the certainty of the evidence was very low mainly due to high imprecision (studies were underpowered to detect a statistically significant difference in crucial outcomes) and the high risk of bias in four out of five studies.

Clinical effectiveness

none of the studies was able to detect a stat. significant difference in crucial effectiveness or safety outcomes

None of the studies was able to detect a statistically significant difference in any of the selected crucial outcomes. The surrogate outcome reduction in cytokine levels further showed inconsistent results with regard to IL-6 measurements.

Safety

ECAT-related UE (2 studies): 0-2%

None of the studies was able to detect a statistically significant difference in adverse events or serious adverse events. However, device-related adverse events were reported by two studies, with two (8.7%) and none (0%) cases in groups receiving ECAT in these studies, respectively.

2. THERAPEUTIC USE OF THE TECHNOLOGY IN PATIENTS WITH SEPSIS OR SEPTIC SHOCK

Available evidence

Two randomised controlled trials with 120 enrolled patients (of whom 117 were analysed) investigated the therapeutic use of the technology in patients with sepsis or septic shock.

ECAT
therapeutic use
in pts with sepsis
2 RCTs (n=117):

Quality of evidence

Overall, the certainty of the evidence was very low mainly due to high imprecision (studies were underpowered to detect a statistically significant difference in crucial outcomes) and the high risk of bias.

Clinical effectiveness

Mortality was reported by two studies: one study (n=97) found a statistically significant difference in 60-day mortality to the detriment of the intervention group when compared to the control group, with 44.7% and 26% (p= 0.039) deceased in these groups, respectively. The study authors noted that this difference is not adjusted for comorbidities and further regression analysis showed no association between the device and mortality. No statistically significant difference was detected in mortality with less follow-up time (28-day mortality in one study and 48 hours mortality in another study). The other selected crucial outcomes were either not statistically significantly different or not statistically tested by the included studies. No statistically significant difference in the surrogate outcome reduction in cytokine levels was detected in one study that reported on this outcome.

effectiveness:
mortality (2 RCTs):
60-days (1 RCT): 44,7 vs. 26%, stat. significant
28-days (1 RCT) & 48 hrs (1 RCT); no stat. significant difference
no stat. significant difference in other crucial outcomes

Safety

Overall adverse events or serious adverse events was reported by one study (n=97): 25 patients (53.2%) in the intervention group as opposed to 12 patients (24%) in the control group suffered from at least one SAE. In the same study, at least one AE occurred in some 30 patients (63.8%) in the intervention group and 25 patients (50%) in the control group (p-values were not reported by the included study). The same study reported on device-related adverse events: Eight adverse events and five serious adverse events occurred – possibly or probably in connection with the study device – in the intervention group (n=47). The other study also reported on device-related (serious) adverse events and noted that no such cases occurred in ten patients receiving ECAT.

SAE (1 RCT):
53,2% vs. 24%
AE (1 RCT):
63,8% vs. 50%
p value NR

ECAT related (S)AEs
in 2 studies:
5 SAEs & 8 AEs
(in 47 pts) & 0 (in 10 pts)

Upcoming evidence

The search for ongoing studies revealed that there are currently 18 ongoing randomised controlled trials, with estimated completion dates within the next two years. All of the ongoing studies compare the use of extracorporeal blood purification devices and standard care as opposed to standard care alone in the following indications:

- Cardiac surgery (intraoperative)
- Cardiac surgery (postoperative)
- Sepsis or septic shock
- Cardiac arrest
- Other indications

18 ongoing studies

strong focus on surrogate endpoints

Many of the ongoing studies defined a change in interleukin levels as opposed to patient-relevant outcomes as primary outcome measures. Hence, these will be likely to be underpowered to be able to detect a statistically significant difference in patient-relevant outcomes. Some of the aforementioned randomised controlled trials may be able to establish the clinical benefit/disbenefit of using ECAT. However, in the absence of a detailed description on the methodological quality of ongoing trials, it is not definitive as to whether the results of these trials can shed more light on the effect of ECAT.

Reimbursement

currently not reimbursed

Currently, ECAT is not reimbursed by the Austrian health care system, neither as a treatment of sepsis, septic shock or SIRS, nor as a preventive treatment during CPB surgery.

Discussion

limitations: imprecision, high RoB in studies

According to GRADE, the overall quality of evidence identified for this review was very low for all of the reported outcomes and indications. The major limitation of the evidence may be associated with imprecision. The available randomised controlled trials defined crucial outcomes as secondary outcomes. As a consequence, the statistical power to detect a difference in patient-relevant outcomes was poor across studies. In addition, most of the primary studies were judged to be with high risk of bias.

basic principle ideas regarding benefit not robust

AWMF S3 guideline currently recommends not to use blood purification in sepsis management

It is noteworthy to mention that many of the basic principle ideas regarding a clinical benefit of removing inflammatory cytokines, e.g., during sepsis, are not as robust as one may anticipate: Significant interactions (including removing antibiotic therapy used in septic patients) could also be harmful for patients. In this context, a clinical practice guideline from Germany (AWMF S3) currently recommends not to use blood purification in sepsis management (including extracorporeal cytokine adsorption therapy), with clinical studies as an exception (expert consensus).

Conclusion

conclusion: insufficient evidence to show a clinical benefit

Current evidence is insufficient to show a clinical benefit of ECAT as an add-on measure preventively in cardiac surgery or therapeutically in patients with sepsis or septic shock. None of the studies was able to demonstrate that ECAT and standard care is more effective than and as safe as standard care alone in these two assessed conditions. Results from well-designed randomised controlled trials – with adequate power to detect differences in patient-relevant outcomes – are lacking. In light of the available evidence and the potential risks associated with the study device, the results of ongoing studies are to be awaited.

Recommendation

inclusion not recommended

On the basis of the available evidence, inclusion in the hospital benefit catalogue is currently not recommended. Reevaluation is recommended in 2022 if larger randomised controlled trials (n>200) with patient-relevant outcomes as primary outcomes are published by then.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Sepsis, septischer Schock und SIRS sind lebensbedrohliche Zustände, die durch eine Überreaktion des Immunsystems ausgelöst werden. Während Sepsis und septischer Schock infektiösen Ursprungs sind, kann SIRS auch durch nicht-infektiöse Auslöser – wie Herzchirurgische Eingriffe unter Verwendung der Herz-Lungen-Maschine (HLM) (kardiopulmonaler Bypass (CPB)) – ausgelöst werden. Gemeinsam mit Sespsis wurde diese Art der Auslösung von SIRS im vorliegenden Bericht analysiert. Die Verwendung der HLM kann eine systemische Entzündungsreaktion während der Operation hervorrufen, die durch Kontaktaktivierung des Blutes durch künstliche Oberflächen ausgelöst wird.

Sepsis, septischer Schock und SIRS sind lebensbedrohliche, systemische Immunreaktionen

Die dysregulierte Überreaktion des Immunsystems auf eine Infektion oder andere Stimuli kann zu multiplen Organdysfunktionen führen. SIRS, Sepsis und septischer Schock haben eine geschätzte Mortalitätsrate von jeweils 7, 16 bzw. 46%.

Mortalität: 7-46 %

PatientInnen mit SIRS oder vermuteter Sepsis weisen eine Kombination diverser Symptome auf. Die Symptome reichen von einem niedrigen Blutdruck, Fieber oder einer Körpertemperatur unter 36° C bis hin zu einer hohen Atemfrequenz, einer beschleunigten Herzfrequenz, einem veränderten mentalen Status und Anzeichen einer Hypoperfusion.

Symptomkombination

Die beiden wichtigsten therapeutischen Prioritäten sind die frühzeitige Identifizierung eines potenziellen infektiösen Ursprungs und die hämodynamische Stabilisierung der PatientInnen. Abseits der frühen antibiotischen Abschirmung gibt es derzeit keine kausale Behandlung für Sepsis, septischen Schock oder SIRS.

Therapie: hämodynamische Stabilisierung und antibiotische Abdeckung

Beschreibung der Technologie

Extrakorporale Zytokinadsorptionstherapie (engl. extracorporeal cytokine adsorption therapy = ECAT) zielt darauf ab, die Zytokinkonzentration im Blut zu reduzieren. Zytokine sind Signalmoleküle, die bei einer physiologischen Immunantwort produziert werden. Bei Sepsis, septischem Schock und SIRS kommt es zu einer Überreaktion, was zu einer erhöhten Freisetzung von Zytokinen führt, die ihrerseits wiederum weitere Immunkaskaden auslösen. Ziel der ECAT ist es, Zytokine aus dem Blut zu entfernen, um eine balancierte Immunantwort wiederherzustellen.

extrakorporale Zytokinadsorption versucht Zytokinkonzentration im Blut zu vermindern

ECAT ist als Ergänzung zur Standardbehandlung von Sepsis oder SIRS vorgesehen. Die therapeutische Anwendung von ECAT ist in den jüngsten internationalen Konsensus-Leitlinien nicht empfohlen.

als Zusatz zur Standardtherapie

Im Erst-Assessment 2017 war CytoSorb® das einzige ECAT-Gerät, das über eine CE-Zertifizierung verfügte. Das Produkt besteht aus einer Einmal-Kartusche, die als Stand-Alone Therapie oder in Kombination mit Dialysemaschinen und HLM eingesetzt werden kann. Die Kartusche ist mit porösen Polymer-Adsorptions-beads gefüllt, die Zytokine und andere Entzündungsmediatoren ähnlicher Größe (Moleküle bis zu einer Größe von 55 kD) adsorbieren.

2 verfügbare ECAT-Produkte Cytosorb® Einmal-Kartusche in Kombination mit HLM verwendbar

Therapiedauer: 48-72 h therapeutisch

Das Blut zirkuliert bis zu maximal 24 Stunden kontinuierlich zwischen dem Absorptionsgerät und der/m PatientIn, wonach die Kartusche ausgetauscht werden muss. Die typische Behandlungsdauer mit ECAT beträgt 48 bis 72 Stunden für PatientInnen mit Sepsis. Die präventive Anwendung während eines herzchirurgischen Eingriffs mit einer HLM wird für eine CPB-Dauer von >120 min empfohlen.

und oXiris® Filter

In den letzten Jahren erhielt ein weiteres Produkt CE-Mark: Der sogenannte oXiris® Filter. Dieses Produkt kann neben Zytokinen auch Edotoxine und uremische Toxine adsorbieren. Das Produkt wird für den Einsatz bei Sepsis vermarktet.

Methoden

Systematische Suche, Studienselektion

Die Fragestellung, die Einschlusskriterien und die Suchstrategie des Berichts wurden im Vergleich zum Erst-Assessment minimal verändert: Es wurden nur randomisierte kontrollierte und prospektive nicht randomisierte kontrollierte Studien in die Evidenzsynthese eingeschlossen.

Datenextraktion und GRADE-Bewertung durch 2 Personen qualitative Synthese der Evidenz

Es wurde eine systematische Literatursuche in verschiedenen medizinischen Datenbanken durchgeführt. Die Studienselektion, die Datenextraktion sowie die Qualitätsbeurteilung der eingeschlossenen Studien erfolgte durch zwei Personen (GG, KH) unabhängig voneinander. Die Qualität der Evidenz wurde nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Klinische Wirksamkeit

entscheidende Endpunkte: Wirksamkeit: Mortalität, Organfunktion, Hospitalisierung

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert: Reduktion der Mortalität, klinische Verbesserung der Organdysfunktion, Verweildauer in der Intensivstation, Verminderung der Hospitalisierungsdauer.

Sicherheit

Sicherheit: SUE/UE

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert: schwere unerwünschte Ereignisse (SUE), und unerwünschte Ereignisse (UE).

Ergebnisse

Verfügbare Evidenz

verfügbare Evidenz: 7 RCTs

Für das Update 2020 konnten im Rahmen der Literaturrecherche sechs neue randomisierte Kontrollstudien identifiziert werden. Die verfügbare Evidenz zur Beurteilung der komparativen Wirksamkeit und Sicherheit umfasst damit insgesamt sieben randomisierte Kontrollstudien: Fünf Studien evaluierten den Einsatz von ECAT als präventive Maßnahme bei kardiologischen Operationen und zwei weitere Studien untersuchten den therapeutischen Einsatz von ECAT bei PatientInnen mit Sepsis oder septischem Schock.

1. PRÄVENTIVER EINSATZ VON ECAT BEI BEI PATIENTEN MIT HERZOPERATIONEN

Fünf Studien mit insgesamt 197 PatientInnen (davon 163 PatientInnen analysiert) untersuchten den präventiven Einsatz der Technologie bei PatientInnen, die sich einer Herzoperation unterziehen. Das Verzerrungspotenzial war niedrig in einer Studie und hoch in den anderen vier Studien.

5 RCTs
RoB:
niedrig in 1/5 Studien
hoch in 4/5 Studien

Qualität der Evidenz

Die Qualität der Evidenz war sehr niedrig, was vor allem auf unzureichende Präzision der Resultate der patientInnenrelevanten Endpunkte innerhalb der Studien und das hohe Verzerrungspotenzial in vier der fünf eingeschlossenen Studien zurückzuführen ist.

Qualität der Evidenz:
sehr niedrig

Klinische Wirksamkeit

Der Endpunkt **Mortalität** wurde in insgesamt fünf Studien (n=163) berichtet: Keine der Studien konnte einen statistisch signifikanten Unterschied zwischen Interventions- und Kontrollgruppe feststellen (Beobachtungszeitraum: bis zu 30 Tage). Die Mortalitätsraten in drei Studien schwankten von 0-6.7% in der Interventionsgruppe und 0-13,3% in der Kontrollgruppe. Eine Studie berichtete von einem Mortalitätsindex (IG: 6.6 ±5.4 vs. KG: 8.12 ±7.5) und eine weitere Studie berichtete lediglich qualitativ, dass keine Unterschiede zwischen Interventions- und Kontrollgruppe festgestellt werden konnten.

Mortalität (5 RCTs):
keine stat. signifikanten Unterschiede

Der Endpunkt **Organfunktion** wurde von keiner der eingeschlossenen Studien gemessen/berichtet.

Organfunktion:
keine Berichterstattung

Die Verweildauer in der Intensivstation wurde von allen fünf eingeschlossenen Studien (n=163) berichtet: Keine der Studien konnte einen statistisch signifikanten Unterschied zwischen Interventions- und Kontrollgruppe feststellen. Drei Studien berichteten von der durchschnittlichen Verweildauer mit jeweils 2,3, 3,2 und 4,3 Tagen in den Interventions- und 2,4, 2,1 und 6,8 Tagen in den Kontrollgruppen. Die anderen zwei Studien berichteten von der medianen Verweildauer in Tagen: in einer Studie waren es knapp zwei Tage (1,8) in der Interventionsgruppe und ein Tag in der Kontrollgruppe. Die andere Studie berichtete von einer medianen Verweildauer von zwei Tagen in der Interventions- und drei Tagen in der Kontrollgruppe.

Verweildauer in Intensivstation (5 RCTs):
kein stat. signifikanter Unterschied

Die Hospitalisierungsdauer in Tagen wurde von drei Studien (n=101) berichtet: Keine der Studien konnte einen statistisch signifikanten Unterschied zwischen Interventions- und Kontrollgruppe feststellen. Die durchschnittliche post-operative Dauer der Hospitalisierung betrug knapp neun Tage (IG: 9,0 und KG: 8,6) in einer Studie und knapp zwölf (IG: 11.8) bzw. 14 Tage (KG: 14.0) in einer anderen Studie. Eine weitere Studie berichtete von einer medianen Hospitalisierungsdauer von neun Tagen in der Interventions- und acht Tagen in der Kontrollgruppe.

Dauer der Hospitalisierung (3 RCTs):
kein stat. signifikanter Unterschied

Sicherheit

Die Anzahl der PatientInnen mit zumindest einem **schweren unerwünschten Ereignis (SUE)** wurde von vier Studien (n=148) berichtet: Die Spannweite der SUEs innerhalb der Interventionsgruppen betrug 0-69,6 % im Vergleich zu 0-53,3 % in den Kontrollgruppen. Keine der Studien konnte einen statistisch signifikanten Unterschied bei SUEs feststellen.

