Extracorporeal cytokine haemadsorption therapy

in patients with sepsis or SIRS

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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.

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List of abbreviations

ACT .....activated clotting time
AE.....adverse event
aPTT .....activated partial thromboplastin time
CPB .....cardiopulmonary bypass
CRRT.....continuous renal replacement therapy
ECAT .....extracorporeal cytokine adsorption therapy
FDA.....Food and Drug Administration
GCS .....Glasgow Coma Scale
HLM.....heart lung machine
ICU.....intensive care unit
IDE.....investigational device exemption
IG.....intervention group/ Interventions Gruppe
IL-6.....Interleukin 6
KG/CG.....control group/Kontroll Gruppe
LPS.....lipopolysaccharides
MAP ..... mean arterial pressure
MODS ..... Multi-Organ Dysfunction Score
MIP-1 α..... Macrophage Inflammatory Protein-1 α
NHS ..... National Health Service
NICE ..... National Institute for Health and Care Excellence
qSOFA..... quick Sepsis-related Organ Failure Assessment score
RCT ..... randomised controlled trials
SAE..... serious adverse event
SOFA..... Sepsis-related/Sequential organ failure assessment score
SIRS..... Systemic Inflammatory Response Syndrome
TNF- α..... Tumour Necrosis Factor α
VAT ..... value added tax

Summary

Introduction

Health Problem

Sepsis, septic shock and SIRS are life-threatening conditions associated with an overreacting immune response. The dysregulated response can lead to multiple organ dysfunction. While sepsis and septic shock have an infectious origin, SIRS may also have non-infectious triggers such as cardiac surgery using the Cardiopulmonary Bypass (CPB). This is of particular interest for this report. SIRS, sepsis and septic shock have a mortality of an estimated 7, 16 and 40% respectively [1].

Sepsis, septischer Schock und SIRS sind lebensbedrohliche, systemische Immunreaktionen

The new 2016 Sepsis-3 definition has two grades: sepsis and septic shock [1]. The previous sepsis definitions published in 1992 emphasized on the role of 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 predictor for sepsis related mortality, thus are not included in the most recent international sepsis definitions. The members of the Sepsis-3 taskforce suggested that sepsis should be considered in the event of an infectious process associated with an increase in 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. SIRS patients are identified by fulfilling two or more of the four SIRS criteria.

neue 2016 Konsensus-Leitlinien für die Definition von Sepsis und septischem Schock

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

>2 der 4 SIRS Kriterien zur Diagnose von SIRS

The two main therapeutic priorities include early identification of a potential infectious origin and 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 [2].

Therapie: Hämodynamische Stabilisierung und antibiotische Abdeckung

Description of Technology

Extracorporeal Cytokine Adsorption Therapy (ECAT) aims to reduce the levels of cytokines in the blood. Cytokines are signalling molecules that are 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. Adsorption therapy is an addition to standard treatment of sepsis or SIRS. ECAT is not recommended by the most recent international sepsis guidelines.

Extrakorporale Zytokin Adsorption versucht Zytokinkonzentration zu vermindern; Zusatz zur Standardtherapie; derzeit von Leitlinien nicht empfohlen

Currently, CytoSorb® is the only ECAT device that received CE marked authorization to enter the EU market. The device consists of a single-use cartridge that can be used as stand-alone therapy and in combination with dialyses machines, and heart-lung machines. The absorber cartridge is filled with sorbent beads, which adsorb the cytokines as they pass through the blood pump.

Einmal-Kartusche in Kombination mit Dialyse und Herzlungenmaschine verwendbar

The patient blood is continuously recirculated between the absorption device and the patient up to maximum 24 hours; afterwards the cartridge needs to be replaced. The typical treatment duration for sepsis patients is 48 hours to 72 hours. The use of CytoSorb® during CPB surgery is recommended for a CPB duration of more than >120 min.

Therapiedauer: 48-72 h therapeutisch, > 2 h präventiv

Methods

Fragestellung

The focus of this assessment was the evaluation of efficacy and safety of extracorporeal haemadsorption therapy in patients with sepsis and Systemic Inflammatory Response Syndrome (SIRS), as well as its preventive use for patients at risk of developing SIRS following cardiopulmonary bypass surgery.

systematische Literatursuche

To answer the research questions on efficacy and safety-related outcomes a systematic literature search in five databases was conducted, without restriction on the search strings. In addition, we performed a hand search and screened information provided by the manufacturer and submitting hospital to identify further relevant studies. The study selection, data extraction and assessing the methodological quality of the studies was performed by two independent researchers.

Domain effectiveness

entscheidende Endpunkte für Wirksamkeit

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

Domain safety

und Sicherheit

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

Results

Available evidence

1 RCT, 2 retrospektive Fallserien

Insgesamt 93 Patienten, 55 bekamen ECAT

We could identify one randomised-controlled trial and one retrospective case series to assess efficacy of ECAT as preventive intervention during CPB surgery. The total number of patients was 77 of which 39 received CytoSorb® therapy. Both studies assessed the preventive use of CytoSorb® during CPB surgery.

To assess safety outcomes, one additional retrospective case series was identified (N=16). Similarly as the two other studies, it assessed the use of CytoSorb® in SIRS patients, yet, therapeutic following CPB surgery.

keine Studie zu Therapie der Sepsis

We could not identify any controlled study on ECAT as therapeutic addition to the treatment of sepsis.

Clinical effectiveness

Daten zur Wirksamkeit: keine signifikanten Ergebnisse in allen wichtigen Endpunkten

wichtige Endpunkte nur von einer Studie berichtet

Regarding the crucial outcomes for effectiveness, one study, a randomised controlled trial (RCT) with 37 patients assessed mortality and improved survival as secondary outcome measure. One out of 19 patients in the intervention group died on the 22nd postoperative day, while all 18 patients in the control group survived the 30 days. The study found no significant differences in the length of stay in intensive care units and in the days of mechanical ventilation. The retrospective case series including 40 patients did not report on any of the crucial effectiveness outcomes. None of the studies reported on the total days of hospitalization or on changes in SOFA score, MODS score, or another measure to assess organ failure.

Safety

None of the studies reported on adverse or serious adverse events for the use of CytoSorb® during CPB surgery or post-operative. In total, the technology was use in 55 patients. Furthermore, no adverse device effects were described.

keine Daten zu AE oder SAE berichtet

Upcoming evidence

In total, we identified seven relevant ongoing trials and one patient registry. Two of the ongoing trials assess the use of CytoSorb® in patients with sepsis, while the others focus on its preventive use during CPB surgery.