SUE (4 Studien):
IG: 0-69,6 %
KG: 0-53,3 %

UE (3 Studien): IG: 0-100% KG: 0-91,3%

Die Anzahl der PatientInnen mit zumindest einem **unerwünschten Ereignis (UE)** wurde von drei Studien (n=118) berichtet: Die Spannweite der UEs innerhalb der Interventionsgruppen betrug 0-100% im Vergleich zu 0-91,3% in den Kontrollgruppen. Keine der Studien konnte einen statistisch signifikanten Unterschied bei UEs feststellen.

ECAT induzierte UEs (2 RCTs): 0-8,7%

ECAT-induzierte UEs wurde von zwei Studien berichtet: Eine Studie berichtete von keinem Fall von ECAT-induzierten UEs in 16 PatientInnen in der Interventionsgruppe. In der anderen Studie traten zwei Fälle von ECAT-induzierten UEs in 23 PatientInnen (8,7%) in der Interventionsgruppe auf.

2. THERAPEUTISCHER EINSATZ VON ECAT BEI PATIENTEN MIT SEPSIS ODER SEPTISCHEM SCHOCK

Verfügbare Evidenz

2 RCTs mit hohem RoB

Zwei randomisierte Kontrollstudien mit insgesamt 120 PatientInnen (von denen 117 analysiert wurden) untersuchten den therapeutischen Einsatz von ECAT bei PatientInnen mit Sepsis oder septischem Schock. Das Verzerrungspotenzial war hoch in beiden Studien.

Qualität der Evidenz

Qualität der Evidenz: sehr niedrig

Die Qualität der Evidenz war sehr niedrig, was vor allem auf unzureichende Präzision der Resultate der patientInnenrelevanten Endpunkte innerhalb der Studien und das hohe Verzerrungspotenzial in den Studien zurückzuführen ist.

Klinische Wirksamkeit

Wirksamkeit: Mortalität: 60 Tage (1 Studie): IG: 44,7 % KG: 26 %, stat. signifikant (p=0.039)

28 Tage (1 Studie): keine stat. signifikanten Unterschiede

48 Stunden (1 Studie): nicht stat. getestet

Der Endpunkt **Mortalität** wurde von beiden Studien berichtet. **60-Tages-Mortalität** wurde von einer Studie (n=97) berichtet: 21 PatientInnen (44.7 %) in der Interventionsgruppe und 13 PatientInnen (26 %) in der Kontrollgruppe verstarben innerhalb von 60 Tagen (Unterschied statistisch signifikant mit p=0,039). Laut AutorInnen ist jedoch darauf hinzuweisen, dass bei Adjustierung auf Komorbiditäten kein statistischer Zusammenhang zwischen Gerät und Mortalität sichtbar war. **28-Tages-Mortalität** wurde von der gleichen Studie (n=97) berichtet: 17 der PatientInnen (36.2 %) in der Interventionsgruppe und neun PatientInnen (18 %) in der Kontrollgruppe verstarben innerhalb von 28 Tagen. **48-Stunden-Mortalität** wurde von der anderen eingeschlossenen Studie (n=20) berichtet: Keine PatientInnen in der Interventionsgruppe und zwei PatientInnen (20 %) in der Kontrollgruppe verstarben innerhalb dieses Zeitraums. Die gleiche Studie berichtete zudem von einer „allgemeinen" Mortalitätsrate von 50 % sowohl in Interventions- als auch Kontrollgruppen, ohne jedoch den Zeitraum zu definieren. Die Unterschiede wurden nicht statistisch getestet.

Organfunktion (2 Studien): kein stat. signifikanter Unterschied

Der Endpunkt **Organfunktion** wurde von beiden Studien (n=117) berichtet: Es wurde kein statistisch signifikanter Unterschied bei der Organfunktionalität zwischen Interventions- und Kontrollgruppe bei Verwendung des MODS Scores (1 Studie; n=97) und des SOFA Scores (1 Studie; n=20) gefunden.

Tage in ICU (1 Studie): kein stat. signifikanter Unterschied

Die **Verweildauer in der Intensivstation** wurde von einer Studie (n=20) berichtet: Im Durchschnitt betrug die Verweildauer 10,2 Tage (SD: 8,5) in der Interventionsgruppe und 10 Tage (SD: 4,3) in der Kontrollgruppe (p-Wert nicht berichtet).

Tage im Spital: NR

Die Hospitalisierungsdauer wurde von keiner der eingeschlossenen Studien berichtet.

Sicherheit

Die Anzahl der PatientInnen mit zumindest einem **schweren unerwünschten Ereignis (SUE)** wurde von einer Studie (n=97) berichtet: Bei 25 PatientInnen (53.2 %) in der Interventionsgruppe und 12 PatientInnen (24 %) in der Kontrollgruppe trat mindestens ein SUE auf (p-Wert nicht berichtet).

SUE (1 Studie):
Pts mit SUEs:
IG: 53,2 %
KG: 24 %

Die Anzahl der PatientInnen mit zumindest einem **unerwünschten Ereignis (UE)** wurde von einer Studie (n=97) berichtet: Bei 30 PatientInnen in der Interventionsgruppe (63.8 %) und 25 PatientInnen (50 %) in der Kontrollgruppe trat mindestens ein UE auf (p-Wert nicht berichtet).

Pts mit UEs (1 Studie):
IG: 63,8 %
KG: 50 %; p-Wert NR

ECAT-induzierte (S)UEs wurde von beiden Studien (n=117) berichtet: Es wurden fünf Fälle (in 47 PatientInnen) in einer Studie und kein Fall (in 10 PatientInnen) in der anderen Studie von ECAT-induzierten SUEs berichtet. Des Weiteren wurden acht Fällen (in 47 Patientinnen) von ECAT-induzierten UEs in einer Studie und keine diesbezüglichen UEs in der anderen Studie (in 10 PatientInnen) berichtet.

ECAT induzierte UEs (2 Studien):
0 UEs/SUEs in 10 pts &
5 SUEs & 8 UEs in 47 pts

Laufende Studien

Die Suche nach laufenden Studien ergab, dass es derzeit 18 laufende randomisierte Kontrollstudien gibt. Laut Informationen aus clinicaltrials.gov sollten diese Studien innerhalb der nächsten zwei Jahre abgeschlossen sein. Alle laufenden Studien vergleichen den Einsatz extrakorporaler Blutreinigungsgeräte in Kombination mit der Standardversorgung im Vergleich zur Standardversorgung bei den folgenden Indikationen:

18 laufende Studien

voraussichtlicher Abschluss der Studien innerhalb der nächsten zwei Jahre lt. Studienregister

- Herzchirurgie (intraoperativ)
- Herzchirurgie (postoperativ)
- Sepsis oder septischer Schock
- Herzstillstand
- sonstige Indikationen (z.B. bei CAR-T Zelltherapie)

Viele der laufenden Studien definierten eine Veränderung der Interleukinkonzentration im Gegensatz zu patientenrelevanten Endpunkten als primäre Endpunkte. Diese Studien sind vermutlich nicht in der Lage, einen statistisch signifikanten Unterschied in patientenrelevanten Endpunkten zu erkennen. Es gibt jedoch ein paar wenige randomisierte kontrollierte Studien, die möglicherweise den potentiellen klinischen Nutzen von ECAT eruieren können. In Ermangelung einer detaillierten Beschreibung der methodischen Qualität laufender Studien ist es nicht endgültig einschätzbar, ob die Ergebnisse dieser Studien mehr Klarheit in Bezug auf den Nutzen von ECAT schaffen können.

starker Fokus auf Surrogatendpunkte in laufenden Studien

Kostenerstattung

Derzeit wird ECAT vom österreichischen Gesundheitssystem nicht erstattet.

derzeit nicht erstattet

Schlussfolgerung und Diskussion

Schlussfolgerung: Unzureichende Evidenz für klinischen Nutzen

Die derzeitige Evidenz ist unzureichend, um einen klinischen Nutzen von ECAT als Zusatzmaßnahme präventiv in der Herzchirurgie oder therapeutisch bei PatientInnen mit Sepsis oder septischem Schock zu belegen. Auf Basis der ausgewählten wesentlichen Endpunkte konnte keine der eingeschlossenen Studien nachweisen, dass ECAT in Kombination mit der Standardversorgung im Vergleich zur alleinigen Standardversorgung in den beiden Indikationen wirksamer und zumindest gleich sicher ist. Es fehlen Ergebnisse aus gut konzipierten, randomisierten Kontrollstudien, die ausreichende Präzision aufweisen bzw. ausreichende statistische Power haben, um Unterschiede in den patientInnenenrelevanten Endpunkten erkennen zu können. In Anbetracht der verfügbaren mangelhaften Evidenz und der potenziellen Risiken, die mit ECAT verbunden sind, müssen Ergebnisse aus laufenden Studien abgewartet werden.

theoretische Basis für Nutzen nicht robust

Es ist überdies wichtig zu erwähnen, dass die theoretische Basis für einen klinischen Nutzen von ECAT nicht robust ist und eine Entfernung von Zytokinen in Sepsis PatientInnen gegebenenfalls auch schaden könnte. In diesem Zusammenhang gibt es eine AWMF S3 Leitlinienempfehlung, die sich gegen Blutreinigungsverfahren (inkl. ECAT) außerhalb der klinischen Forschung – also in der klinischen Praxis – ausspricht (Expertenkonsensus).

Empfehlung

daher Erstattung derzeit nicht empfohlen

Auf der Grundlage der verfügbaren Evidenz wird die Aufnahme in den Leistungskatalog derzeit nicht empfohlen. Die Re-Evaluierung wird 2022 empfohlen, wenn bis dahin größere randomisierte kontrollierte Studien (n>200) mit patientenrelevanten Endpunkten als primäre Endpunkte veröffentlicht werden.

Summary of the previous assessment

This chapter summarises the results of the initial assessment published in 2017 [1]. The reader is referred to this report for a nuanced description regarding the health problem and current use as well as the technological characteristics. Information was checked for accuracy and updated in case changes occurred within the past years.

Zusammenfassung des MELs in 2017

Informationen auf Aktualität überprüft

Health problem and characteristics of the technology

Definitions: sepsis, septic shock and SIRS

Sepsis, septic shock and SIRS are life-threatening conditions associated with an overreacting immune response. The dysregulated response can lead to multiple organ dysfunction. Whilst sepsis and septic shock have an infectious origin, SIRS may also have non-infectious triggers such as cardiac surgery using the cardiopulmonary bypass (CPB). SIRS, sepsis and septic shock have a 28-day mortality of an estimated 7%, 16% and 46%, respectively [2, 3].

Sepsis, septischer Schock und SIRS sind lebensbedrohliche systemische Immunreaktionen

Sepsis may stem from an infection of any part of the body, most commonly from the lungs, intestine or urinary tract. In an estimated 30% of sepsis cases the causative infection cannot be identified and can only be assumed by the clinical presentation of the patient [2, 3]. Patients with suspected sepsis often present themselves with tachycardia, fever, hypotension and leukocytosis [2].

Sepsis: kausale Infektion oft nicht messbar

The 2016 Sepsis-3 definition makes two distinctions [3]: between sepsis and septic shock. The previous sepsis definitions published in 1992 emphasised the role of the systemic inflammatory response syndrome (SIRS) as a key element of the sepsis definition. However, evidence showed that SIRS criteria are non-specific and insensitive as predictors for sepsis-related mortality, and are therefore not included in the most recent international sepsis definition.

Unterschied Sepsis und septischer Schock

Veränderung in SOFA Score um 2 Punkte führt zur Diagnose der Sepsis

The members of the Sepsis-3 task force suggested that sepsis should be considered in the event of an infectious process associated with an increase in the sepsis-related organ failure assessment (SOFA) score of two points or more.

Patients with septic shock would be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater, and serum lactate level greater than 2 mmol/L (>18 mg/dl) in the absence of hypovolemia [3]. Septic shock is an extensive vasodilatory reaction that leads to hypoperfusion of the body [2, 3]. Due to the vasodilation of the arteries and capillaries, the blood is pooled in the periphery of the circulatory system, causing severe hypotension.

septischer Schock

Septic shock is a subset of sepsis with a substantially greater risk of mortality due to a particularly profound systemic response. Clinically, the status of septic shock is distinguished from sepsis by the persistence of hypotension that requires vasopressor therapy to maintain a mean arterial pressure of 65 mmHg and serum lactate level greater than 2mmol/L (18mg/dL) in absence of hypovolemia [3].

Abgrenzung zu Sepsis: Persistenz von Blutdruckabfall und erhöhtes Serum Lactat

SIRS: dysregulierte Immunreaktion, mit oder ohne zugrunde liegender Infektion

SIRS is a clinical syndrome of a dysregulated inflammatory response that may or may not be accompanied by an infection.

>2 der 4 SIRS Kriterien zur Diagnose von SIRS

SIRS is clinically defined by having at least two of the following criteria:

- Temperature >38°C or <36°C
- Heart rate of more than 90 beats per minute
- Respiratory rate more than 20 beats per minute or PaCO2 of less than 32 mmHg
- Abnormal white blood cell count (>12,000/mm^3 or <4,000/mm^3) [3, 4]

If patients present with at least two out of the four parameters, they meet the criteria for the condition of SIRS [3].

Natural course and standard care of sepsis, septic shock or SIRS

Prognose: unbehandelte Sepsis oder septischer Schock kann letal enden

Left untreated, sepsis and septic shock can have a lethal outcome. Even with the optimal therapy, the mortality of sepsis is high, with estimated rates ranging from 10% to 52% [2]. Mortality is lower in younger patients without comorbidities.

Sepsis-Überlebende berichten von schlechter QoL

SIRS-Prognose abhängig von Ätiologie

After hospital discharge, patients can have a higher risk of further sepsis and readmission to the hospital. The long-term prognosis is an increased risk of death following hospital discharge, with most deaths occurring in the first six months [5]. Furthermore, sepsis survivors reported limitations on their quality of life in terms of functional restrictions, such as sustained restrictions in neurocognitive functions, post-traumatic distress disorder or depression. This condition is described as critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) [6]. The natural course and prognosis of SIRS depends on the underlying condition and the aetiological source of SIRS.

Behandlung:

The two main therapeutic priorities for patients with sepsis include early identification of the infectious origin and early initiation of supportive care to ensure haemodynamic stabilisation [7].

Sepsis und septischer Schock:

Früherkennung, supportive Therapie zur hämodynamischen Stabilisieruung

Early and adequate antibiotic treatment is essential for the treatment of sepsis ('hit hard and hit early strategy'). Intravenous antibiotic therapy should be started within the first hours, and after obtaining blood cultures [6]. If the pathogen is not obvious and unknown, the initial antibiotic therapy should be a combination of broad-spectrum antibiotics that are effective for gram-negative and gram-positive bacteria, such as third or fourth generation cephalosporin or carbapenem [8][1]. Furthermore, potential infective sources, i.e., devices and vascular access lines, should be controlled and if possible, removed.

The second priority in patients with sepsis and septic shock is to achieve haemodynamic stabilisation. Initial therapeutic priorities include securing of the airway, ensuring adequate oxygenation of the blood, and treating hypoperfusion and hypotension. Some patients require mechanical ventilation and intubation [7].

keine wesentlichen Unterschiede der SIRS-Behandlung

Since SIRS is a syndrome rather than a disease, the treatment and management of a patient with SIRS depends on the inciting cause. The symptomatic management and stabilisation of the patient is essential and similar to the supportive management of sepsis [10].

[1] The guideline was updated/revised in 2018, with no significant changes with regard to the retrieved information presented herein [9]

Features of extracorporeal cytokine adsorption therapy (ECAT)

ECAT soll Zytokin-Level im Blut reduzieren

Extracorporeal cytokine adsorption therapy (ECAT) aims to reduce the levels of cytokines in the blood. The normal immune response to infection is a localised process aiming to control bacterial invasion. If this reaction becomes generalised and extends to normal tissue remote from the initial site of injury or infection, a systemic inflammatory response ensues. The uncontrolled inflammatory process leads to an excessive release and overproduction of cytokines [10-12].

Zytokine sind körpereigene Proteine, die bei Steuerung der Immunreaktionen als Signalmoleküle dienen

Funktionsweise vieler Zytokine ist noch nicht bekannt

Cytokines are small proteins (25kDa) that serve as signalling molecules during an immune response. They are released by various cell types upon initial activating stimuli such as endotoxin and lipopolysaccharides (LPS) on the bacterial cell wall. Cytokines can have pro-inflammatory as well as anti-inflammatory capacities. The number of identified cytokines is large and increasing, whilst the underlying signalling pathways and various effects of different cytokines are still not completely understood today [11]. However, there is evidence that an elevated level of cytokines is associated with the development of SIRS and is a poor prognosis [11, 13, 14].