7 kontrollierte Studien und eine Registerstudie

Reimbursement

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

derzeit nicht rückerstattet

Discussion

ECAT is a new technology with very limited clinical evidence available. Only one study met our initial inclusion criteria, and thus, all studies that provided clinical data of more than five patients were included.

neue Technologie mit sehr wenig Evidenz

There was no data on the effect or safety of ECAT in patients with sepsis and septic shock. Moreover, the strength of evidence is very low for the preventive use of ECAT during CPB surgery. Although we could identify one randomised study, the risk of bias of this study was high, due to a small sample size, insufficient blinding, and a high rate of loss to follow-up (30%). The study sample of the RCT was not powered to draw conclusions on mortality, or other patient-relevant benefits. Only one of the two observational studies included a control group, however, failed to state patient characteristics or report on crucial outcomes. Furthermore, considering the various potential adverse effects of ECAT, safety endpoints were not reported by any of the studies, and only mentioned in the discussion. The number of patients included in the studies was small, and stemmed entirely from single centre studies. In view of the small study population and the two different indications, the results of the studies cannot be generalised to a larger population.

keine Daten zur Wirksamkeit bei Sepsis, nur geringe Daten zur präventiven Anwendung

Qualität der Evidenz sehr niedrig da
hohes Bias Risiko
geringe Fallzahl
fehlende Verblindung und Kontrollgruppen

Sicherheitsendpunkte nicht berichtet

Conclusion

The current evidence does not suffice to prove that ECAT in patients with sepsis, septic shock and SIRS is effective and safe. Clinical benefits in terms of patient-relevant outcomes in both indications need to be demonstrated in order to introduce ECAT into practice. A re-evaluation is recommended in 2019, if results from RCTs or CT including more than 100 patients are available.

Evidenz unzureichend: Aufnahme nicht empfohlen

Re-Evaluierung: 2019

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Sepsis, septischer Schock und SIRS sind lebensbedrohliche, systemische Immunreaktionen

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 nicht-infektiöse Auslöser – wie Herzchirurgische Eingriffe unter Verwendung der Herz-Lungen-Maschine (HLM) (kardiopulmonaler Bypass (CPB)) – haben. Dies ist für den vorliegenden Bericht von besonderer Bedeutung. Die Verwendung der HLM kann eine systemische Entzündungsreaktion während der Operation hervorrufen, die durch Kontaktaktivierung des Blutes durch künstliche Oberflächen ausgelöst wird.

Mortalität 7-40 %

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. 40 %[1].

Diagnose von Sepsis mittels SOFA score

Die im Jahr 2016 aktualisierte „Internationale Konsensus Leitlinie zur Definition und Diagnose der Sepsis“ (*SCCM/ESICM consensus guideline*) enthält Empfehlungen zur Beurteilung der Organdysfunktion von PatientInnen mit vermuteter Sepsis. Die Beurteilung sollte mit dem qSOFA (quick Sepsis-bezogenem Organ-Dysfunktions Score) beziehungsweise dem vollen SOFA-Score erfolgen (siehe Table 4-1) [1].

Diagnose von SIRS: 2 von 4 Kriterien

Für die Diagnose des SIRS (Systemic Inflammatory Response Syndrom) müssen mindestens zwei der vier SIRS Kriterien erfüllt sein [3]:

- erhöhte oder verminderte Körpertemperatur,
- erhöhte oder verminderte Leukozytenzahl
- Tachykardie (Herzrasen)
- erhöhte Atemfrequenz.

Symptomkombination

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.

Therapie: hämodynamische Stabilisierung und antibiotische Abdeckung

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, septischem Schock oder SIRS[2].

Beschreibung der Technologie

extrakorporale Zytokinadsorption versucht Zytokinkonzentration im Blut zu vermindern

Extrakorporale Zytokinadsorptionstherapie (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 der Zytokine führt, die ihrerseits wiederum weitere Immunkaskaden auslösen. Ziel der ECAT ist es, Zytokine aus dem Blut zu entfernen, um eine balancierte Immunantwort wiederherzustellen.

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; in Leitlinien derzeit nicht empfohlen

Derzeit ist CytoSorb® das einzige ECAT-Gerät, das über eine CE- Zertifizierung verfügt. 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-Adsorptionsbeads gefüllt, die Zytokine, und andere Entzündungsmediatoren ähnlicher Größe (Moleküle bis zu einer Größe von 55 kD) adsorbieren.

Einmal-Kartusche in Kombination mit Dialyse und HLM verwendbar

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.

Therapiedauer: 48-72 h therapeutisch, >2 h präventiv

Methoden

Im folgenden Bericht gingen wir der Frage nach, ob extrakorporale Zytokinadsorptionstherapie (ECAT) als therapeutischer Zusatz zur Standardtherapie für PatientInnen mit Sepsis, septischem Schock und SIRS wirksam und sicher ist. Des Weiteren wurden die Wirksamkeit und Sicherheit einer präventiven Zytokinadsorptionstherapie bei herzchirurgischen Eingriffen mit Einsatz der HLM geprüft.

Fragestellung

Zur Beantwortung der Forschungsfragen, wurde eine systematische Literatursuche in fünf Datenbanken durchgeführt (Medline via Ovid, Embase, the Cochrane Library, CRD). Ergänzend erfolgten eine Suche in Studienregistern, eine Studienanfrage bei den Herstellern, sowie eine unsystematische Handsuche. Die Daten der entscheidungsrelevanten Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

systematische Literatursuche in 5 Datenbanken, Handsuche, Studienregister Suche

Bewertung der Qualität mit GRADE

Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studien wurde von zwei Autorinnen (KH, CW) unabhängig voneinander durchgeführt.

Klinische Wirksamkeit

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert: Verbesserung des Überlebens, klinische Verbesserung der Organdysfunktion, Aufenthaltsdauer in intensivmedizinischen Stationen, Verminderung der Hospitaliserungsdauer.

entscheidende Endpunkte: Wirksamkeit: Überleben, klinische Verbesserung, Hospitalisierung

Sicherheit

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

Sicherheit: Komplikationsraten

Ergebnisse

Verfügbare Evidenz

1 RCT, 2 retrospektive Fallserien

insgesamt 93 Patienten, 55 bekamen ECAT

Insgesamt konnten drei Studien identifiziert werden, in denen klinische Daten zu ECAT erhoben wurden. Die Gesamtzahl der PatientInnen betrug 93, von denen 55 PatientInnen eine CytoSorb® Therapie erhielten. Für die Beurteilung der Wirksamkeit von ECAT wurde eine randomisierte kontrollierte Studie (RCT) und eine retrospektive Fallserie eingeschlossen. Beide Studien untersuchten die präventive Anwendung von CytoSorb® während herzchirurgischer Eingriffe mit HLM.

Für die Bewertung der sicherheitsbezogenen Endpunkte konnte zusätzlich eine retrospektive Ein-Arm-Fallserie identifiziert werden. Die Fallserie mit insgesamt 16 Patienten berichtete über die Anwendung von ECAT bei PatientInnen mit SIRS nach herzchirurgischen Eingriffen mit HLM.

keine Studie zur Therapie der Sepsis

Zur therapeutischen Anwendung von ECAT bei Sepsis konnte keine kontrollierte Studie identifiziert werden.