Überschuss an pro-inflammatorischen Zytokinen korreliert mit Sepsis-Schweregrad und Mortalität

The main pro-inflammatory cytokines known today are Interleukin 1 (IL-1), IL-6, IL-8, Tumour Necrosis Factor α (TNF- α) and Macrophage Inflammatory Protein-1 α (MIP-1 α). Studies have shown a correlation between the level of IL-6 and the severity of sepsis and subsequent mortality. Furthermore, an elevated level of IL-6 following CPB was associated with worsening lung function and the development of SIRS [13]. The simultaneous release of anti-inflammatory cytokines such as IL-10 and IL-13 aims to balance and control an inflammatory response. The loss of control of this balanced, localised reaction leads to systemic inflammation with potentially detrimental consequences such as SIRS, sepsis and septic shock [10].

ECAT soll Überschuss an Zytokinen ausgleichen

The principal idea behind extracorporeal adsorption therapies is to remove these inflammatory molecules from the blood in order to restore a balanced immune response [15]. Originally, extracorporeal blood purification therapies were used in septic patients in order to replace the function of failing organs, for instance, to support the kidney or liver function. By adding an adsorbing haemofilter into the blood purification device, molecules from the blood are bound to the surface of the adsorber and eliminated from the blood [12].

CytoSorb® war einzige Technologie mit CE-Mark bis 2017

CytoSorb® was found to be the only CE-marked ECAT device in the European Union by the previous HTA report published in 2017 [1]. The device consists of a single-use cartridge that can be used as stand-alone therapy and in combination with dialysis machines and heart-lung machines. The absorber cartridge is filled with sorbent beads which adsorb the cytokines as they pass through the blood pump. The patient's blood is continuously recirculated between the absorption device and the patient up to a maximum of 24 hours; afterwards the cartridge needs to be replaced. Typically, the treatment duration for sepsis patients is 48 to 72 hours. The preventive use of ECAT during CPB surgery lasts as long as the heart-lung machine is connected. For a CPB duration of more than >120 min, the use of CytoSorb® during CPB surgery is recommended [16].

1 weiteres Gerät hat seit dem letzten Assessment CE-Mark erhalten (oXiris®)

The previous HTA report [1] identified four further devices in the pre-clinical stage. In recent years, only one additional device (oXiris®) received a CE mark authorisation in 2017 [17, 18]. This product is an extracorporeal blood purification set that can adsorb endotoxin, cytokines and uremic toxins. The product is marketed to be used in sepsis management.

Scope 2017

The detailed PICO inclusion criteria of the initial assessment can be found in [1]. The slightly modified PICO table is depicted in Table 1-1.

Results

verfügbare Evidenz in 2017: 1 RCT & 2 Beobachtungsstudien

In 2017, one randomised controlled trial (RCT) [19] and one retrospective case series [20] were included to assess the efficacy of ECAT as a preventive intervention during CPB surgery. The total number of patients was 77, of who 39 received CytoSorb® therapy. Both studies assessed the preventive use of CytoSorb® during CPB surgery [1].

To assess safety outcomes, one additional retrospective case series [21] was identified (16 patients). Similar to the two other studies, it assessed the use of CytoSorb® in SIRS patients; however, therapeutically following CPB surgery.

The review authors of the previous assessment could not identify any controlled study on ECAT as a therapeutic addition to the treatment of sepsis [1].

Clinical effectiveness

in 2017: unzureichende Evidenz, die nachweist, dass ECAT wirksam und sicher ist

Regarding the crucial outcomes for effectiveness, one randomised controlled trial [19] with a high risk of bias was included. The study found no statistically significant differences in 30-day mortality, the length of stay in intensive care units (ICU) and in the days of mechanical ventilation. The retrospective case series [20] including 40 patients did not report on any of the crucial effectiveness outcomes. None of the studies reported on the total days of hospitalisation or on changes in the SOFA score, MODS score, or another measure to assess organ failure.

Safety

None of the studies [19-21] reported on adverse events (AE) or serious adverse events (SAE) for the use of CytoSorb® during CPB surgery or post-operatively. In total, the technology was used in 55 patients. Furthermore, no adverse device events were described.

Recommendation

Empfehlung aus 2017: Re-Evaluierung in 2019

In 2017, ECAT was not recommended to be included in the catalogue of benefits. The authors further recommended to reevaluate the technology in 2019 [1].

UPDATE 2020

1 Scope

The scope of this update is the extracorporeal cytokine adsorption in sepsis, septic shock and SIRS; these were the only indications analysed in this assessment. In contrast to 2017, we applied stricter inclusion criteria with regard to the study design because RCTs were published.

Update-Assessment 2020
Einschränkung auf RCTs & prospektive NRCTs

There are other substances (e.g., ticagrelor, bilirubin, myoglobin) in the blood that may be adsorbed in other indications (e.g., rhabdomyolysis) that are beyond the scope of this assessment.

1.1 PICO question

Is ECAT as an addition to standard care in comparison to standard care alone in patients with SIRS, sepsis or septic shock as safe concerning adverse events and more effective concerning mortality, organ function and recovery?

ECAT therapeutisch

Is ECAT as a preventive therapy in patients undergoing CPB as safe concerning adverse events and more effective concerning mortality, organ function and recovery?

ECAT präventiv

Table 1-1: Inclusion criteria

Population	❁ Patients with SIRS, sepsis, septic shock (abdominal septis, pneumonia with septic shock, septic arthritis, UTI) or SIRS (systemic inflammatory response syndrome) International Classification of Diseases (ICD)-10 R65.20 Sepsis; Septic shock; R65.21 [3] ❁ As a preventive measure against SIRS in patients undergoing elective cardiopulmonary bypass surgery (CPB) Adults of all ages >18 MeSH Terms: Severe Sepsis C01.539.757, C23.550.470.790.500; Septic Shock C01.539.757.800, C23.550.470.790.500.800, C23.550.835.900.712; SIRS C23.550.470.790, C23.550.835.900
Intervention	1. Cytokine adsorption as a therapeutic intervention in patients with SIRS, sepsis or septic shock 2. Cytokine adsorption therapy as a preventive intervention during cardiopulmonary bypass surgery Alternative terms (selection): ❁ hem(a)adsorption ❁ haemadsorption ❁ extracorporeal blood purification ❁ extracorporeal cytokine adsorption ❁ cytokine removal therapy ❁ cytokine filter Product names: CytoSorb® (CytoSorbents), oXiris® (Baxter)

Control	Standard care for SIRS sepsis and septic shock[2,] Standard care after coronary bypass surgery
Outcomes	
Efficacy	Clinical endpoints: ❁ Improved survival/reduced mortality ❁ Improved clinical outcomes: organ functions (Sepsis-related Organ Failure Assessment, SOFA score or Multiple Organ Dysfunction score, MODS) ❁ Days in ICU ❁ Days of hospitalisation ❁ Ventilator-free days Surrogate endpoints: ❁ Decrease in dose of vasopressor drugs ❁ Decrease in blood cytokine levels
Safety	❁ Perioperative/periprocedural or postoperative/postprocedural (serious) adverse events
Study design	
Efficacy	❁ Randomised controlled trials with at least 20 pts ❁ Prospective non-randomised controlled trials with at least 20 pts
Safety	❁ Randomised controlled trials with at least 20 pts ❁ Prospective non-randomised controlled trials with at least 20 pts

[2] Cytokine adsorption therapy serves as an addition to *standard care*, as defined in [22]

2 Methods

The study was undertaken in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [23, 24].

2.1 Research questions

Clinical effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of ECAT on mortality?
D0005	How does ECAT affect symptoms and findings (severity, frequency) of sepsis or SIRS?
D0006	How does the technology affect progression (or recurrence) of sepsis or SIRS?
D0011	What is the effect of ECAT on patients' body functions?
D0012	What is the effect of ECAT on generic health-related quality of life?
D0013	What is the effect of ECAT on disease-specific quality of life?
D0017	Were patients satisfied with ECAT?

Safety	
Element ID	**Research question**
C0008	How safe is ECAT in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying ECAT?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ECAT?
C0007	Is ECAT associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of ECAT?

2.2 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 10th and 11th of December 2019 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

Zeitraum: 2016-2019

The systematic search was limited to the years 2016 to 2019 and, in Medline and Embase, to only articles published in English or German. After deduplication, 286 citations were included overall. The specific search strategy employed can be found in the Appendix.

ergänzende manuelle Suche

Furthermore, a web-based manual search (e.g., on websites of the manufacturers) was conducted to strengthen the systematic search, resulting in eight potentially relevant hits.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 31st of January 2020, resulting in 74 potentially relevant hits.

insgesamt 294 Publikationen identifiziert

Manufacturers from the most common products (CytoSorbents Europe Corporation) submitted 17 publications, of which 0 new citations were identified. A list providing information on 19 ongoing studies was further provided.

2.3 Flow chart of study selection

Literaturauswahl

Overall, 294 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

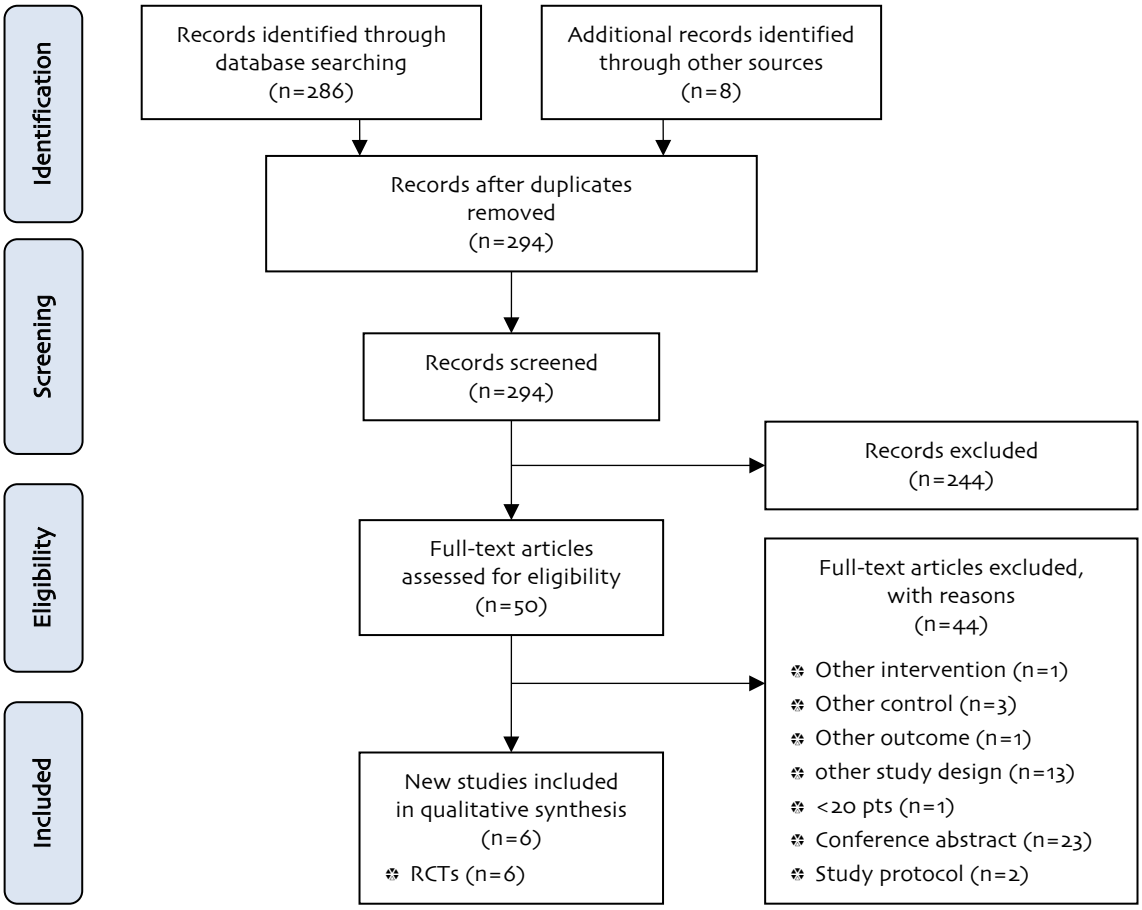

Figure 2-1: Flow chart of study selection from update search (PRISMA Flow Diagram)

2.4 Analysis

Datenextraktion aus Studien

Relevant data from eligible studies were systematically extracted into data-extraction tables. The single-data extraction method with verification by another researcher was utilised: One researcher (GG) extracted the data and another researcher (KH) checked the extracted data.

Qualitätsbeurteilung der Studien mit Cochrane RoB Tool (v.1)

Two independent researchers (GG, KH) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool [25].

All discrepancies were resolved by consensus or by involving a third researcher (CW) in case it could not be resolved.

2.5 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

In addition, we used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) to synthesise the identified evidence [26]. GRADE evidence tables and a GRADE summary of findings tables were hereby created. No inferential statistical analysis was conducted in the absence of high quality data derived from RCTs.

3 Clinical effectiveness

3.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

wesentliche Endpunkte:

- Reduced mortality
- Improved clinical outcomes (organ function) assessed with a MODS or SOFA score
- ICU length of stay (in days)
- Length of hospitalisation (in days)

Mortality is an intuitive and highly patient-relevant measure when assessing a clinical benefit of ECAT [27]. Moreover, we selected further outcomes that evaluate organ function (MODS or SOFA score) and alterations in individual measures of ICU intervention (ICU length of stay, length of hospitalisation) [27].

Mortalität
Organfunktion
Tage in ICU
Tage im Spital

The most common scoring systems to assess organ dysfunction are the MODS or SOFA score. Both of these scoring systems aim at describing a sequence of complications in critically ill patients. Six organ systems are considered for evaluation: respiratory, cardiovascular, renal, hematologic, neurologic and hepatic. For each organ system, a function can be rated from normal (0) to most abnormal (4) [28, 29]. The main difference between these scores is in the context of evaluating cardiovascular function [30]: whilst blood pressure in combination with the level of adrenergic support is considered within the SOFA score, the pressure-adjusted heart rate is used as a composed variable in MODS [29].

ICU length of stay and length of hospitalisation provide an aggregate measure of disease burden of these patients surviving sepsis [27]. These variables are measured quantitatively, usually in days or hours.

In analogy of the original systematic review published in 2017 [1], further patient-relevant (ventilator-free days) and surrogate (decrease in vasopressor drugs; cytokine levels: reduction of IL-6) outcomes were defined as relevant to assess the effectiveness of the technology under investigation. These outcomes are described, but due to the limited or unclear relevance for patient outcomes, the evidence on these outcomes will not impact on the drawn recommendations.

weitere relevante Endpunkte:
beatmungs-freie Tage,
Reduktion der Katecholamine,
Reduktion des Zytokin-Levels

3.2 Included studies

7 RCTs

In order to assess the efficacy of ECAT, we found six new RCTs to be included [31-34] in addition to the RCT [19] already been included in the initial assessment published in 2017 [1]. The body of evidence of all RCTs will be described in this evidence synthesis.

5 Studien zu ECAT (präventiv) bei Herzchirurgie; 2 weitere Studien zu ECAT (therapeutisch) bei Sepsis

Five studies investigated ECAT as a preventive measure against SIRS in cardiac surgery [19, 31-34], whilst two studies [35, 36] investigated the benefit of using ECAT as a therapeutic intervention in sepsis or septic shock.

Study characteristics and results of the included studies are displayed in Table A-1/Table A-2 and in the evidence profile in Table A-4/Table A-5.

3.3 Results

3.3.1 ECAT in cardiac surgery

Included studies

Study characteristics

ECAT (präventiv) bei kardio-OP mit kardiopulmonalem Bypass

For the use of ECAT as a preventive measure against SIRS in cardiac surgery, five RCTs fulfilled the inclusion criteria. Four studies were conducted in Europe [19, 31, 33, 34] and one further study [32] was conducted in the United States.

5 RCTs hohes RoB in 4/5 Studien niedriges RoB in 1/5 Studien

Overall, the RoB of the included studies was high in four of them [19, 31, 32, 34] and low in one other [33]. It is noteworthy to state that three out of five studies were sponsored by the industry [31-33].

In all of the included studies, the intervention group received standard care and haemadsorption with CytoSorb® during CPB. The control groups received 'no intervention'/standard care alone in all included studies.

Patient characteristics, follow-up and outcomes

197 Pts eingeschlossen

Davon analysiert: Wirksamkeit: 82 vs. 81

Sicherheit (nur 4 RCTs): 74 vs. 74

Overall, the studies enrolled 197 patients who received ECAT (n=99) or standard care without ECAT (n=98). The loss to follow-up rate was insufficiently reported by two studies [32, 33] and ranged from 4.8% to 33.3% in the intervention group and 9.1% to 37.5% in the control group in the other three studies [19, 31, 34]. Finally, the number of patients analysed for efficacy outcomes was 82 receiving ECAT and 81 receiving standard care alone. Only four studies reported on safety outcomes, with 74 analysed patients each in the intervention group as well as the control group across studies.

Einschlusskriterien: geringe Unterschiede

In all of the studies, ECAT was performed during cardiac surgery, yet the specific inclusion/exclusion criteria differed slightly across studies and one study [34] did not specify its eligibility criteria.

durchschnittliches Alter: IG: 50-67,9 J.; KG: 54-72,7 J.

Age was reported differently across studies: Three studies [31, 32, 34] reported on age using the mean as a measure of central tendency, ranging from 50 to 67.9 years in the intervention groups and 54 to 72.7 in the control groups. The other two studies only reported on the median age of patients in the in-

tervention and control groups: In one study [19] the median age was 64 and 69 years, respectively, whilst the other study [33] reported a median age of 67 and 69 years, respectively

Four studies [19, 32-34] reported on the percentage of female patients in their sample: This ranged from 13% to 44.5% in the intervention groups as opposed to 0% to 26.7% in the control groups. Another study [31] did not report on the percentage of female patients in their sample.

Geschlecht:
13-44,5 % Frauen in IG und 0-26,7 % Frauen in KG

All of the included studies [19, 31-34] used surrogate outcomes such as the reduction of inflammatory cytokines as their primary outcome measures. Secondary outcomes covered patient-relevant outcomes such as mortality and length of stay in the ICU.

Primäre Endpunkte: Surrogate

The length of follow-up was 30 days in two studies [19, 32] and 'hospital discharge' (not further specified) in the remaining three studies [31, 33, 34].

Follow-up: bis zur Entlassung/30 Tage

Study characteristics and the results of included studies are displayed in the data extraction table (see Table A-1) and in the evidence profile (see Table A-4) that can be found in the Appendix.

Mortality

D0001 – What is the expected beneficial effect of ECAT on mortality?

Mortality was reported as a secondary outcome by all of the included studies up to three months' follow-up. Across three studies [19, 33, 34], mortality ranged from 0/13 (0%) to 1/15 (6.7%) in the ECAT group, as opposed to a range of 0/10 (0%) to 2/15 (13.3%) in patients undergoing standard care treatment.

Mortalitätsrate in 3 Studien:
IG: 0-6,7%
KG: 0-13,3%

One further study solely reported that there was no difference in mortality [32]; another study [31] reported on a mean mortality index of 6.6±5.4 in the intervention group as opposed to 8.12±7.5 in the control group.

None of the studies were able to detect a statistically significant difference in mortality.

Mortalitätsindex in 1 Studie:
IG: 6,6±5,4
KG: 8,12±7,5
mangelnde Berichterstattung in weiteren Studie

Morbidity

D0005 – How does ECAT affect symptoms and findings (severity, frequency) of SIRS or sepsis?

To answer this research question, the crucial outcome 'improved clinical outcomes of organ functions' was used and evaluated by a change in the MODS or SOFA score.

keine Studie erhob/berichtete SOFA oder MODS

None of the included studies reported on clinical outcomes of organ function.

In addition, the evidence shows inconsistent results with regard to the surrogate outcome change in cytokine concentration: One study [32] found the device to be associated with reduced IL-6 levels, whilst another study [33] found higher IL-6 levels in the intervention group when compared to the control group throughout study time points. Two further studies [19, 31] found no difference in IL-6 levels between the intervention and control group and the remaining study [34] did not report on this outcome.

Reduktion von Zytokin IL-6:

widersprüchliche Ergebnisse

D0006 – How does the technology affect progression (or recurrence) of sepsis or SIRS?

In order to answer this research question, the length of ICU stay, days of hospitalisation, days of ventilator therapy, and need of vasopressor therapy were applied as indicators for disease progression.

Tage in ICU: kein stat. signifikanter Unterschied

Length of ICU stay was reported by all included studies [19, 31-34]: None of these could detect a statistical difference when comparing this outcome between the intervention and control groups. Three studies [19, 31, 32] reported on mean ICU stay, which ranged from 2.3 to 4.3 days in the intervention groups as opposed to 2.1 to 6.8 days in the control groups. The other two studies [33, 34] reported on median values: One study reported on 1.8 and 1.0 days; the other study reported on 2 and 3 median days of ICU stay in the intervention and control group, respectively.

Dauer der Hospitalisierung, kein stat. signifikanter Unterschied

Days of hospitalisation were reported by three out of five included studies [31, 32, 34]: None of the studies was able to detect a statistically significant difference when comparing days of hospitalisation between the intervention and control groups. Mean post-surgery days of hospitalisation in the intervention and control groups was 9.0 and 8.6 days in one study [31] and 11.8 and 14 days in another study [32]. One further study [34] reported on 9.0 and 8.0 median days of hospitalisation in the intervention and control group, respectively.

Beatmung und Medikamentierung (Katecholamine):

kein stat. signifikanter Unterschied

Days of ventilator therapy were reported by two out of five included studies [19, 33]: None of these studies was able to detect a statistically significant difference. In one study [19], mean days of ventilator therapy were 0.7 and 0.2 in intervention and control group, respectively. The other study [33] reported on 5.0 and 8.0 median hours of ventilator therapy.

Reduction of vasopressor therapy was reported by three out of five included studies [19, 31, 33]: Catecholamine support between treatment groups was reported in two studies, with no statistically significant differences in these studies [19, 31]. Similarly, no statistically significant difference was found in the need for vasopressor therapy more broadly, with two studies reporting on this outcome [19, 33].

Function

D0011 – What is the effect of the technology on patients' body functions?

keine Evidenz zu Körperfunktionalität

None of the studies reported results on the patient's body functions.

Health-related quality of life

D0012 – What is the effect of ECAT on generic health-related quality of life?

D0013 – What is the effect of ECAT on disease-specific quality of life?

keine Evidenz zu QoL

None of the studies reported results on the health-related quality of life or on the disease-specific quality of life.

Patient satisfaction

D0017 – Were patients satisfied with ECAT?

keine Evidenz zu Patientenzufriedenheit

None of the studies assessed patient satisfaction.

3.3.2 ECAT in sepsis and septic shock

Included studies

Study characteristics

For the therapeutic use of ECAT in patients with sepsis or septic shock, two RCTs fulfilled the inclusion criteria. The studies were conducted in Hungary [35] and Germany [36].

ECAT therapeutisch in Sepsis/septischer Schock

Overall, the RoB of the included studies was high. One study [36] was sponsored by the industry, whilst another study [35] was funded by a publicly funded body.

2 RCTs hohes RoB

In all of the included studies, the intervention group received standard care and haemadsorption with CytoSorb® in sepsis or septic shock. The control groups received 'no intervention'/standard care alone in all included studies.

Patient characteristics, follow-up and outcomes

Overall, the studies enrolled 120 patients receiving ECAT and standard care (n=58) or standard care without ECAT (n=62). The loss to follow-up rate was insufficiently reported by one study [35] whilst the other study [36] reported on a rate of 2.1% in the intervention group as opposed to 3.9% in the control group. Finally, the number of analysed patients was 57 receiving ECAT in addition to standard care and 60 receiving standard care alone.

120 Pts eingeschlossen

davon analysiert: 57 vs. 60

The inclusion/exclusion criteria were homogenous across studies.

homogene Einschlusskriterien

Age was reported differently across studies: One study [35] reported on a mean age of 60 ±10 in the intervention group and 71 ±14 in the control group. The other study [36] reported on a median age of 66 (range: 55-73) in the intervention group as opposed to 65 (range: 56.5-71) in the control group.

Overall, the percentage of female patients in the intervention and control group was 30% and 40%, respectively, in one study [35] and 25.5% and 30% in the other study [36].

One of the included studies selected surrogate outcomes (reduction of cytokine levels) as primary outcome measures [36]; the other study [35] selected organ dysfunction and inflammatory response as a primary outcome, but had a considerably smaller sample (n=20).

Fokus auf Surrogatendpunkte

The length of follow-up was 48 hours in one study [35] and 60 days in the other [36].

Follow-up: 2-60 Tage

Study characteristics and results of included studies are displayed in the data extraction table (see Table A-2) and in the evidence profile (see Table A-5) that can be found in the Appendix.

Mortality

D0001 – What is the expected beneficial effect of ECAT on mortality?

Mortalität:
60 Tage (1 Studie):
IG: 44,7 %
KG: 26 %, stat. signifikant (p=0.039)

28 Tage (1 Studie):
keine stat. signifikanten Unterschiede

48 Stunden (1 Studie):
nicht stat. getestet

Two studies reported on mortality rates as a secondary outcome: One study [36] with 97 analysed patients found a statistically significant difference in 60-day mortality, with 21 (44.7%) and 13 (26%) deceased patients in the intervention and control group, respectively (p=0.039). The difference in 60-day mortality is unadjusted for comorbidities. The authors noted that this difference was not seen after adjusting for comorbidities and baseline imbalances (p=0.19). The same study found no statistically significant difference in 28-day mortality, with 17 (36.2%) and 9 (18%) deceased patients in intervention and control group, respectively (p=0.073).

In the other study [35] with 20 analysed patients, mortality was reported, but no statistical testing was conducted. Five out of ten patients (50%) died in the intervention and control group, respectively, in this study. Within 48 hours, none of the ten patients died in the intervention group, as opposed to two out of ten (20%) deceased patients in the control group.

Morbidity

D0005 – How does ECAT affect symptoms and findings (severity, frequency) of SIRS or sepsis?

Organfunktion

To answer this research question, the crucial outcome 'improved clinical outcomes of organ functions' was used and evaluated by a change in the MODS or SOFA score.

MODS-Score (1 Studie):
kein stat. signifikanter Unterschied

The outcome **MODS score** was reported by one of the included studies [36], detecting no difference between groups (no further information was reported).

SOFA-Score (1 Studie):
kein stat. signifikanter Unterschied

The **SOFA score** was reported by the other included study [35], detecting no statistically significant difference between the intervention and control group up to 48 hours' follow-up.

Zytokinlevel (1 Studie):
kein stat. signifikanter Unterschied

The surrogate outcome **change in cytokine concentration** in the blood was reported by one of the included studies [36]: The study did not detect a difference in IL-6 systemic plasma levels between the intervention and control group (p=0.15).

D0006 – How does the technology affect progression (or recurrence) of sepsis or SIRS?

In order to answer this research question, the length of ICU stay, days of hospitalisation, days of ventilator therapy, and need of vasopressor therapy were applied as indicators for disease progression.

Tage in ICU (1 Studie):
kein stat. signifikanter Unterschied
Tage im Spital: NR

Length of ICU stay was reported by one of the included studies [35]: On average, the length of ICU stay was 10.2 (±8.5) and 10.0 (±4.3) days in the intervention and control group, respectively (p-value not reported).

Days of hospitalisation was not reported by any of the included studies.

Tage mit künstlicher Beatmung (1 Studie):
kein stat. signifikanter Unterschied

Days of ventilator therapy was reported by one study [36], with a median time (in days) of 17.5 (IQR: 8.6-25.9) in the intervention group and 12.1 (IQR: 7.0-23.1) in the control group. The difference was not statistically significant (p=0.306).

Reduction of vasopressor therapy was reported by one of the included studies [35], stating narratively that a significant reduction in need or vasopressor support was detected in the intervention group. This reduction was not shown in the control group (no further information were reported).

Reduktion Vasopressortherapie (1 Studie): signifikante Reduktion in Interventionsgruppe

Function

D0011 – What is the effect of the technology on patients' body functions?

None of the studies reported results on the patient's body functions.

keine Evidenz zu Körperfunktionalität

Health-related quality of life

D0012 – What is the effect of ECAT on generic health-related quality of life?

D0013 – What is the effect of ECAT on disease-specific quality of life?

None of the studies reported results on the health-related quality of life or on the disease-specific quality of life.

keine Evidenz zu QoL

Patient satisfaction

D0017 – Were patients satisfied with ECAT?

None of the studies assessed patient satisfaction.

keine Evidenz zu Patientenzufriedenheit

4 Safety

4.1 Outcomes

ECAT can lead to device- and procedure-related side effects. One potential side effect of extracorporeal circuits is the clotting of the blood in the circuit, which can, for instance, block the circuit or send a blood clot into the patient, which subsequently can cause an embolic event. Furthermore, a leakage of the device and a disconnection of the bloodline can cause sudden excessive blood loss.

Interventions-bezogene Endpunkte: Blutgerinnsel, Blutverlust durch Leck oder Trennung, Luftembolie

The *instructions for use* of CytoSorb® specifically advise the user to control the pressure of the extracorporeal circuit and tightly monitor anticoagulation to reduce the risk of blot clotting [37, 38]. Air entering the bloodlines and the circuit can result in serious injury and even death, as this could cause air embolism. The manufacturers further warn that, in rare cases, hypersensitivity reactions may occur during the treatment. In the event of a hypersensitivity reaction, the physician would have to decide whether to return the blood to the patient [37, 38].

Hypersensibilitäts-Reaktionen, Hypotension, Temperaturveränderung, Muskelkrämpfe, Übelkeit

The following outcomes were, therefore, defined as *crucial* to derive a recommendation:

wesentliche klinische Endpunkte für Empfehlung: Peri- und postoperative AE/SAE

- serious adverse events (SAE; peri- or postoperatively)
- adverse events (AE; peri- or postoperatively)

In accordance with the European Commission guidelines for medical devices on SAE reporting, the following definitions applied [39]:

AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or related to the procedures involved (any procedure in the clinical investigation plan).

EC-Guidelines zu Definitionen von Nebenwirkungen und Komplikationen bei Medizinprodukten

SAE is an adverse event that led i) to death, ii) to a serious deterioration in the health of the subject that either resulted in a life-threatening illness or injury, iii) a permanent impairment of a body structure or a body function, iv) in-patient hospitalisation or prolongation of existing hospitalisation, v) medical or surgical intervention to prevent a life-threatening illness or injury.

Differenzierung UE, SUE, ECAT induzierte UE/SUE

A serious adverse device effect (SADE) or device-related AE/SAE is an adverse event related to the use of a medical device that has resulted in any of the consequences characteristic of a serious adverse event.

4.2 Included studies

A description of the eligible evidence can be found in Section 3.2. Study characteristics and results of included studies are further displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-4/Table A-5.

4.3 Results

4.3.1 ECAT in cardiac surgery

Patient safety

C0008 – How safe is ECAT and standard care in comparison to standard care alone?

Sicherheit ECAT bei kardio-OP

Safety outcomes were reported in four out of five included studies [19, 31-33] that analysed safety outcomes in 148 patients overall. None of the studies was able to detect a statistically significant difference in safety outcomes.

Berichterstattung in 4 Studien (n=148)

In absolute numbers, 57 and 55 cases of SAEs were reported in the intervention and control groups, respectively. There were some further 144 and 167 cases of AEs in the intervention and control groups, respectively.

Pts mit SUEs: 0-69,6 % vs. 0-53,3 %

Pts mit UEs: 0-100 % vs. 0-91,3 %

In two studies [19, 31], no SAEs or AEs were reported in neither the intervention nor the control group. In the two remaining studies, the number of patients with at least one SAE in the intervention group and control group was eight (53.3%) vs. eight (53.3%) in one study [33] and 16 (69.6%) vs. 11 (47.8%) in another study [32]. AEs were reported in one study [32]: 23 (100%) and 21 (91.3%) patients had at least one AE in the intervention group and control group, respectively. One further study [33] reported on 23 and 30 total AEs in the intervention and control group, respectively – without reporting the number of patients in who these AEs occurred.

ECAT induzierte UEs (2 RCTs): 0-8,7 %

The outcome of device-related AEs was reported by two studies [19, 32]: In one study [19], no device-related AEs occurred. The other study [32] reported on two patients (8.7%) with at least one device-related AE.