Klinische Wirksamkeit

Daten zur Wirksamkeit: keine signifikanten Ergebnisse in allen wichtigen Endpunkten

Ein RCT mit 37 PatientInnen berichtete von einer 30-Tage Mortalität als sekundären Endpunkt. Ein/e der 19 PatientInnen der Interventionsgruppe verstarb am 22. postoperativen Tag, während alle 18 PatientInnen in der Kontrollgruppe eine Überlebensdauer von mindestens 30 Tagen hatten. Die Studie wies darüber hinaus keine signifikanten Unterschiede bei der Aufenthaltsdauer in Intensivstationen und bei den Tagen der mechanischen Beatmung auf.

wichtige Endpunkte nur von einer Studie berichtet

Die retrospektive Fallserie mit 40 PatientInnen enthielt keine Daten zu den empfehlungsrelevanten Endpunkten. Des Weiteren berichtete keine der Studien über die Gesamtdauer des Krankenhausaufenthaltes oder über Änderungen im SOFA Score zur Beurteilung des Organversagens.

Sicherheit

keine Daten zu unerwünschten Ereignissen und Nebenwirkungen

Keine der Studien berichtete explizit über unerwünschte oder schwerwiegende Ereignisse bei der Anwendung von CytoSorb® während der Herzchirurgie oder postoperativ bei PatientInnen mit SIRS. Darüber hinaus wurden keine unerwünschten produktbezogenen Ereignisse beschrieben.

Zur therapeutischen Anwendung bei Sepsis konnten keine Daten identifiziert werden.

Laufende Studien

7 kontrollierte Studien und eine Registerstudie

Insgesamt konnten sieben laufende Studien und ein PatientInnenregister identifiziert werden. Zwei der laufenden Studien beurteilen die Verwendung von CytoSorb® bei PatientInnen mit Sepsis, während die anderen sich auf den präventiven Einsatz während der Herzchirurgie mit HLM konzentrieren.

Kostenerstattung

derzeit keine Erstattung

Derzeit wird ECAT vom österreichischen Gesundheitssystem nicht erstattet.

Diskussion

neue Technologie mit sehr wenig Evidenz

ECAT ist eine neue Technologie, für die wenig klinische Evidenz verfügbar ist. Nur eine Studie erfüllte die ursprünglichen Einschlusskriterien, worauf-hin alle Studien, die klinische Daten von mehr als fünf PatientInnen enthielten, eingeschlossen wurden, um die Technologie bewerten zu können.

keine Daten zur Wirksamkeit bei Sepsis, nur geringe Daten zur präventiven Anwendung

Qualität der Evidenz sehr niedrig da hohes Bias Risiko geringe Fallzahl fehlende Verblindung und Kontrollgruppen

Aus den Studien gehen keine Daten zur Wirksamkeit oder Sicherheit von ECAT bei PatientInnen mit Sepsis und septischem Schock hervor. Darüber hinaus ist die Stärke der Evidenz eines präventiven Einsatzes von ECAT in die HLM sehr gering. Es konnte ein RCT identifiziert werden, allerdings wies diese ein hohes Bias Risiko, aufgrund einer zu geringen Stichprobengröße, unzureichender Verblindung und einem hohen Loss to follow up (30 %), auf. Eine schlussfolgernde Aussage über den Endpunkt Mortalität oder andere patientenrelevante Endpunkte können aufgrund geringer Power nicht getroffen werden. Nur eine der beiden Beobachtungsstudien umfasste eine Kontrollgruppe, jedoch berichtete diese weder von PatientInnencharakteristiken noch von entscheidenden Ergebnissen. Darüber hinaus wurden relevante Sicherheitsendpunkte von keiner der Studien explizit analysiert sondern lediglich in den Diskussionen erwähnt. In Anbetracht der verschiedenen potenziellen nachteiligen Auswirkungen von ECAT hebt dies die geringe Evidenzlage besonders hervor. Angesichts der kleinen Studienpopulation und der zwei unterschiedlichen Indikationen können die Ergebnisse der Studien nicht auf eine größere Population verallgemeinert werden.

Sicherheitsendpunkte nicht berichtet

Empfehlung

Evidenz unzureichend: Aufnahme nicht empfohlen

Die gegenwärtige Studienlage lässt keine Rückschlüsse zu, ob eine Behandlung mittels ECAT bei Sepsis, septischem Schock oder SIRS wirksam oder sicher ist. Gleichsam ist auch für den präventiven Einsatz von ECAT bei kardiopulmonalen Bypass Operationen zu wenig Evidenz vorhanden, um die Wirksamkeit und Sicherheit der Intervention bewerten zu können.

Re-evaluierung 2019

Neue Studien werden möglicherweise einen wichtigen Einfluss auf die Einschätzung des Effekts haben. Eine neuerliche Evaluierung wird im Jahr 2019 vorgeschlagen, jedoch nur wenn neue Ergebnisse aus RCT's für beide Indikationen vorliegen und diese mehr als 100 eingeschlossenen PatientInnen umfassen. Die Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen.

1 Scope

1.1 PICO question

PIKO-Fragen: ECAT therapeutisch

Is extracorporeal cytokine adsorption therapy (ECAT) as 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 overall survival, organ function and recovery?

ECAT präventiv

Is ECAT as preventive therapy in patients undergoing cardiopulmonary bypass surgery (CPB) as safe concerning adverse events, and more effective concerning overall survival, organ function and recovery?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	❖ Patients with SIRS, sepsis, septic shock (Abdominal septic, 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 [1] ❖ As 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 therapeutic intervention in patients with SIRS, sepsis or septic shock 2) Cytokine adsorption therapy as 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)
Control	Standard care for SIRS sepsis and septic shock[1] Standard care after coronary bypass surgery

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

Outcomes	
Efficacy	*Clinical endpoints:* • Improved survival • Improved clinical outcomes: organ functions (Sepsis-related Organ Failure Assessment, SOFA score or Multiple Organ Dysfunction score, MODS) • Days in ICU • Days of hospitalization • Ventilator free days *Surrogate endpoints:* • Decrease in dose of vasopressor drugs • Decrease in blood cytokine levels
Safety	• Perioperative/periprocedural adverse events and complications • Postoperative/postprocedural adverse events and complications
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series, single arm studies

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is extracorporeal cytokine haemadsorption therapy(ECAT)?
B0002	What is the claimed benefit of ECAT in relation to the comparator(s)?
B0003	What is the phase of development and implementation of ECAT?
B0004	Who administers ECAT and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use ECAT?
B0009	What supplies are needed to use ECAT?
A0020	For which indications has ECAT received marketing authorisation or CE marking?
A0021	What is the reimbursement status of ECAT?
Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is ECAT used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors forsepsis or SIRS?
A0004	What is the natural course ofsepsis, septic shock or SIRS?
A0005	What are the symptoms and the burden of disease or health condition for the patients?
A0006	What are the consequences of sepsis for the society?
A0024	How is sepsis and SIRS currently diagnosed according to published guidelines and in practice?
A0025	How is the sepsis and SIRS currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is ECAT utilised?
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 Sources

Description of the technology

Quellen

- Hand search in the POP, MDS, Synergus, Ohtanen and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Hand search for background publications in UptoDate and Deximed databases
- Documentation provided by the manufacturers

Health problem and Current Use

- Hand search in the POP, MDS, Synergus, Ohtanen and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Hand search for treatment guidelines, epidemiologic data, national registries
- Documentation provided by the manufacturers

2.3 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted on the 23.12.2016 in the following databases:

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

insgesamt 618 Publikationen identifiziert

The systematic search was not limited to a specific study design, language or period. After deduplication, overall 592 citations were included. The specific search strategy employed can be found in the appendix.

Manufacturers from the only CE-marked product CytoSorb® submitted a literature list with 32 publications of which 2 new citations were identified.

By hand-search, an additional 24 studies were found, resulting in overall 618 hits.

2.4 Flow chart of study selection

Literaturauswahl

Overall 616 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.

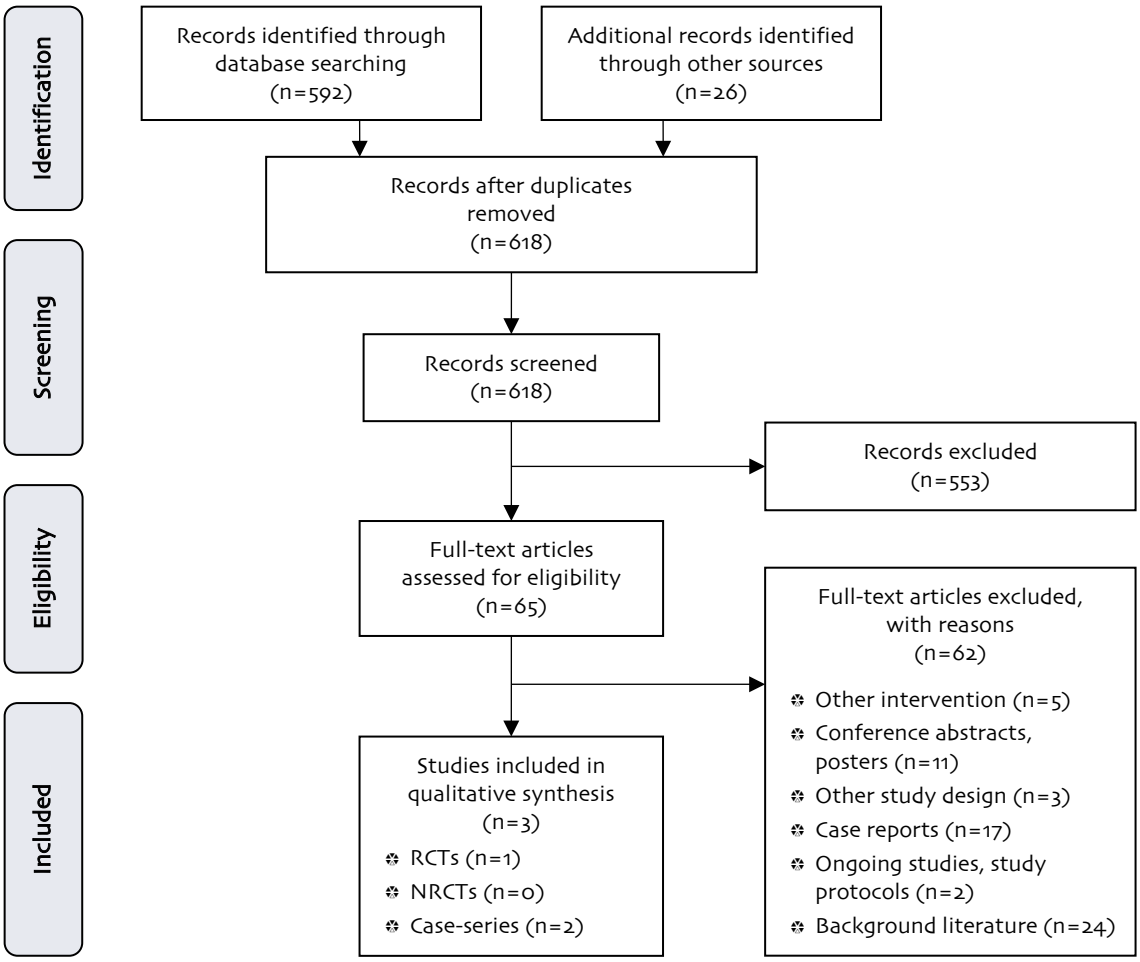

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion aus Studien

We retrieved data from the selected studies (see Chapter 2.4) and systematically extracted them into the data-extraction-tables (see Appendix Table A-1 and Table A-2). No further data processing (e.g. indirect comparison) was applied.

Qualitätsbeurteilung der Studien mit Cochrane RoB und IHE Checkliste

Two independent researchers (KH, CW) systematically assessed the quality of evidence and risk of bias using the Cochrane Risk of Bias tool for RCTs and the IHE Risk of Bias checklist for case series [4]. The risk of bias analysis for each individual study can be found in the Appendix (Table A-3 and Table A-4).

2.6 Synthesis

qualitative Synthese der Evidenz

Due to the heterogeneity of studies, only a qualitative and not a quantitative analysis of efficacy and safety data was possible. The questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

In addition, a GRADE evidence table was created in order to synthesize data on each selected outcome category across studies (Table 7-1) [5]. Where available, data on critical outcomes were included in the evidence table.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is extracorporeal cytokine haemadsorption therapy?

Extracorporeal cytokine adsorption therapy (ECAT) aims to reduce excessive levels of cytokines in the blood to control an overreacting systemic immune response of the body.

Extrakorporale Zytokin Adsorptions Therapie soll Zytokin Level

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 [6-8].

im Blut bei überschießenden Immunantworten reduzieren

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, while, to date, the underlying signalling pathways and various effects of different cytokines are not completely understood [6]. However, there is evidence that an elevated level of cytokines is associated with the development of a systemic inflammatory response syndrome (SIRS), and a poor prognosis [6, 9, 10].

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

Funktionsweise vieler Zytokine ist noch nicht bekannt

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 cardiopulmonary bypass surgery(CPB) was associated with worsening lung function and the development of SIRS [9].

Überschuss an Pro-inflammatorischen Zyktokinen (IL-6, IL-1, TNF- α) korreliert mit Sepsis Schweregrad und Mortalität

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 the systemic inflammation with potential detrimental consequences such as SIRS, sepsis and septic shock [8].

simultane Freisetzung Anti-inflammatorischer Zytokine (IL-10, IL-13) führt zu balancierter Immunantwort

The principal idea behind extracorporeal haemadsorption therapies is to remove these inflammatory molecules from the blood in order to restore a balanced immune response [11]. Originally, extracorporeal blood purification therapies have been 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 [7].