The categories of adverse events were reported by the two studies in which cases occurred [32, 33]: In one study [33], common adverse events in the intervention group (n=15) were arrhythmias, surgical complications and acute kidney injury, occurring in five (33.3%), four (26.7%) and four (26.7%) patients, respectively. Respiratory and neurological AEs (including stroke) occurred in two patients (13.3%), respectively. Lastly, cardiogenic shock, haemorrhagic shock, distributive shock, infections or acute liver failure occurred in one patient (6.7%), respectively. In the control group (n=15), eight patients (53.3%) had arrhythmias. Surgical complications, infections and acute kidney injury occurred in four (26.7%) of the patients, respectively. Three further patients (20%) suffered from neurological AEs (20%). Lastly, distributive shock and electrolyte disorders occurred in two patients (13.3%) and one patient (6.7%), respectively.

In the other study [32], event categories were reported for SAEs only: In the intervention group (n=23), the following types of SAEs occurred: cardiac disorders in ten patients (43%), followed by renal and urinary disorders in six patients (26%). Blood/lymphatic disorders occurred in four patients (17%). SAEs in the respiratory thoracic and mediastinal area or procedural complications or SAEs in the vascular area occurred in three patients (13%), respectively. Metabolism/nutrition disorders occurred in two patients (9%), whilst no nervous system disorders (0%) occurred at all. In the control group (n=23), cardiac disorders as well as renal and urinary disorders occurred in six patients (26%), respectively. Further five patients (22%) suffered from respiratory thoracic and mediastinal disorders. Procedural complications occurred in four patients (17%). In addition, vascular disorders, metabolism/nutrition disorders as well as nervous system disorders were recorded in three patients (13%), respectively. One further patient in the control group (4%) suffered from blood/lymphatic system disorders.

UE Kategorien in 1 RCT (n=30):
Atemwege: 13,3 vs. 0 %
kardiogen: 6,7 vs. 0 %
hämorrhag.: 6,7 vs. 0 %
distributiver Schock: 6,7% vs. 13,3 %
Arrhythmie: 33,3 vs. 53,3 %
chir. Komplikationen: 26,7 vs. 26,7 %
Infektionen: 6,7 vs. 26,7%
akutes Leberversagen: 6,7 vs. 0 %
akute Nierenschädigung: 26,7 vs. 26,7 %
neurolog.: 13,3 vs. 20 %
Elektrolytstörung: 0 vs. 6,7 %

SUE Kategorien in 1 RCT (n=23)
kard. Störgn: 43 vs. 26 %
resp./thorakal/ mediastinal: 13 vs. 22 %
prozedural: 13 vs. 17 %
Niere/Harnw.: 26 vs. 26 %
Blutgefäße: 13 vs. 13 %
Lymphsystem: 17 vs. 4 %
Stoffwechsel: 9 vs. 13%
Nervensystem: 0 vs. 13%

C0002 – Are the harms related to dosage or frequency of applying ECAT?

None of the studies reported results to answer this question.

keine Evidenz

C0004 – How does the frequency or severity of harms change over time or in different settings?

None of the studies reported results on how the frequency and severity of potential harms change over time.

keine Evidenz

C0005 – What are the susceptible patient groups that are more likely to be harmed by the use of ECAT?

No evidence was found to answer this research question.

keine Evidenz

C0007 – Is ECAT associated with user-dependent harms?

No evidence was found to answer this research question.

keine Evidenz

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of ECAT?

No evidence was found to answer this research question.

keine Evidenz

4.3.2 ECAT in sepsis and septic shock

Patient safety

C0008 – How safe is ECAT and standard care in comparison to standard care alone?

Sicherheit (2 RCTs) 1 Studie mit adäquater Berichterstattung zu UE/SUE

One out of two studies [36] reported on overall AEs/SAEs.

In absolute numbers, one study [36] reported on 26 and 15 SAEs in the intervention and control group, respectively. The same study reported 53 and 48 AEs in intervention and control group, respectively.

Pts mit SUEs: 53,2 % vs. 24 % Pts mit UEs: 63,8 % vs. 50 % p-value NR

The number of patients with at least one SAE and AE was reported by the same study [36]: 25 patients (53.2%) in the intervention group as opposed to 12 patients (24%) in the control group suffered from at least one SAE. In the same study, at least one AE occurred in some 30 patients (63.8%) in the intervention group and 25 patients (50%) in the control group. P-values were not reported by the included study.

ECAT induzierte UEs (2 Studien): 0 UEs/SUEs in 10 pts & 5 SUEs & 8 UEs in 47 pts

Device-related AEs/SAEs were reported by both studies [35, 36]. Five device-related SAEs and eight device-related AEs occurred in 47 patients receiving ECAT in one study [36]. The other study [35] mentioned narratively that no device-related AEs occurred in ten patients receiving ECAT.

None of the studies reported on specific event categories for AEs/SAEs.

C0002 – Are the harms related to dosage or frequency of applying ECAT?

keine Evidenz

None of the studies reported results to answer this question.

C0004 – How does the frequency or severity of harms change over time or in different settings?

keine Evidenz

None of the studies reported results on how the frequency and severity of potential harms change over time.

C0005 – What are the susceptible patient groups that are more likely to be harmed by the use of ECAT?

keine Evidenz

No evidence was found to answer this research question.

C0007 – Is ECAT associated with user-dependent harms?

keine Evidenz

No evidence was found to answer this research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of ECAT?

keine Evidenz

No evidence was found to answer this research question.

5 Quality of evidence

RoB: niedrig in 1 RCT & hoch in 6 RCTs

RoB for individual studies was assessed with the Cochrane RoB tool [25] and is presented in Table A-3 in the Appendix. The RoB is low in one RCT and high in the remaining six RCTs. The risk of bias was increased mainly due to uncertainties with regard to the generation of the randomisation sequence and allocation concealment, as well as the lack of blinding in several studies.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [26] for each outcome individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference.

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Stärke der Evidenz ECAT bei kardio-OP (präventiv): sehr niedrig

The ranking according to the GRADE schema for the research questions can be found in the summary of findings table below and in the evidence profile in the Appendix (see Table A-4 and Table A-5).

ECAT bei Sepsis (therapeutisch): sehr niedrig

Overall, the strength of evidence for the effectiveness and safety of ECAT in combination with standard care in comparison to standard care alone is very low for both preventive (cardiac surgery) and therapeutic (sepsis or septic shock) use.

Table 7-1: Summary of findings table of ECAT in cardiac surgery

Outcomes	Anticipated effects (ECAT and standard care vs. standard care alone)	№ of analysed pts (studies)	Certainty of the evidence (GRADE)	Comments
Efficacy				
Mortality	None of the studies was able to detect a statistically significant difference in mortality up to 30 days follow-up. Ranges of mortality rates (3 studies): 0-6.7% vs. 0-13.3% Mortality index (1 study): 6.6 ±5.4 vs. 8.12 ±7.5 One further study solely reported that there was no difference in mortality rates without reporting on these.	163 (5 RCTs)	⊕◯◯◯ VERY LOW [a, b]	
Organ function assessed with: SOFA/MODS score	-	(0 studies)	-	-
Length of stay in ICU (in days)	None of the studies was able to detect a statistically significant difference in LoS in ICU. Mean LoS in ICU in 3 studies: 2.3-4.3 vs. 2.1-6.8 days Median LoS in ICU in 2 studies: 1.8-2 vs. 1-3 days	163 (5 RCTs)	⊕◯◯◯ VERY LOW [a, b]	
Days of hospitalisation	None of the studies was able to detect a statistically significant difference in days of hospitalisation. Mean post-surgery hospitalisation (2 studies): 9-11.8 vs. 8.6-14 days Median days of hospitalisation (1 study): 9 vs. 8 days	101 (3 RCTs)	⊕◯◯◯ VERY LOW [a, b]	
Safety				
(Serious) adverse events (SAE/AE)	None of the studies was able to detect a statistically significant difference in SAEs or AEs SAEs (4 studies): 0-69.6% vs. 0-53.3% AEs (3 studies): 0-100% vs. 0-91.3%. Device-related AEs (2 studies):0-8.7%	148 (4 RCTs)	⊕◯◯◯ VERY LOW [a, b]	Range of patients with at least one (S)AE in %

Abbreviations: ***AE*** *– adverse events;* ***ECAT*** *– extracorporeal cytokine haemadsorption therapy;* ***ICU*** *– intensive care unit;* ***LoS*** *– length of stay;* ***pts*** *– patients;* ***RCT*** *– randomised controlled trial;* ***SAE*** *– serious adverse events.*

Explanations

[a] *The risk of bias was high in all studies except for Poli 2019 [33].*
Especially the uncertainties with regard to the generation of the randomisation sequence and allocation concealment may be described as serious limitations.

[b] *None of the studies were powered to detect a difference in this outcome. Small number of cases/small number of enrolled patients.*

GRADE Working Group grades of evidence

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*
Moderate certainty: *We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different*
Low certainty: *Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect*
Very low certainty: *We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect*

Table 7-2: Summary of findings table of ECAT in sepsis or septic shock

Outcomes	Anticipated effects (ECAT and standard care vs. standard care alone)	№ of analysed pts (studies)	Certainty of the evidence (GRADE)	Comments
Efficacy				
Mortality	60-day mortality (1 study; n=97): 21 (44.7%) vs. 13 (26%); p=0.039 28-day mortality (1 study; n=97): 17 (36.2%) vs. 9 (18%); p=0.073 48-hr mortality (1 study, 20 pts): 0 (0%) vs. 2 (20%), p-value NR Overall mortality in the same study (no specific follow-up time reported): 5 (50%) vs. 5 (50%); p-value NR	117 (2 RCTs)	⊕◯◯◯ VERY LOW [a, b]	Differences are unadjusted for comorbidities
Organ function assessed with: SOFA/MODS score	MODS score (1 study; n=97): no difference between IG and CG (no further information reported) SOFA score (1 study; n=20): no significant difference between IG and CG	117 (2 RCTs)	⊕◯◯◯ VERY LOW [a, b]	
Length of stay in ICU (in days)	10.2 ± 8.5 vs. 10.0 ± 4.3; p-value NR	20 (1 RCT)	⊕◯◯◯ VERY LOW [a, b]	
Days of hospitalisation	-	(0 studies)	-	
Safety				
(Serious) adverse events (SAE/AE)	SAEs (1 study; n=97): 25 (53.2%) vs. 12 (24%), p-value NR AEs (1 study; n=97): 30 (63.8%) vs. 25 (50%), p-value NR Device-related SAE (2 studies):5 (in 47 pts) & 0 (in 10 pts) Device-related AE (2 studies):8 (in 47 pts) & 0 (in 10 pts)	117 (2 RCTs)	⊕◯◯◯ VERY LOW [a, b]	n (%) of patients with at least one (S)AE. Device-related (S)AEs only reported in total cases.

Abbreviations: ***AE*** *– adverse events;* ***ECAT*** *– extracorporeal cytokine haemadsorption therapy;* ***ICU*** *– intensive care unit;* ***LoS*** *– length of stay;* ***pts*** *– patients;* ***RCT*** *– randomised controlled trial;* ***SAE*** *– serious adverse events.*

Explanations

[a] *The risk of bias was high in the included study/ies.*
Especially the uncertainties with regard to the generation of the randomisation sequence and allocation concealment may be described as serious limitations.

[b] *None of the studies were powered to detect a difference in this outcome. Small number of cases/small number of enrolled patients.*

GRADE Working Group grades of evidence

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*
Moderate certainty: *We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different*
Low certainty: *Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect*
Very low certainty: *We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect*

6 Discussion

The use of extracorporeal cytokine adsorption therapy is an add-on measure that aims to reduce inflammatory cytokines potentially leading to improved patient-relevant outcomes such as reduced mortality and improved organ function. This update report aimed at synthesising the currently available evidence with regard to the comparative efficacy and safety of the device.

Update 2020

Overall, the update report captures evidence from seven randomised controlled trials [19, 31-36]: One study [19] was already included in the assessment in 2017 [1] and six further studies [31-36] were published in the past years.

Evidenz aus 7 RCTs

Preventive use of the technology in patients undergoing cardiac surgery

Five studies with a total of 197 enrolled patients (of whom 163 were analysed) investigated the preventive use of the technology in patients undergoing cardiac surgery. The certainty of the evidence was very low mainly due to the high imprecision (studies were underpowered to detect a statistically significant difference in crucial outcomes) and the high risk of bias in four out of five included studies.

ECAT als präventive Maßnahme
5 Studien (n=163):

Efficacy: None of the studies was able to detect a statistically significant difference in any of the selected crucial outcomes. The surrogate outcome reduction in cytokine levels further showed inconsistent results with regard to IL-6 measurements.

keine stat. signifikanten Unterschiede bei wesentlichen Wirksamkeits- und Sicherheitsendpunkten
fehlende Präzision in Studien;

Safety: None of the studies was able to detect a statistically significant difference in adverse events or serious adverse events. However, device-related adverse events were reported by two studies, with two (8.7%) and none (0%) cases in these studies, respectively.

ECAT bedingte UE (2 Studien): 0-2%

Therapeutic use of the technology in patients with sepsis or septic shock

Two additional studies with 120 enrolled patients (of whom 117 were analysed) investigated the therapeutic use of the technology in patients with sepsis or septic shock. The certainty of the evidence was very low mainly due to the high imprecision (studies were underpowered to detect a statistically significant difference in crucial outcomes) and the high risk of bias.

ECAT zur Therapie der Sepsis
2 Studien (n=117):
Wirksamkeit:

Efficacy: One study found a statistically significant difference in 60-day mortality to the detriment of the intervention group when compared to the control group, with 44.7% and 26% (p=0.039) dying in these groups, respectively. After adjusting for comorbidities, no association between the device and mortality was shown. No statistically significant difference was detected in mortality with less follow-up time (28-day mortality in one study and 48-hour mortality in another study). The other selected crucial outcomes were either not statistically significantly different or not statistically tested by the included studies. No statistically significant difference in the surrogate outcome reduction in cytokine levels was detected in one study.

Mortalität (2 RCTs):
60-Tage (1 RCT):
44.7 vs. 26 %,
stat. signifikant;
28-Tage (1 RCT) &
48 Stunden (1 RCT):
kein stat. signifikanter Unterschied;

Safety: One study (n=97) reported on overall adverse events or overall serious adverse events: 25 patients (53.2%) in the intervention group as opposed to 12 patients (24%) in the control group suffered from at least one SAE. In the same study, at least one AE occurred in some 30 patients (63.8%) in the intervention group and 25 patients (50%) in the control group (p-values were not reported).

keine stat. signifikanten Unterschiede in anderen wesentlichen Endpunkten,
fehlende Präzision

ECAT bedingte (S)UEs in 2 Studien: 8 UEs & 5 SUEs (in 47 pts) & 0 (in 10 pts)

The same study reported on device-related adverse events: Eight and five adverse or serious adverse events respectively occurred – possibly or probably in connection with the study device – in the intervention group (n=47). The other study also reported on device-related (serious) adverse events and noted that no such cases occurred in ten patients receiving ECAT.

unzureichende Evidenz für klinischen Nutzen von ECAT

Hence, the available evidence failed to show that extracorporeal cytokine adsorption therapy as an add-on therapeutic or preventive measure – in patients with sepsis or septic shock and patients undergoing cardiac surgery, respectively – leads to clinically-relevant improvements in outcomes such as reduced mortality and improved organ function.

Einbettung in bestehendes Wissen:

The results of this systematic review are aligned with the results from other recent systematic reviews.

2 SRs in 2019 & 1 SR in 2018: potentieller Nutzen, aber fehlende Evidenz für patientInnerelevante Endpunktverbesserungen

One recent systematic review from 2019 [40] used less strict inclusion criteria and identified eight studies, consisting of three RCTs and further five observational studies (n<50 in these studies). The authors concluded that there is insufficient evidence to support extracorporeal blood purification techniques – both in sepsis and other acute conditions.

konsistente Interpretation der Studien von seitens der Review-AutorInnen

In 2019, a literature review [41] on the use of CytoSorb® published a similar interpretation of the currently available evidence. The authors reviewed studies in both humans and animal experimental models, concluding that the available RCTs have not demonstrated any clinical benefit of using CytoSorb®, whilst experimental models, as well as observational studies, have often shown dramatic clinical improvements. Hence, the authors noted that the evidence precludes any final conclusion on the potential clinical benefit of using CytoSorb®. The authors stressed that – in the absence of clear evidence demonstrating a clinical benefit – the potential for increased adverse events and cost must be reflected.