ECAT:
soll Überschuss an Zytokinen ausgleichen

Marketed Products

mehrere Adsorptionsträger derzeit untersucht

Several cytokine adsorbing columns are currently being investigated for their potential in eliminating cytokines and other molecules from the blood:

- CYT-860-DHP (Toray Industries, Inc., Tokyo, Japan),
- Lixelle® (Kaneka Co., Osaka, Japan)
- CTR-001 Column (Kaneka Co., Osaka, Japan)
- MPCF-X and
- CytoSorb® (Cytosorbents Co., USA) [12].

Unterschiede in Aufbau und Adsorptionsrate

These adsorptive columns vary in their structure and adsorption rate. Preclinical studies have shown beneficial effects in survival rates in animal sepsis models [13].

CytoSorb® einziger Adsorber mit CE-Kennzeichnung (seit 2011) Klasse 2b Medizinprodukt

Currently, CytoSorb® is the only CE-marked extracorporeal haemadsorption device in the European Union (EU). CytoSorb® is a Class 2b medical device and received market authorization in 2011. It is marketed in almost all EU Member States, with the exception of eastern European countries. Globally, it is commercialised in 42 countries, amongst others in Australia, Chile, Russia, India, Saudi Arabia, India, and Turkey (Information by manufacturer).

Anwendung als Stand-alone Therapie oder in Kombination mit Nierenersatztherapie oder Herzlungenmaschine

The device consists of a single-use haemadsorption cartridge that can be used as stand-alone therapy with standard blood pumps, in combination with continuous renal replacement therapy (CRRT) or during cardiopulmonary bypass (CPB) surgery.

The adsorber cartridge is filled with sorbent, porous polymer beads of the size of a grain of salt. The beads capture and adsorb molecules as the blood passes through the pump. Smaller molecules (5-60 kDa) such as pro- and anti-inflammatory cytokines get captured in the net of pores, while larger molecules can pass through [13].

B0002 – What is the claimed benefit of ECAT in relation to the comparators?

ECAT als Zusatz zur Standard Therapie; keine kausale Therapie bei Sepsis oder für Zytokinadsorption

Rather than being a causal therapy for sepsis ECAT, is intended as an addition to standard treatment of sepsis. There is neither a direct comparator for the causal treatment of sepsis nor a standard therapeutic option to adsorb cytokines from the blood.

The claimed major benefit for the use of cytokine adsorption is to reduce the level of cytokines and thus the inflammatory response.

weitere Blutreinigungsverfahren

Other blood purification mechanisms were proposed to remove excessive levels of cytokines from the blood:

- Haemoperfusion
- Plasma or whole blood exchange
- Coupled plasma filtration
- High volume haemofiltration

jede Methode hat Vor- und Nachteile Ergebnisse aus klinischen Studien widersprüchlich

Several reviews exist that summarised the differences between the blood purification techniques and their suggested advantages and disadvantages [7, 11, 13]. While there are some studies showing benefits for haemoperfusion, haemofiltration and plasma exchange, the results remain preliminary [14]. Furthermore, opposing studies showed limited or no clinical advantage [15].

In summary, no clear evidence is available to date that verifies the efficacy and safety of these procedures [11, 13, 15]. The most recent international consensus guideline on the management of sepsis does not recommend the use of any of the blood purification therapies, reasoning that the available trials are small, insufficiently blinded with a high risk of bias [2]. Larger randomised trials will be necessary to assess potential benefits and compare interventions with each other.

es liegt keine klare Evidenz zum Nutzen dieser Verfahren vor

In comparison to these techniques the claimed major advantage of the CytoSorb® device is its large surface of area of 40,000 m² compared to classic haemofiltration devices [13]. Conversely, CytoSorb® does not have the capacity to remove endotoxins, which was suggested to be its main disadvantage [13].

große Adsorptionskapazität, jedoch keine Adsorption von Endotoxinen

The adsorbing capacity of the CytoSorb® cartridge is asserted concentration dependent, thus, the higher the cytokine level in the blood the faster they will be adsorbed. Conversely, if the cytokines concentration is low there will be no complete elimination of cytokines from the blood. This intends to prevent overtreatment [16].

CytoSorb® wirkt abhängig von Zytokin-Konzentration im Blut

B0003 – What is the phase of development and implementation of ECAT?

The principle of filtering and adsorbing molecules from the blood is not new and has been used in haemodialysis machines for a few decades. The first studies proposing the idea of extracorporeal removal of pro-inflammatory cytokines for the treatment of sepsis were published around the year of 1995. However, similarly, as to other extracorporeal blood purification techniques, haemadsorption devices are in an early stage of implementation, with only limited clinical data being available to date [13, 15].

Prinzip ist nicht neu seit 1995

Blutreinigung mit Hämadsorption befindet sich aber in frühem Stadium der Erprobung

Only two randomised controlled trials have been completed until today; results are published for only one of them (see synthesis of results). The technology is in an experimental stage and its use is not established in clinical practice. An international patient registry has been created in order to report cases of compassionate use and to evaluate safety profiles outside of randomised controlled trials (RCT) [17].

2 klinische Studien (RCTS), davon 1 veröffentlicht

While awaiting the results of the clinical trials, CytoSorbents launched the next generation of the haemadsorption device 'CytoSorb®-XL in September 2016 presenting initial results from *in vitro* studies [18]. In comparison to the original device CytoSorb®, CytoSorb®-XL has the additional capacity to remove endotoxin from the blood.

zweite Generation, CytoSorb®-XL bereits in Entwicklung

In a press release the manufacturer claims a potential addressable market in the US and in Europe of more than $1.5 billion for CytoSorb® for its use during CPB surgery alone. Overall, the manufacturer claims a $20 billion market potential of CytoSorb® for critical care applications worldwide[2].

hoher potentieller Marktumsatz

[2] http://www.prnewswire.com/news-releases/cytosorbents-announces-fda-approval-to-commence-initial-us-cardiac-surgery-study-300028992.html

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers ECAT and in what context and level of care is it provided?

B0008 – What kind of special premises are needed to use ECAT?

B0009 – What supplies are needed to use the technology?

3 Anwendungsmodi: als Stand-Alone Therapie, in Kombination mit CRRT und während CPB

in ICU und Kardio-OPs

There are three modes of application of the CytoSorb® technology: as standalone therapy, in combination with CRRT and during cardiopulmonary bypass procedures.

The setup of the technology and the application procedure is claimed to be simple with only little training efforts required. CytoSorb® has standard dialysis connectors that are compatible with the most commonly used haemodialysis machines, CRRT devices and heart-lung machines. The technology is used in intensive care units and in operating rooms during cardiac surgery.

Personnel that acquired appropriate training in the management of extracorporeal therapies can administer CytoSorb®. A physician should direct the use of CytoSorb® and should have received training in the correct use of the technology [19].

PatientInnen müssen antikoaguliert werden, aPTT und ACT sollten regelmäßig überprüft werden

Patients need to be effectively anticoagulated at the start of the treatment with heparin or citrate. The aPTT (activated partial thromboplastin time) and ACT (activated clotting time) when using heparin anticoagulation, or ionized calcium for citrate anticoagulation should be checked regularly during treatment to ensure adequate anticoagulation [16].

Before the start of the treatment, the supply tube system must be airlessly prefilled with a minimum of two litres sterile isotonic saline solution. Pressure monitoring of the bloodline between the device and the blood pump is recommended throughout the treatment [19].

einmalige Verwendung der Kartuschen

Therapiedauer: 48-72h

The patient blood is continuously recirculated between the absorption device and the patient. The usage of one cartridge should not exceed 24 hours; reuse might lead to secondary infections or clotting. The absorber can be replaced daily for a maximum of seven days of continuous ECAT treatment. The typical treatment duration for sepsis patients is 48 hours to 72 hours [16]. The preventive use of ECAT during CPB surgery lasts as long as the heart-lung machine is connected. The use of CytoSorb® during CPB surgery is recommended for a CPB duration of more than >120 min [16].

diverse zusätzliche Materialien notwendig

Materials required for the setup of the technology are the sterile CytoSorb® cartridge, bloodlines that are compatible with the used blood pump system, plastic scissor clamps, isotonic saline solution, and female Luer connectors to connect with the CytoSorb® blood ports. The roller blood pump should be capable of delivering up to 400 mL/min blood flow rate. The typical flow rate is 150- 500 ml/min [19].

Regulatory & reimbursement status

A0020 – For which indications have ECAT devices received marketing authorisation or CE marking?

CytoSorb®: EU CE-Mark seit 2011

In Europe, CytoSorb® received its CE mark in 2011 as the first haemadsorption device indicated for the treatment of conditions with excessive cytokine levels.

USA: keine Zulassung, aber IDE-Zulassungsstudie seit 2015 Pilotstudie beendet, aber Ergebnisse noch nicht veröffentlicht

In the US, the manufacturer CytoSorbents, Inc currently seeks market approval at the Food and Drug Administration (FDA). A safety and feasibility trial on CytoSorb® use during complex cardiac surgery was initiated in 2015 under the Investigational Device Exemption (IDE)[3] (NCT02566525). According to the manufacturers, this first pilot study was recently completed; the results are still pending.

2 Indikationsbereiche: SIRS+Sepsis: therapeutisch und prophylaktisch

Excessive cytokine levels occur in several conditions.
The two main indications for the use of CytoSorb® are

- the therapeutic treatment of SIRS and sepsis
- the preventive intraoperative or post-operative use of CytoSorb® during cardiac surgery to prevent SIRS.

These two fields of application are also the focus of the majority of ongoing trials on the clinical use of CytoSorb®.

A0021 – What is the reimbursement status of ECAT?

At present, ECAT is not included in the Austrian benefit catalogue.

derzeit nur in Deutschland (seit 2017) rückerstattet

In Germany, the technology has been added to the German OPS catalogue (Operationen und Prozedurenschlüssel) and the InEK (Entgeltsystem im Krankenhaus) in November 2016, the addition is effective with 01.01.2017. Since 2017, German hospitals can directly negotiate an individual reimbursement for the CytoSorb® therapy. To the knowledge of the authors, Germany is the first European country to reimburse CytoSorb® therapy.

UK-Preis: 920£/1.067 EUR

There are no official list prices of CytoSorb® treatment available in Germany or Austria. In a recent Medtech innovation briefing on CytoSorb® published by the National Institute for Health and Care Excellence (NICE) the UK list price of one single use CytoSorb® device is 920£ (1066.70 EUR[4]), excluding VAT (value added tax) [20]. As adjunctive treatment, the costs of the technology would be an addition to the costs of standard care.

[3] http://cytosorb-therapy.com/pressarticle/cytosorbents-submits-ide-application-fda-u-s-cytosorb-cardiac-surgery-trial/

[4] http://www.xe.com/currencyconverter; official exchange rates, 24/01/2017

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is ECAT used?

derzeit 2 Indikationsbereiche: SIRS+Sepsis: therapeutisch und prophylaktisch

Currently, several indications are being investigated for the use of ECAT. The common denominator of these conditions is an excessive level of cytokines in the blood. The main indications and primary focus of ongoing research are the treatment and prevention of SIRS and sepsis, as afore described in A0020.

weitere Indikationen in Fallstudien berichtet

Case reports on first clinical applications of CytoSorb® in other hyper-inflammatory conditions have been published or presented at conferences, and include the following (not subject of this assessment):

- Polytrauma and rhabdomyolysis
- Serious burn injury
- Severe acute pancreatitis
- Various types of liver failure
- Severe cardiogenic shock

A0002 – What is the disease or health condition in the scope of this assessment?

Sepsis, septischer Schock und SIRS sind mit einer dysfunktionalen Immunreaktion assoziiert

The focus of this assessment is the application of ECAT devices in patients with sepsis and septic shock. Furthermore, we assessed its effectiveness as a preventive intervention for patients undergoing cardiopulmonary bypass surgery who risk developing SIRS.

Sepsis, septic shock and SIRS are closely linked conditions that are associated with a dysfunctional immune response.

trotz medizinischem Fortschritt: Mortalität und Morbidität bei Sepsis und septischem Schock hoch

Despite the therapeutic advances of recent years, the mortality and morbidity of sepsis and septic shock remained high. Even with optimal treatment, the mortality of sepsis and septic shock is estimated to be more than 10% and more than 40% respectively [1].

2016: neue Konsensus Definitionen zu Sepsis und septischem Schock von internationalen Fachgesellschaften

The definitions of sepsis and septic shock have evolved since the 1990s. In 2016, new international consensus definitions (Sepsis-3 guidelines) on sepsis and septic shock were published by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) and endorsed by several national and international societies [1]. These consensus definitions were also considered for the purpose of this assessment. The Sepsis-3 definition has two grades: sepsis and septic shock. Notably, one key recommendation from the new definitions is that SIRS is no longer included in the definition of sepsis, due to the lacking sensitivity and specificity of the criteria to detect patients with sepsis.

Definition Sepsis

Sepsis ist eine lebensbedrohliche Organdysfunktion

Sepsis is a clinical syndrome that exists on a continuum of severity ranging from an infection and bacteraemia (bacteria in the blood) to severe multi organ dysfunction with septic shock [3]. According to the SCCM/ESICM task force, sepsis is defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [1].

kausale Infektion oft nicht nachweisbar

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 [1, 21]. Patients with suspected sepsis present themselves often with tachycardia, fever, hypotension and leucocytosis [21].

Organ-Dysfunktion kann mittels SOFA score nachgewiesen werden

Clinically, the organ dysfunction can be identified by an acute change in the SOFA score (Sepsis-related Organ Failure Assessment) by two or more points, which is associated with an in-hospital mortality greater than 10% [1].

Begriff ‚schwere Sepsis' wurde für redundant befunden und aus den Konsensus Leitlinien gestrichen

The 2016 SCCM/ESICM consensus definitions noted that the term *severe sepsis* is redundant under the present terminology of sepsis and septic shock [1]. Originally, severe sepsis referred to sepsis with organ dysfunction or sepsis with tissue hypoperfusion, which today is included in the definitions of septic shock [1, 22].