Another literature review published in 2018 [42] assessed the clinical utility of extracorporeal haemadsorption therapy in different indications. The review identified seven studies (two RCTs, six observational studies) and concluded that extracorporeal blood purification – used for patients with sepsis or septic shock – can normalise serum cytokine levels. However, the study authors also concluded that this has not consistently led to improved patient-relevant outcomes.

theoretische Basis von ECAT nicht robust

It is noteworthy to mention that many of the basic principle ideas regarding a clinical benefit of removing inflammatory cytokines, e.g., during sepsis, are not as robust as one may anticipate [43]: Significant interactions (including removing antibiotic therapy used in septic patients) could also be harmful for patients.

in AWMF S3 Leitlinie derzeit nicht empfohlen

In this context, one clinical practice guideline (AWMF S3) from Germany [9] currently recommends not to use blood purification in sepsis management (including extracorporeal cytokine adsorption therapy) with clinical studies as an exception (expert consensus).

Limitations

Limitationen: fehlende Präzision in Studien; Verzerrungspotenzial hoch in 6/7 Studien

The results of this updated systematic review should be interpreted in light of its limitations. The major limitation of the evidence may be associated with imprecision. The available randomised controlled trials defined crucial outcomes mostly as secondary outcomes. As a consequence, the statistical power to detect a difference in a patient-relevant outcome was poor across studies. Moreover, most of the primary studies were judged to be with a high risk of bias.

In addition, excluding retrospective studies may have led to not capturing studies with a bigger sample size. However, retrospective studies are more prone to internal validity concerns due to the limited information on confounding variables and the general disability to control for these variables in a convincing and adequate manner, as can be done in high-quality randomised controlled trials. Thus, including retrospective studies would have not changed the conclusion one can draw with regard to the effectiveness of extracorporeal cytokine adsorption therapy.

Ongoing studies

18 laufende RCTs

The search for ongoing studies revealed that there are currently 18 ongoing randomised controlled trials, with estimated completion dates within the next two years. All of the ongoing studies compare the use of ECAT and standard care as opposed to standard care alone in the following indications:

Indikationen:

- **Cardiac surgery (intraoperative)**: Seven randomised controlled trials with the number of enrolled patients ranging from 20 to 400. Of these, three studies have a larger sample size (250-400 enrolled pts) and defined patient-relevant primary outcomes such as a change in the SOFA score or the incidence or severity of acute kidney injury.

intraoperative kard. OP: 7 RCTs

- **Cardiac surgery (postoperative):** One randomised controlled trial with 40 enrolled patients. The study defined the cumulative vasopressor need and the total amount of fluid administration as the primary outcome.

postoperative kardiologische OP: 1 RCT

- **Sepsis or septic shock:** Six randomised controlled trials with the number of enrolled patients ranging from 32 to 144. Three out of six studies (32-124 enrolled pts) defined patient-relevant primary outcomes such as reversal of shock, vasopressor dose reduction or RIFLE stadium L or E after acute kidney injury related to sepsis as the primary outcome. The remaining three ongoing studies defined surrogate outcomes as primary outcome measures.

Sepsis oder septischer Schock: 6 RCTs

- **Cardiac arrest:** Two randomised controlled trials with 20 and 40 enrolled patients, respectively. One study defined 30-day survival as the primary outcome and the other study used surrogate outcomes as primary outcome measures.

plötzlicher Herzstillstand: 2 RCTs

- **Other indications:** Two randomised controlled trials with 34 and 60 enrolled patients, respectively. One study assesses the use of CytoSorb® as an additive treatment of CAR-T-associated cytokine release and the other ongoing study investigates the effect of an 'installed cytokine adsorber' during cardiopulmonary bypass on the incidence of early rejection, cytokine and complement level.

andere Indikationen: add-on bei CAR-T Therapie: 1 RCT direkt in CPB installiert: 1 RCT

Many of the ongoing studies defined a change in interleukin levels as opposed to patient-relevant outcomes as primary outcome measures. These studies are not likely to show conclusive results to assess the effectiveness of ECAT. Few currently ongoing multicentre randomised controlled trials may be able to establish the clinical benefit/disbenefit of using ECAT as an add-on to standard care treatment. However, in the absence of a detailed description on the methodological quality of these ongoing trials, it is not definitive as to whether the results of these trials can shed more light on the effect of ECAT.

starker Fokus auf Surrogatendpunkte

In addition, ongoing research is being done on blood purification techniques in further indications. CytoSorbents, for instance, recently got CE approval for removing ticagrelor in patients undergoing cardiac surgery [38, 44].

Forschung von weiteren Blutreinigungsverfahren in anderen Indikationen laufend

Conclusion

Schlussfolgerung: Unzureichende Evidenz für klinischen Nutzen

The evidence is insufficient to show a clinical benefit of ECAT as an add-on measure preventively in cardiac surgery or therapeutically in patients with sepsis or septic shock. None of the studies was able to demonstrate that ECAT and standard care is more effective than and as safe as standard care alone in these two assessed conditions. Results from well-designed randomised controlled trials – with adequate power to detect differences in patient-relevant outcomes – are lacking. In light of the available evidence and the potential risks associated with the study device, the results of ongoing studies are to be awaited.

7 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove that ECAT and standard care to be used in cardiac surgery or sepsis management is more effective than and as safe as standard care alone. New study results will potentially influence the effect estimate considerably.

Evidenz unzureichend: derzeit nicht empfohlen

The reevaluation is recommended in 2022 if larger randomised controlled trials (n>200) with patient-relevant outcomes as primary outcomes are published by then.

Re-Evaluierung in 2022

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Extracorporeal cytokine adsorption therapy (ECAT) during cardiac surgery: Results from randomised controlled trials

Author, year	Bernardi, 2016 [19]	Garau, 2019 [31]	Gleason, 2019 [32]	Poli, 2019 [33]	Wagner, 2019 [34]
Country	Austria	Germany	USA	Switzerland	Czech Republic
Sponsor	Medical University of Vienna; materials partially funded by CytoSorbents Europe GmbH	CytoSorbents Europe GmbH	CytoSorbents Corporation	CytoSorbents Europe GmbH	Institutional grant from the Center for Cardiovascular and Transplant Surgery
Intervention/Product	Haemadsorption with CytoSorb® during CPB	Haemadsorption with CytoSorb® during CPB	Haemadsorption with CytoSorb® during CPB	Haemadsorption with CytoSorb® during cardiac surgery	Haemadsorption with CytoSorb® during cardiac surgery
Comparator	No intervention	No intervention	No intervention	No intervention	No intervention
Study design	RCT (focus on feasibility)	Pilot RCT	Pilot RCT	Pilot RCT	RCT
Number of pts[3]	46 24 vs. 22	43 21 vs. 22	46 23 vs. 23	30[4] 15 vs. 15	Randomised: 32[5] 16 vs. 16
Loss to follow-up, n (%)	8 (33.3) vs. 6 (27.3)	1 (4.8) vs. 2 (9.1)	NR	NR	3 (18.1) vs. 6 (37.5)
Analysed pts	16 vs. 16	20 vs. 20	Efficacy: 18 vs. 20 Safety: 23 vs. 23	15 vs. 15	13 vs. 10
Inclusion criteria	elective cardiac surgical intervention with an expected CBP duration >120 minutes	coronary artery bypass grafting, aortic valve replacement or a combined procedure, with an expected CPB time of more than 120 min	Elective cardiac surgery requiring cardiopumonary bypass with anticipated duration of >180 mins	At least one of the following; • age >75 years, • double valve replacement, • complex surgery with expected CPB duration > 120 min, • redo cardiac surgery, • pre-operative chronic renal failure (glomerular filtration rate < 30 ml/min) or chronic heart failure (< 40% left ventricular ejection fraction)	Not stated

[3] At time of randomisation.

[4] 30 patients were both randomised and analysed. Loss to follow-up was not reported potentially because none of the patients dropped out/were excluded for the analysis.

[5] Enrolment process poorly reported.

Author, year	Bernardi, 2016 [19]	Garau, 2019 [31]	Gleason, 2019 [32]	Poli, 2019 [33]	Wagner, 2019 [34]
Exclusion criteria	✿ Emergency procedures ✿ Heart transplantation ✿ Elective left ventricular assist device (LVAD) implantation ✿ Pulmonary thromboendarterectomy ✿ Declined informed consent ✿ Serum creatinine > 2mg/dl ✿ Body mass index < 18 ✿ Age < 18 years ✿ Pregnant woman ✿ Receiving chemotherapy or diagnosed with any disease state (e.g., AIDS) that has produced leukopenia ✿ Receiving anti leukocyte drugs ✿ Receiving TNF-alpha blockers, immunosuppressive drugs (e.g. tocilizumab) ✿ CRP > 2mg/dl ✿ History of stroke ✿ Bilirubin >2mg/dl	✿ Age of less than 18 years ✿ Body Mass Index (BMI) of less than 18 kg/m² ✿ Pregnancy ✿ Atrial fibrillation ✿ Use of immuno-suppressive medication ✿ Leukopenia ✿ Emergency and urgent surgery ✿ Rethoracotomy ✿ Serum creatinine of more than 2 mg/dL ✿ Transplant surgery ✿ Refusal of written informed consent	✿ Platelet count < 20,000/uL ✿ Body mass index <18 ✿ Pregnant women ✿ Life expectancy of <14 days ✿ End stage organ disease ✿ Active infection ✿ Undergoing cardiac transplant or ventricular assist device explant, isolated primary coronary artery bypass grafting (CABG) or single valve procedure ✿ Contraindication to anticoagulation with heparin ✿ Declined informed consent	✿ End-stage renal disease (dialysis dependence) ✿ Active infectious endocarditis ✿ emergency or off-pump procedure ✿ Receipt of non-steroidal anti-inflammatory medication (except for low-dose aspirin) or corticosteroids within 7days ✿ Enrolment in another conflicting study	✿ Patients excluded from the study included those with ✿ rheumatoid arthritis, ✿ asthma, ✿ cancer, ✿ autoimmune disease or those receiving steroidal or nonsteroidal anti-inflammatory drug therapy
Age of patients mean ±SD, yrs	Median (range): 64(30-81) vs. 69 (51-81); p=0,1737	67.9 ±12.7 vs. 72.7 ±9.2; p-value NR	Efficacy:67 ±7 vs. 60 ±17; p=0.11 Safety: 66 ±8 vs. 61 ±17; p=0.2	Median (range): 67 (44 - 76) vs. 69 (49 - 80)	50 ± 10 vs. 54 ± 15
Gender female, n (%)	Total: 11 (29.7%), 7 (36.8%) vs. 4 (22.2%)	NR	Efficacy: 8 (44.5) vs. 5 (25) Safety: 10 (43.5) vs. 5 (21.7)	2 (13) vs. 4 (26.7)	2 (13.3) vs. 0 (0)
Primary Outcome Measures	Differences of cytokines IL-1β, IL-6, IL-18, TNF-α, IL-10 during cardiopulmonary bypass	Reduction of inflammatory cytokines	**Efficacy**: Change in pfHb from pre-sternotomy baseline to the end of CPB **Safety:** Assessment of device-related serious adverse events (SAEs) until ICU discharge	Difference in key cytokine levels in peri-operative period: (IL1, IL2, IL4, IL6, IL-6, IL-10, INF γ, MCP-1, TNF alpha)	Effects of intraoperative cytokine HA on myocardial, monocyte and vascular miRNAs plasma levels
Secondary Outcome Measures	✿ Serum CRP changes ✿ ex vivo LPS induced TNF-α production ✿ Drug treatment Vasopressor dose, Insulin dose	hemodynamic measurements	✿ ventilator time (h) through ICU discharge, ✿ days in the ICU ✿ days in the hospital post-CPB through discharge	✿ vasopressor and inotropic support (need for any vasoconstrictor or inotrope) within 24 h of ICU admission,	Hematological, biochemical and clinical variables

Author, year	Bernardi, 2016 [19]	Garau, 2019 [31]	Gleason, 2019 [32]	Poli, 2019 [33]	Wagner, 2019 [34]
Secondary Outcome Measures *(continuation)*	✿ Volemic status: Need of fluid components (crystalloid, colloid solutions), Need for blood products (erythrocytes, fresh frozen plasma, platelets), Body impedance, Body weight ✿ Changes in procalcitonin, albumin, fibrinogen and total blood count ✿ Length of ICU stay ✿ 30 days mortality		**Efficacy:** ✿ incidence and progression of postoperative acute kidney injury **Safety:** ✿ adverse events (AEs; device-related or not) through 30 days ✿ postprocedure;vital signs (blood pressure, pulse and temperature) ✿ safety laboratory assessments (hematology, comprehensive metabolic panel, and arterial blood gas) until ICU discharge	**Efficacy**: ✿ need for any mechanical assistance (IABP, ECMO), ✿ mechanical ventilation duration, ✿ fluid balance, ✿ incidence of AKI ✿ need for post-operative ✿ renal replacement therapy ✿ ICU length of stay **Safety**: numerous safety outcomes incl. AEs and SAEs	
Length of Follow-up	30 days	hospital discharge	30 days	Hospital discharge	Hospital discharge
Mean CPB time/treatment time in min ±SD (range)	CPB time: 191 min. (range 112-288 min) vs. 170 min (83-274)	Duration of surgery: 259.2 ±51.7 vs. 253 ±51.44	CPB time: 3.8 ± 1.3 vs. 3.3 ± 1.1	CPB time median (IQR): 145 (130–183) vs. 138 (87–207)	Bypass time: 198 ± 15 vs. 182 ± 44
Outcomes					
Efficacy					
Mortality, n (%)	1 (2.7) vs. 0 (0)	NR Mean Mortality index: 6.6 ±5.4 vs. 8.12±7.5, p-value NR	No difference (no further information reported)	1 (6.7) vs. 2 (13.3); p=1.0	0 (0) vs. 0 (0); p-value NR[6]
MODS score	NR	NR	NR	NR	NR
SOFA score	NR.	NR	NR	NR	NR
LoS in ICU, in days ±SD	2.3 (+/-2) vs. 2.4 (+/-1.9), p=0.87	Only reported in hrs: 76 ± 42.6 vs. 51.1 ±21.1; p-value NR	4.3 ± 3.3 vs. 6.8 ± 12.7; p=0.38	Median (IQR): 1.8 (0.9–2.0) vs. 1.0 (0.9–8.9), p=1.0	Median (range): 2 (1-3) vs. 3 (1-4), p=0.085
Days of hospitalisation in days ±SD	NR	Post-surgery: 9±5.2 vs. 8.6 ±2.5; p-value NR	Post-surgery: 11.8 ± 5.9 vs. 14.0 ± 14.1; p=0.49	NR[7]	Median (range): 9 (7-14) 8 (7-15), p=0.419
Days of ventilator therapy	0.7 (+/- 1.6) vs. 0.2 (+/- 0.4); p=0.19	NR	NR	Only reported in hrs, median (IQR): 5 (0–16) vs. 8 (2–102); p>0.05	NR
Reduction of vasopressor therapy	No difference between IG and CG	Catecholamine-support: No difference between IG and CG (p-value NR)	NR	Need for any vasoconstrictor, n (%): 14 (93.3) vs. 13 (86.7); p>0.05	NR

[6] At 3 months.

[7] Overall hospital LoS: 12.5 (6.0–19.0) vs. 12.0 (11.0–17.0); p>0.05.