Parameter im SOFA Score

Table 4-1: Sepsis Related Organ Failure Assessment Score, adapted from Vincent et al. 1996 [23]

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
			with respiratory support	
Coagulation Platelets x $10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.i
Central nervous system Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal Creatinine, mg/dl or urine output ml/d	1.2-1.9	2.0-3.4	3.5-4.9 or < 500 ml/d	>5.0 or < 200ml/d

[a] *Adrenergic agents administered for at least 1h (doses given are in µg/kg min)*

Definition septic shock

Definition septischer Schock SCCM/ESICM:

Septic shock is an extensive vasodilatory reaction that leads to hypoperfusion of the body [1, 21]. Due to the vasodilation of the arteries and capillaries, the blood is pooled in the periphery of the circulatory system causing severe hypotension.

Abgrenzung zur Sepsis: Persistenz von Blutdruckabfall und erhöhtes Serum Lactat

The SCCM/ESICM guidelines define septic shock as 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 65mmHG and serum lactate level greater than 2mmol/l (18mg/dL) in absence of hypovolemia [1].

Definition SIRS

Definition SIRS: dysregulierte Immunreaktion, mit oder ohne zugrunde liegender Infektion

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

SIRS-Kriterien

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 $PaCO_2$ of less than 32mmHg
- Abnormal white blood cell count (> 12,000/mm^3 or < 4,000/mmm^3) [1, 22]

Seit 2016: SIRS Kriterien für Sepsis Definition ungeeignet, da schlechte Vorhersagekraft

Until 2016, the international consensus definition for severe sepsis required suspected or proven infection, organ failure, and clinical signs that meet two or more criteria for SIRS [3]. However, this definition has fallen out of favour because many patients who fulfilled the criteria for SIRS did not develop severe sepsis [1, 21]. Furthermore, research showed that its predictive capacity on mortality was poor compared with other scoring tools such as the SOFA score [1].

viele Ursachen für SIRS möglich

The aetiology of SIRS is broad and, apart from infectious causes, comprises non-infectious conditions such as autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, or surgery.

Entstehung von SIRS durch verschiedene Auslöser die zur überschießenden Immunantwort führen

Independent from the aetiology of SIRS, the underlying pathophysiologic mechanisms that trigger the excessive immune response are similar. Nonspecific insults that can arise from chemical, traumatic or infectious stimuli lead to the natural immune response of inflammation. An inflammatory cascade is triggered, involving multiple humoral and cellular responses that lead to the release and production of cytokines [8].

A0003 – What are the known risk factors to develop sepsis or SIRS?

Risikofaktoren: Alter > 65 Jahre, Immunsuppressive Therapien, Vorerkrankungen wie Diabetes, Krebs, Pneumonie

Several risk factors are associated with developing sepsis [21]. The incidence of sepsis increases disproportionally in patients above the age of 65 years, and advanced age is considered a predictor of sepsis-related mortality. Older patients die sooner during hospitalisation and elderly sepsis- survivors show worse long-term outcomes compared to younger survivors [24]. Further risk factors include immunosuppression, and disease conditions, such as diabetes, cancer, community-acquired pneumonia, and patients with trauma and major surgical procedures [21]. Moreover, genetic factors that may alter the innate immune response and increase susceptibility to specific microorganisms have been identified that seem to contribute to a higher risk of developing sepsis [25].

nosokomiale Infektionen in Intensivstationen und vorangegangene Hospitalisierung

Due to the high rate of nosocomial infectious in intensive care units (ICU) admission to an ICU increases the risk of developing sepsis. Similarly, previous hospitalisation increases the risk of developing sepsis by three-fold in the 90 days following discharge [26]. Patients who were admitted for infection-related conditions, in particularly for infections with bacterium Clostridium difficile, are at greatest risk.

Risikofaktoren für SIRS: vgl. oben

sowie bei/nach kardialen Eingriffen mithilfe einer Herz-Lungenmaschine

Similarly as to sepsis, the risk of developing SIRS is higher for patients with advanced age, immunosuppression, and underlying conditions that affect the immune system. One particular risk factor relevant for this assessment is the risk of developing SIRS after cardiac surgery. The use of the heart-lung machine during surgery provokes a systemic inflammatory response, triggered by contact activation of blood by artificial surfaces. In most cases, this immune response is transient and self-terminating at the end of CBP. However, some patients (2-10%) develop SIRS with major organ dysfunction and poor outcomes [27, 28].

A0004 What is the natural course of sepsis, septic shock and SIRS?

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% [21]. Mortality is lower in younger patients without comorbidities.

Sepsis-Überlebende berichten von schlechterer QoL

After hospital discharge, patients can have a higher risk of further sepsis and re-admission 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 [29]. 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) [3].

SIRS Prognose: abhängig von Ätiologie

The natural cause and prognosis of SIRS depends on the underlying condition and the aetiological source of SIRS.

Effects of the disease or health condition on the individual and society

A0005 – What are the symptoms and the burden of disease or health condition for the patient?

anfangs unspezifische Symptome, oft assoziiert mit kausaler Infektion

später Zeichen des Schocks und Organversagens

Patients with suspected sepsis or SIRS present themselves with a combination of several non-specific symptoms: hypotension, fever or temperature below 36° C, a high respiratory rate, an accelerated heart rate (> 90 beats/min), an altered mental status with symptoms of acute confusion, and signs of hypoperfusion. Additionally, they may show symptoms that are specific to the infectious origin, for example, coughing and dyspnoea in cases of pneumonia [21]. As the disease progresses patients may develop symptoms of shock with signs of severe hypoperfusion, such as absent bowel sounds (Ileus) and cyanosis [8].

A0006 – What are the consequences of sepsis for the society?

Inzidenz steigt aufgrund demographischen Veränderungen, Immunsuppressiva, multi-resistenter Infektionen, verbesserter Früherkennung

As a consequence of the demographic changes with advancing age, increased use of immunosuppression and rising occurrence of multi-resistant infections the incidence of sepsis is increasing in the past 20 years. This increase was also associated with better early detection strategies and growing awareness of the disease, yet it is anticipated that the sepsis incidence will keep rising in the future [21].

In Germany, the direct medical costs for the treatment of septic patients in an intensive care unit were estimated to be 1.77 billion Euro annually, which represents 30% of the total intensive care budgets in Germany [3]. The UK National Health Service (NHS) annual reference cost for sepsis in 2014/2015 were £6400 to £9673 per patient with sepsis [20].

hohe Kosten:
30 % der ICU Kosten

For Austria, the latest accessible information on costs of sepsis stem from 2002; the total direct costs were calculated to be between 192 million Euros to 272 million Euros annually [30]. Direct costs represent only 20-30% of the total costs of sepsis, whereby the other 70% arise from indirect costs of productivity loss [31].