Author, year	Bernardi, 2016 [19]	Garau, 2019 [31]	Gleason, 2019 [32]	Poli, 2019 [33]	Wagner, 2019 [34]
Reduction in IL 6 Levels	IL-6 pg/ml: • after CBP:Median Int: 62.9 vs. Co: 63.6, p= 0.326 • 2 h: 120.8 vs. 118.7; p=0.6781 • 24 h: 111.6 vs. 120.9; p= 0.9837 • 48 h: 89.0 vs. 120.9; p= 0.3809	IL-6 concentration: no difference between IG and CG (p=0.384)	Study device found to be associated with reduced IL-6 levels (no further information reported)	IL-6 higher in IG than control throughout study time points	NR
Safety					
Overall adverse events, n	None reported	None reported	AEs: 121 vs. 137 SAEs: 44 vs. 43	AEs: 23 vs. 30 SAEs: 13 vs. 12 11 (73.3%) vs. 10 (66.7%)[8], p=1.0	NR
AE, n (%)	0 (0) vs. 0 (0)	0 (0) vs. 0 (0)	23 (100) vs. 21 (91.3); p-value NR[8]	NR	NR
SAE, n (%)	0 (0) vs. 0 (0)	0 (0) vs. 0 (0)	16 (69.6) vs. 11 (47.8); p-value NR[8]	SAE: 8 (53.3) vs. 8 (53.3), p=1.0[9]	NR
Device-related AEs, n (%)	0 (0)	NR	2 (8.7)	NR	NR
AE/SAE/DAE event categories, n (%)	NA	NA	Reported for SAEs (solely): Cardiac disorders: 10 (43) vs. 6 (26) Respiratory, thoracic and mediastinal disorders: 3 (13) vs. 5 (22) Procedural complication: 3 (13) vs. 4 (17) Renal and urinary disorders: 6 (26) vs. 6 (26) Vascular disorders: 3 (13) vs. 3 (13) Blood/lymphatic system disorders: 4 (17) vs. 1 (4) Metabolism/nutrition disorders: 2 (9) vs. 3 (13) Nervous system disorders: 0 (0) vs. 3 (13)	Reported for AEs[10]: Respiratory: 2 (13.3) vs. 0 (0) Cardiogenic shock: 1 (6.7) vs. 0 (0) Haemorrhagic shock: 1 (6.7) vs. 0 (0) Distributive shock: 1 (6.7) vs. 2 (13.3) Arrhythmias: 5 (33.3) vs. 8 (53.3) Surgical complications: 4 (26.7) vs. 4 (26.7) Infection: 1 (6.7) vs. 4 (26.7) Acute liver failure: 1 (6.7) vs. 0 (0) Acute kidney injury: 4 (26.7) vs. 4 (26.7) Neurological AE (including stroke): 2 (13.3) vs. 3 (20.0) Electrolyte disorders: 0 (0) vs. 1 (6.7)	NR

Abbreviations: ***AE*** *– adverse events;* ***CG*** *– control group;* ***CPB*** *– cardiopulmonary bypass;* ***ECAT*** *– extracorporeal cytokine adsorption therapy;* ***ICU*** *– intensive care unit;* ***IG*** *– intervention group;* ***IL*** *– interleukin;* ***IQR*** *– interquartile range;* ***LoS*** *– length of stay;* ***n. s.*** *– not statistically significant;* ***NA*** *– not applicable;* ***NR*** *– not reported;* ***pts*** *– patients;* ***RCT*** *– randomised controlled trial;* ***s. s.*** *– statistically significant;* ***SAE*** *– serious adverse events;* ***SD*** *– standard deviation.*

[8] Patients with at least one AE/SAE.

[9] Patients with at least one SAE.

[10] "Patients only counted once for each event category even if they had multiple events in that category".

Table A-2: Extracorporeal cytokine adsorption therapy (ECAT) during sepsis or septic shock: Results from randomised controlled trials

Author, year	Hawchar, 2019 [35]	Schädler, 2019 [36]
Country	Hungary	Germany
Sponsor	Research grants from the National Research Development and Innovation Office of Hungary	CytoSorbents Corporation
Intervention/Product	ECAT in septic shock	CytoSorb hemoperfusion in sepsis or septic shock
Comparator	No intervention	No intervention
Study design	RCT	Multicentre RCT
Number of pts[11]	20[12] 10 vs. 10	100 48 vs. 52
Loss to follow-up, n (%)	NR	1 (2.1) vs. 2 (3.9)[13]
Analysed pts	10 vs. 10	47 vs. 50
Inclusion criteria	✿ Intubated, mechanically ventilated patients with suspected septic shock of medical origin ✿ Invasive hemodynamic monitoring guided demand for norepinephrine >10 µg/min ✿ Elevated lactate concentrations >2.0 mmol/L ✿ Procalcitonin (PCT) concentration ≥ 3 ng/mL after first 6 hrs of resucitation and antibiotic therapy with no improvement	✿ Signed informed consent document (ICD) ✿ Male or female ≥ 18 and ≤ 80 years of age ✿ Subjects must have diagnosis of ARDS or ALI, based on ARDSNet Definition, established within last 72 hours, confirmed by clinical, radiological, or physiologic findings ✿ Subject must be intubated ≤ 3 days on a ventilator prior to enrollment ✿ Subjects must have confirmed diagnosis of sepsis ✿ Subject must have had at least 24 hours of antibiotic therapy ✿ Pre-menopausal female subjects must have negative pregnancy test ✿ Subject must be available for periodic blood sampling, study related assessments, and management at the treating institution for the duration of the study. Subject must have permanent home address to allow completion of 60 day follow-up ✿ Subject or health care proxy has the ability to understand and willingness to sign the informed consent form
Exclusion criteria	✿ Patients under 18 years of age ✿ Acute or chronic renal insufficiency requiring renal replacement therapy; ✿ Pregnancy (β-hCG test positivity) ✿ Operation in connection with the septic condition of the patient; ✿ End-stage cardiomyopathy ✿ Acute coronary syndrome ✿ Cardiogenic shock; hemato-oncological diseases;	✿ Currently participating in another clinical study involving investigational chemical compound, biologic, or device within the last 30 days prior to the start of this trial. ✿ Neuromuscular disease that impairs the ability to ventilate spontaneously, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barré syndrome and myasthenia gravis ✿ Increased intracranial pressure, tricyclic antidepressant overdose, hemoglobin SS, hemoglobin SC or other conditions where hypercapnia would be contraindicated ✿ Severe chronic respiratory disease including hospitalisation within last 6 months for respiratory failure ✿ Morbid obesity (Body Mass Index ≥40 kg/m²)

[11] At time of randomisation

[12] It is assumed that all randomised patients were also analysed without any loss to follow-up.

[13] "In 22 patients, no valid measurement of the primary endpoint was available due to technical problems with the cytokine blood probe management. These patients were excluded from all further analyses." These difficulties did not affect measurement of the extracted patient-relevant outcomes.

Author, year	Hawchar, 2019 [35]	Schädler, 2019 [36]
Exclusion criteria *(continuation)*	✿ Admission after cardiac arrest ✿ Immune-compromised patients due to HIV positivity and active AIDS or organ transplantation or on chronic steroid treatment (>10 mg/day prednisolone) ✿ Thrombocytopenia (b20 G/L) ✿ Other coagulopathies contraindicating extracorporeal therapies.	✿ Burns > 30% BSA, bone marrow transplant, lung transplant or end stage hepatic liver failure ✿ Subject with mean arterial pressure ≤ 60 mmHg regardless of use of pressor agents. ✿ Subject with active malignancy receiving chemotherapy or radiation treatment within last 60 days ✿ Subjects with AIDS, CD4 count of < 200 or 14%, or the presence of an AIDS defining illness (HIV+ subjects may be enrolled) ✿ Subject with acute coronary syndrome ✿ Subjects with decompensated heart failure with New York Heart Association (NYHA) classification IV ✿ Subjects with Chronic Kidney Disease (CKD) stage 5 will be excluded ✿ Subjects with end stage hepatic liver failure ✿ Subjects on immunosuppressive agents, excluding corticosteroids ✿ Platelets ≤ 20,000/mm^3 ✿ Subjects on anti-TNF therapy ✿ Subjects about to receive or receiving drotrecogin alpha (Xigris) therapy ✿ Subject is pregnant or breastfeeding ✿ Subject has a known allergy to any component of the CytoSorb hemoperfusion device ✿ Subject has any active disease condition that could limit compliance with the study procedure, including but not limited to the following: acute coronary syndrome, life-threatening cardiac arrhythmia, or psychiatric or social conditions, considered by investigator(s) to preclude successful completion of the study
Age of patients mean ±SD, yrs	60 ± 10 vs. 71 ± 14	66.0 (median; range: 55-73) vs. 65 (median; range: 56.5-71)
Gender female, n (%)	3 (30) vs. 4 (40)	12 (25.5) vs. 15 (30)
Primary Outcome Measures	Effects of early (started within 24 h after ICU administration), 24-h long cytokine-adsorption therapy on organ dysfunction and inflammatory response in patients with septic shock and data on safety.	Relative IL-6 levels as a percent (%) of baseline in subjects receiving CytoSorb treatment in conjunction with the standard of care as compared to control subjects receiving only the standard of care for ARDS/ALI in the setting of sepsis. [Time Frame: 7 Days]
Secondary Outcome Measures	NR	Ventilator Free Days, Reduction cytokines TNF-α, IL-1b, IL-10, CRP, 28-day all cause mortality, Oxygen Index (OI), P/F ratios, MODS scores [Time Frame: 28 Days]
Length of follow-up	48 hrs	60 days
Mean CPB time/ treatment time	NR	NR
Outcomes		
Efficacy		
Mortality, n (%)	Overall: 5 (50) vs. 5 (50), p-value NR Within 48 hrs: 0 (0) vs. 2 (20), p-value NR	60-day mortality: 21 (44.7%) vs. 13 (26%); p=0.039 28-day mortality: 17 (36.2%) vs. 9 (18%); p=0.073[14, 15]

[14] Note: The proportion of patients receiving renal replacement therapy at the time of enrolment was higher in the treatment group (31.9%) when compared to the control group (16.3%)

[15] Multivatriate Cox regression model on overall survival (adjustment for patient morbidity and baseline imbalances using) revealed no association of study intervention and mortality (p=0.19)

Author, year	Hawchar, 2019 [35]	Schädler, 2019 [36]
MODS score	NR	No difference between groups (no further information reported)
SOFA score	No significant diference between IG and CG (p-value NR) IG: T0=13.6±3.2; T12=13.1±3.6;T24=13±5.4; T48=11.6±6.3) CG: T0=12.8±3.9; T12=12.9±5.0; T24=12.6±5.9; T48 = 11.0 ± 6.3)	NR
LoS in ICU, in days ±SD	10.2 ± 8.5 vs. 10.0 ± 4.3, p-value NR	NR
Days of hospitalisation in days ±SD	NR	NR
Days of ventilator therapy	NR	17.5 (median; IQR: 8.6-25.9) vs. 12.1 (median; IQR: 7.0-23.1 days), p = 0.306
Reduction of vasopressor therapy	Stated narratively that a signiicant reduction in need or vasopressor support was detected in CytoSorb group. In the control group, this reduction was not shown (no further informatsion were reported).	NR
Reduction in IL 6 Levels	NR	No detection of differences between IG and CG in systemic plasma IL-6 (n=75; p=0.15).[16]
Safety		
Overall adverse events, n	NR	AE: 53 vs. 48; p-value NR SAE:26 vs. 15; p-value NR
AE, n (%)	NR	30 (63.8) vs. 25 (50)[17], p-value NR
SAE, n (%)	NR	25 (53.2) vs. 12 (24)[17], p-value NR
Device-related AEs, n (%)	0 (0)	AE:8 [18] SAE: 5[18]
AE/SAE/DAE event categories, n (%)	NR	NR

Abbreviations: ***AE*** *– adverse events;* ***CPB*** *– cardiopulmonary bypass;* ***ECAT*** *– extracorporeal cytokine adsorption therapy;* ***ICU*** *– intensive care unit;* ***IL*** *– interleukin;* ***IQR*** *– interquartile range;* ***LoS*** *– length of stay;* ***n. s.*** *– not statistically significant;* ***NR*** *– not reported;* ***pts*** *– patients;* ***RCT*** *– randomised controlled trial;* ***s. s.*** *– statistically significant;* ***SAE*** *– serious adverse events;* ***SD*** *– standard deviation.*

[16] No further information reported. Significant IL-6 elimination when comparing IG before and after the intervention.
Note: for this endpoint, 22 patients were excluded from the analysis because of difficulties cytokine blood probe management.

[17] Pts with at least one AE/SAE.

[18] Possibly or probably in connection with study device. Percentage not estimable.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [45] and in the Guidelines of EUnetHTA [46].

Table A-3: Risk of bias – study level (randomised studies), see [25]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Bernardi, 2016 (NCT01879176) [19][19]	Yes	Unclear	Yes	No	No	No[20]	High
Garau, 2019 [31]	Unclear	Yes	Yes	No	Unclear[21]	No[22]	High
Gleason, 2019 (REFRESH I) [32]	Unclear	Unclear	Unclear	No	Yes	No[23, 24]	High
Hawchar, 2019 (ACESS Study) [35]	Unclear	Yes	Unclear	No[25]	Yes	No[26]	High
Poli, 2019 (NCT02775123) [33]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schädler, 2017 (NCT00559130) [36]	Yes	No[27]	No	No	Yes	No[28]	High
Wagner, 2019 [34]	Yes	Unclear	Yes	No	Unclear[29]	Yes	High

[19] The risk of bias assessment of this study was re-used from the original assessment [1]

[20] Few participants, high loss to follow up, no ITT (intention to treat) analysis.

[21] The study report fails to include results for key outcomes (28-days survival, days until recovery, systolic and diastolic function, kidney function etc) that would be expected to have been reported for such a study.

[22] Study received an unrestricted grant by manufacturer.

[23] Inappropriate influence of funders suspected: It is stated that "the company reserved and exercised the right to review any manuscripts or presentations for factual errors prior to submission".

[24] On the 13.01.2020, we asked the study authors for information on the specific method of sequence generation, allocation concealment and blinding. We were forwarded to the sponsors who could not provide us with this essential information. The credibility of the study is, therefore, affected negatively.

[25] It was suspected, but not clearly stated, that treating physicians were not blinded.

[26] Reasons for exlusion of patients not justified: inclusion of patients with renal insufficiency unclear.

[27] Study faced problems with allocation sequence concealment (irregularities with regard to using sealed randomisation envelopes).

[28] Baseline imbalance suspected: In 22 of 97 patients no valid measurement of the primary endpoint was available due to technical problems with cytokine blood probe management; these patients were excluded from further analysis; Patients were different at baseline, which lead to different baseline characteristics: 38,9 % of treatment group vs. 17,9% of control group received renal replacement therapy.

[29] No study protocol available. Secondary outcomes not sufficiently described.

Table A-4: Evidence profile: Efficacy and safety of ECAT in cardiac surgery

Certainty assessment							№ of analysed patients		Effect (ECAT and standard care vs. standard care alone)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECAT and standard care	standard care alone		
EFFICACY										
Mortality										
5 [19, 31-34]	RCT	serious [a]	not serious	not serious	very serious [b]	none	82	81	None of the studies was able to detect a statistically significant difference in mortality up to 30 days follow-up. **Ranges of mortality rate** (3 studies): 0-6.7% vs. 0-13.3% **Mortality index** (1 study): 6.6 ±5.4 vs. 8.12 ±7.5 One further study solely reported that there was no difference in mortality rates without reporting on these.	⊕◯◯◯ VERY LOW
Organ function (assessed with: SOFA/MODS score)										
0	-	-	-	-	-	-	-			-
Length of stay in ICU (in days)										
5 [19, 31-34]	RCT	serious [a]	not serious	not serious	very serious [b]	none	82	81	None of the studies was able to detect a statistically significant difference in LoS in ICU. **Mean LoS in ICU** (3 studies): 2.3-4.3 vs. 2.1-6.8 days **Median LoS in ICU** (2 studies): 1.8-2 vs. 1-3 days	⊕◯◯◯ VERY LOW
Days of hospitalisation										
3 [31, 32, 34]	RCT	serious [a]	not serious	not serious	very serious [b]	none	51	50	None of the studies was able to detect a statistically significant difference in days of hospitalisation. **Mean post-surgery hospitalisation** (2 studies): 9-11.8 vs. 8.6-14.0 days **Median days of hospitalisation** (1 study): 9 vs. 8 days	⊕◯◯◯ VERY LOW
SAFETY										
(Serious) adverse events										
4 [19, 31-33]	RCT	serious [a]	not serious	not serious	very serious [b]	none	74	74	None of the studies was able to detect a statistically significant difference in SAEs or AEs **SAEs** (4 studies): 0-69.6% vs. 0-53.3% **AEs** (3 studies): 0-100% vs. 0-91.3%. **Device-related AEs** (2 studies):0-8.7%	⊕◯◯◯ VERY LOW

Explanations

[a] *Risk of bias was high in all studies except for Poli 2019 [33]. Especially the uncertainties with regard to the generation of the randomisation sequence and allocation concealment may be described as serious limitations.*

[b] *None of the studies were powered to detect a difference in this outcome.*
Small number of cases/small number of enrolled patients.

Abbreviations

AE *– adverse events;* ***ECAT*** *– extracorporeal cytokine haemadsorption therapy;* ***ICU*** *– intensive care unit;* ***LoS*** *– length of stay;* ***pts*** *– patients;* ***RCT*** *– randomised controlled trial;* ***SAE*** *– serious adverse events.*

Table A-5: Evidence profile: Efficacy and safety of ECAT in sepsis or septic shock

Certainty assessment							№ of analysed patients		Effect (ECAT and standard care vs. standard care alone)	Certainty
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect ness	Impre-cision	Other considerations	ECAT and standard care	standard care alone		
EFFICACY										
Mortality										
2 [35, 36]	RCT	serious [a]	not serious	not serious	very serious [b]	none	57	60	Stat. significant differences in 60 days mortality in 1 study **60-day mortality** (1 study; n=97): 21 (44.7%) vs. 13 (26%); p=0.039 **28-day mortality** (1 study; n=97): 17 (36.2%) vs. 9 (18%); p=0.073 **48-hr mortality** (1 study, 20 pts): 0 (0%) vs. 2 (20%), p-value NR Overall mortality in the same study (no specific follow-up time reported): 5 (50%) vs. 5 (50%); p-value NR	⨁◯◯◯ VERY LOW
Organ function (assessed with: SOFA/MODS score)										
2 [35, 36]	RCT	serious [a]	not serious	not serious	very serious [b]	none	57	60	**MODS score** (1 study; n=97): no difference between IG and CG (no further information reported) **SOFA score** (1 study; n=20): no significant difference between IG and CG	⨁◯◯◯ VERY LOW
Length of stay in ICU (in days)										
1 [35]	RCT	serious [a]	not serious	not serious	very serious [b]	none	10	10	10.2 ± 8.5 vs. 10.0 ± 4.3; p-value NR	⨁◯◯◯ VERY LOW
Days of hospitalisation										
0	-	-	-	-	-	-	-		-	-
SAFETY										
(Serious) adverse events										
2 [35, 36]	RCT	serious [a]	not serious	not serious	very serious [b]	none	57	60	**n (%) of patients with at least one (S)AE:** SAEs (1 study; n=97): 25 (53.2%) vs. 12 (24%), p-value NR AEs (1 study; n=97): 30 (63.8%) vs. 25 (50%), p-value NR **Device-related (S)AEs only reported in total cases (2 studies):** Device-related SAE (2 studies):5 (in 47 pts) & 0 (in 10 pts) Device-related AE (2 studies): 8 (in 47 pts) & 0 (in 10 pts)	⨁◯◯◯ VERY LOW

Explanations

[a] *Risk of bias was high in the included study/ies. Especially the uncertainties with regard to the generation of the randomisation sequence and allocation concealment may be described as serious limitations.*

[b] *None of the studies were powered to detect a difference in this outcome. Small number of cases/small number of enrolled patients.*

***Abbreviations: AE** – adverse events; **CG** – control group; **ECAT** – extracorporeal cytokine adsorption therapy; **ICU** – intensive care unit; **IG** – intervention group; **LoS** – length of stay; **pts** – patients; **RCT** – randomised controlled trial; **SAE** – serious adverse events.*

Applicability table

Table A-6: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	**Prevention of SIRS and sepsis:** 5/7 studies assessed haemadsorption treatment as a preventive measure for patients undergoing cardiac surgery with CPB. This presents only a small fraction of patients that are at risk of developing SIRS and sepsis. The use of minimal invasive heart surgery and off-pump procedures is becoming more frequent, affecting the potential use of haemadsorption. **Treamtent of SIRS, sepsis and septic shock:** 2/7 studies investigated the therapeutic use of haemadsorption treatment in patients with sepsis or septic shock. Sepsis and septic shock stem from a variety of different causes and, hence, it there is heterogeneity with regard to the spectrum of the disease, differences in treatment as well as outcomes.
Intervention	All studies used haemadsorption with CytoSorb® as an add-on measure to standard care. We did not suspect any applicability concerns with regard to the intervention.
Comparators	Standard care was used as a comparator by all seven included studies. Treatment may vary according to setting (both between countries and hospitals).
Outcomes	Most frequently, surrogate outcomes such as change in IL-6 levels were used as primary outcomes across studies. Crucial (patient-relevant) outcomes such as mortality or organ function as well as safety parameters were secondary outcomes by all included studies. Hence, patient-relevant outcomes were often insuficiently powered to detect a difference or not statistically tested.
Setting	All of the studies were conducted in Europe or the United States. The procedure took place in hospital intensive care units and in operating rooms, relecting the setting where the technology is deployed. Standard care may vary according to setting (both between countries and hospitals) as highlighted above.

List of ongoing randomised controlled trials

Table A-7: List of ongoing randomised controlled trials of ECAT in various indications

Identifier/ Trial name	Intervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
Cardiac Surgery intraoperative							
NCT03266302/ REMOVE	Standard of Care + CytoSorb-Therapy	Standard of Care alone	SOFA score before and up to 7 days after surgery.	RCT	250	07/2020	Jena University Hospital
NCT02297334/ RECCAS	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Reduction of interleukin-6 (IL-6) during cardiac surgery.	RCT	40	08/2017	Universitätsklinikum Hamburg-Eppendorf
REMOTE	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Cytokine levels following CPB (72 hrs)	RCT	80	05/2019	Klinikum Nürnberg
NCT03892174/ RECREATE	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Change in quantitative expression of monocytic Human Leukocyte Antigen (mHLA)-DR expression (Antibodies per cell on Cluster of Differentiation (CD)14+ monocytes/macrophages, assessed using a quantitative standardised assay) [Time Frame: From baseline (pre-OR, t1) to day 1 post-OR (t3)]	RCT	54	12/2020	University Hospital Inselspital, Berne
REFRESH II (AKI)	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Incidence or severity of acute kidney injury (AKI) in the first 48 hours after cardiopulmonary pulmonary bypass (CPB) [Time Frame: From start of CPB through 48 hours after CPB], Kidney Disease Improving Global Outcomes (KDIGO) definitions for AKI.	RCT	400	10/2020	CytoSorbents, Inc
NCT03945708	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Use of vasoactive substances [Time Frame: 48 hours]. Use of norepinephrine in ICU.	RCT	20	12/2020	CytoSorbents, Inc
NCT02518087/ NA	Standard of Care + oXiris	Standard of Care alone	Non presence of AKI-CS within the first 7 days after cardiac surgery. [Time Frame: 7 days]	RCT	340	12/2019	Hospital Universitari de Bellvitge
Cardiac Surgery postoperative							
NA/ CYTATION[30]	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Cumulative vasopressor need and total amount of fluid administration.	RCT	40	12/2021	Academic Hospital Maastricht
Sepsis or septic shock							
NCT02588794/ CASAKI	Standard of Care + CytoSorb-Therapy	Standard of Care alone	RIFLE stadium L or E after acute kidney injury related to sepsis [Time Frame: 3 months]	RCT	124	2017	Technische Universität München

[30] Information kindly provided by CytoSorbents®.

Identifier/ Trial name	Intervention	Comparison	Primary Outcomes	Type of Study	No of pts planned	Estimated study completion date	Sponsor
NA/ MICSS-AKI[30]	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Measurement of sublingual microcirculation with vessel density and flow parameters.	RCT	40	2022	Erasmus University Medical Center Rotterdam
NCT04013269/ ACYSS	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Percentage of patients with a vasopressor dose reduction of at least 25% from baseline for at least 6 hours within the first 48 hours of treatment.	RCT	32	03/2022	Universitätsklinikum Hamburg-Eppendorf CytoSorbents, Inc
NCT03847961/ NA	Standard of Care + CA330 hemoadsorption	Standard of Care alone	Reduction rate of IL-6 serum concentration at the initiation of first adsorption and at the end of the second adsorption [Time Frame: from the initiation of first adsorption until the end of the second adsorption, assessed up to 24hours]	RCT	144	02/2020	First Affiliated Hospital, Sun Yat-Sen University
NCT03866083/ NA	Standard of Care + CytoSorb-Therapy	Standard of Care alone	Reversal of shock in both groups [Time Frame: 72 hours]	RCT	50	06/2019	Institute of Liver and Biliary Sciences, India
NCT03426943/ NA	Standard of Care + oXiris ™	Standard of Care	Interleukin 6 (IL-6) plasmatic concentration [Time Frame: 24 hours after the initiation of CVVH] Endotoxin plasmatic mass concentration [Time Frame: 24 hours after the initiation of CVVH]	RCT	40	03/2022	Hospices Civils de Lyon
Cardiac Arrest							
NCT03523039/ CATCH	Hemoadsorption with CytoSorb®	Post-cardiac arrest management	Change in cytokine levels from baseline to 72 hrs post randomisation, adverse events	RCT	40	11/2021	Centre Hospitalier Universitaire Vaudois
NCT03685383/ CYTER	eCPR + CytoSorb	eCPR without CytoSorb	30 day survival	RCT	20	11/2019	University Hospital Freiburg
Other indications							
NCT03145441/ NA	Installed cytokine adsorber (CytoSorb®) in CPB	CPB without Installed cytokine adsorber (CytoSorb®)	Incidence of early rejection, cytokine and complement level.	RCT	60	07/2020	Semmelweis University
NCT04048434/ CYTORELEASE	CytoSorb as additive treatment of CAR-T associated cytokine release	Standard of Care alone	IL-6 change [Time Frame: 24 hrs]	RCT	34	12/2021	Hannover Medical School CytoSorbents, Inc

Abbreviations: ***CPB*** *– cardiopulmonary bypass;* ***NA*** *– not available;* ***RCT*** *– randomised controlled trial;*

Literature search strategies

Search strategy for Cochrane

Search Name: Cytokine Adsorption in Septic Patients (Update 2020)	
Last saved: 11/12/2019 13:12:26	
Comment: MEL 2020 (GG)	
ID	Search
#1	MeSH descriptor: [Sepsis] explode all trees
#2	Severe Sepsis* (Word variations have been searched)
#3	MeSH descriptor: [Shock, Septic] explode all trees
#4	Septic Shock* (Word variations have been searched)
#5	Abdominal sep* (Word variations have been searched)
#6	Septic Arthrit* (Word variations have been searched)
#7	MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees
#8	(System* Inflam* Respon* Syndrom*) (Word variations have been searched)
#9	SIRS:ti,ab,kw (Word variations have been searched)
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 OR #9
#11	MeSH descriptor: [Cytokines] explode all trees
#12	MeSH descriptor: [Adsorption] explode all trees
#13	#11 and #12 (Word variations have been searched)
#14	(Cytokine* near (Adsorption* or Adsorb*)) (Word variations have been searched)
#15	MeSH descriptor: [Hemadsorption] explode all trees
#16	Haemadsor* (Word variations have been searched)
#17	Haemadsor* (Word variations have been searched)
#18	Hemo-adsor* (Word variations have been searched)
#19	Haemo-adsor* (Word variations have been searched)
#20	Hemadsor* (Word variations have been searched)
#21	(blood near purif*) (Word variations have been searched)
#22	(Cytokine* near filt*) (Word variations have been searched)
#23	CytoSorb* (Word variations have been searched)
#24	Cyto-Sorb* (Word variations have been searched)
#25	(Cytokine* near Remov*) (Word variations have been searched)
#26	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 (Word variations have been searched)
#27	#10 and #26 with Cochrane Library publication date Between Dec 2016 and Dec 2019 (Word variations have been searched)
11.12.2019/80 Hits	

Search strategy for CRD

Search Name: Extracorporeal Cytokine Adsorption in Sepsis (MEL Update 2020) GG	
Search date: 11.12.2019	
ID	Search
1	(Cytokine* NEAR (Adsorption* OR Adsorb*))
2	MeSH DESCRIPTOR Cytokines EXPLODE ALL TREES

3	MeSH DESCRIPTOR Hemadsorption EXPLODE ALL TREES
4	(Hemadsor*)
5	(Haemadsor*)
6	(Haemoadsor*)
7	(Haemo-adsor*)
8	(Blood NEAR purif*)
9	(Cytokine* NEAR filt*)
10	(CytoSorb*)
11	(Cyto-Sorb*)
12	(Cytokine* NEAR Remov*)
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES
15	(Sepsis*)
16	MeSH DESCRIPTOR Shock, Septic EXPLODE ALL TREES
17	(Septic)
18	MeSH DESCRIPTOR Systemic Inflammatory Response Syndrome EXPLODE ALL TREES
19	(System* Inflam* Respon* Syndrome*)
20	(SIRS)
21	(Abdominal sep*)
22	(Septic Arthrit*)
23	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	#13 AND #23
25	(#13 AND #23) WHERE LPD FROM 23/12/2016 TO 11/12/2019
26	(#13 AND #23) FROM 2016 TO 2019
27	#25 OR #26
1 Hit	

Search strategy for Embase

No.	Query Results	Results	Date
#30.	#29 AND [23-12-2016]/sd NOT [11-12-2019]/sd	215	10 Dec 2019
#29.	#10 AND #28	652	10 Dec 2019
#28.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	4,865	10 Dec 2019
#27.	cytosorb*	245	10 Dec 2019
#26.	'cyto sorb*'	15	10 Dec 2019
#25.	cytosorb:tn,dn	81	10 Dec 2019
#24.	'extra-corporeal blood purif*':ti,ab,de,kw	6	10 Dec 2019
#23.	'extracorporeal blood purif*':ti,ab,de,kw	267	10 Dec 2019
#22.	'haemo-adsor*':ti,ab,de,kw	1	10 Dec 2019
#21.	'haemadsor*':ti,ab,de,kw	206	10 Dec 2019
#20.	'haemoadsor*':ti,ab,de,kw	26	10 Dec 2019
#19.	'hemo adsor*':ti,ab,de,kw	5	10 Dec 2019
#18.	hemoadsor*:ti,ab,de,kw	214	10 Dec 2019
#17.	hemaadsor*:ti,ab,de,kw		10 Dec 2019
#16.	hemadsor*:ti,ab,de,kw	1,579	10 Dec 2019
#15.	'hemadsorption'/exp	1,061	10 Dec 2019

#14.	(cytokine* NEAR/5 (adsorption* OR adsorb* OR remov* OR filt*)):ab,ti,de,kw	1,561	10 Dec 2019
#13.	#11 AND #12	1,593	10 Dec 2019
#12.	'adsorption'/exp	95,811	10 Dec 2019
#11.	'cytokine'/exp	1,516,749	10 Dec 2019
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	281,774	10 Dec 2019
#9.	sirs:ti,ab	9,108	10 Dec 2019
#8.	'system* inflam* response syndrome*':ti,ab,de,kw	13,873	10 Dec 2019
#7.	'systemic inflammatory response syndrome'/exp	266,636	10 Dec 2019
#6.	'septic arthrit*':ti,ab,de,kw	7,229	10 Dec 2019
#5.	'abdominal septic':ti,ab,de,kw	187	10 Dec 2019
#4.	'septic shock*':ti,ab,de,kw	57,463	10 Dec 2019
#3.	'septic shock'/exp	50,984	10 Dec 2019
#2.	'severe sepsis*':ti,ab,de,kw	14,343	10 Dec 2019
#1.	'sepsis'/exp	259,887	10 Dec 2019

Search strategy for Medline

Search date: 10.12.2019		
ID	Search	Results
1	exp Sepsis/	138,817
2	Severe Sepsis*.mp.	9,973
3	exp Shock, Septic/	24,749
4	Septic Shock*.mp.	25,261
5	Abdominal septic*.mp.	153
6	Septic Arthrit*.mp.	6,218
7	exp Systemic Inflammatory Response Syndrome/	143,249
8	System* Inflam* Response* Syndrome*.mp.	9,621
9	SIRS.ti,ab.	6,276
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	165,186
11	exp Cytokines/	789,853
12	exp Adsorption/	74,482
13	11 and 12	691
14	(Cytokine* adj5 (adsorption* or adsorb* or remov* or filt*)).mp.	962
15	exp Hemadsorption/	969
16	H?em?a?dsor*.mp.	1,839
17	Extra?corporeal blood purif*.mp.	215
18	Cyto?Sorb*.mp.	129
19	13 or 14 or 15 or 16 or 17 or 18	3,530
20	10 and 19	368
21	remove duplicates from 20	302
22	Results (i.e. PMIDs) from the original search of 23.12.2016	380
23	21 not 22	75

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