Daten aus Österreich:
192-272 Mio EUR
jährlich (2002)

Current clinical management of the disease or health condition

A0024 – How is sepsis and SIRS currently diagnosed according to published guidelines and in practice?

A combination of clinical parameters, laboratory, microbiologic and haemodynamic data leads to the diagnosis of sepsis. Often, the diagnosis is made retrospectively. Suspected sepsis patients are initially diagnosed at the bedside upon clinical presentation, and the tentative diagnosis is later confirmed when laboratory or microbiological data returns. The identification of the underlying infection is highly supportive of the diagnosis of sepsis, however, not always possible [21].

Diagnostik:
Kombination aus klinischen, labortechischen, mikrobilogischen und hämodynamischen Parametern

Patients with suspected infection likely to develop sepsis can be identified by applying the qSOFA score (quickSOFA), a quick and simplified scoring tool developed by the Sepsis-3 guideline task force to facilitate bedside screening of sepsis inside and outside from hospital settings. The qSOFA criteria consist of a respiratory rate of more than 22/min, an altered mental state with a GCS < 15 and a systolic blood pressure of less than 100mgHg [1]. If the qSOFA score is positive, organ dysfunction should be assessed according to the full SOFA score variables.

qSOFA score:
vereinfachtes Diagnosetool am Krankenbett

Laboratory signs of sepsis are unspecific, but can be associated and evidential for the underlying organ dysfunction or infection. Relevant laboratory parameters include leukocytosis or leucopenia, white blood cell count with more than 10% immature progenitor cells, hyperglycaemia in the absence of diabetes, elevated CRP levels, arterial hypoxemia, acute oliguria, creatinine increase, coagulation abnormalities, thrombocytopenia, and increased levels of bilirubin and lactate [21]. Figure 4-1 provides an overview of the diagnostic algorithm to identify patients with sepsis, developed by the sepsis-3 taskforce.

Labor-Parameter für Sepsis:
unspezifisch

The diagnostic criteria for SIRS were described above. If patients present themselves with at least two out of the four parameters, they meet the criteria for the condition of SIRS [1].

Diagnose SIRS:
2 von 4 klinischen SIRS Kriterien

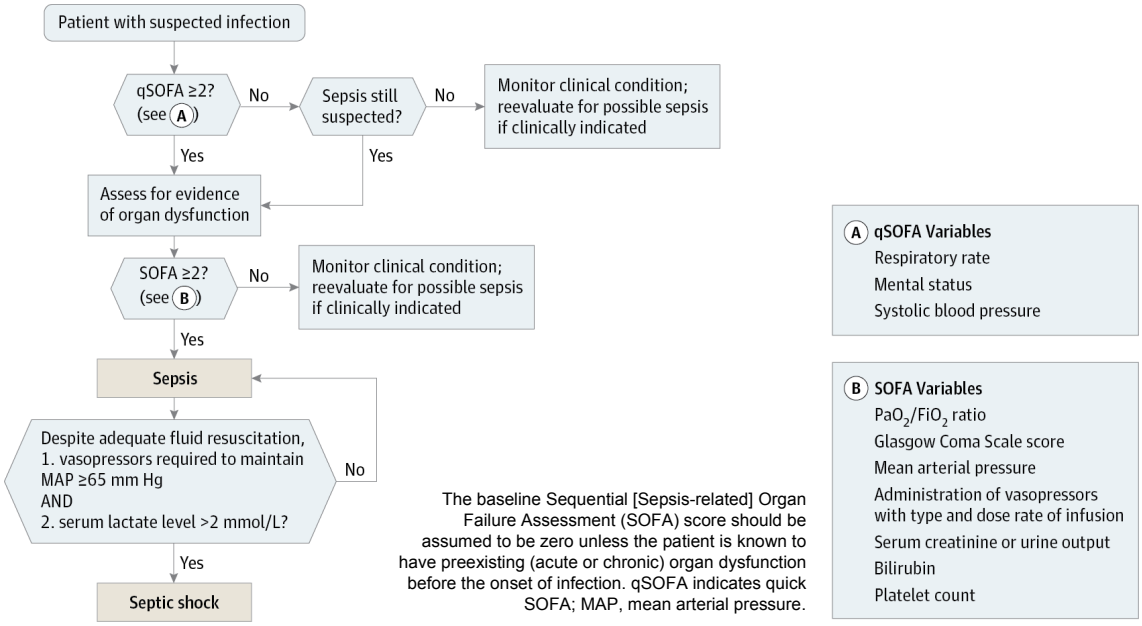

Figure 4-1: Clinical criteria to identify patients with sepsis and septic shock, developed by the SCCM/ESICM taskforce, from Singer et al. 2016 [1]

A0025 – How is sepsis and SIRS currently managed according to published guidelines and in practice?

Sepsis: Früherkennung, supportive Therapie zur hämodynamischen Stabilisierung

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 [32].

The *Surviving Sepsis Campaign International Guidelines for the Management of severe sepsis and septic shock* recommended a care bundle of specific interventions to be completed within the first three and first six hours of the management of a septic patient (see Figure 4-2) [33].

Figure 4-2: Surviving Sepsis Campaign patient management in the first 6 hours; from Dellinger et al, 2013 [33]

SURVIVING SEPSIS CAMPAIGN CARE BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
- Measure central venous pressure (CVP)*
- Measure central venous oxygen saturation ($ScvO_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥ 70%, and normalization of lactate.

Control of septic focus

Früherkennung und Behandlung der Verursacher-Infektion mit Antibiotika

The early identification of the primary site of infection is essential, and the only causal therapeutic measure in the treatment of sepsis to date. Moreover, the identification of an infection is needed to distinguish sepsis from SIRS [32].

Early and adequate antibiotic treatment is essential for the treatment of sepsis ('hit early and hit hard-strategy'). Intravenous antibiotic therapy should be started within the first hours, and after obtaining blood cultures [3]. 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 [34]. Furthermore, potential infective sources, i.e. devices and vascular access lines, should be controlled and if possible, removed.

Supportive therapy

hämodynamische Stabilisierung:

The second priority in patients with sepsis and septic shock is to achieve haemodynamic stabilisation.

Behandlung von Hypoperfusion und Hypotension

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 [32].

The most recent international guideline (2016) commissioned by the Surviving Sepsis Campaign recommends an initial volume therapy with crystalloid fluids of minimum 30mL/kg to be given within the first 3 hours (strong recommendation, low quality of evidence) [2]. Further fluid administration should be guided by frequent reassessment of the haemodynamic status (best practise statement). The initial target mean arterial pressure (MAP) should be 65mm HG in patients in shock requiring vasopressors (strong recommendation, moderate quality of evidence).

2016 Leitlinien: Therapieoptionen mit unterschiedlicher Evidenzlage

The Surviving Sepsis Campaign Guidelines provides detailed recommendations for the optimal fluid therapy, vasopressor therapy, airway and ventilation management and further adjunctive therapeutic options, such as insulin therapy [2]. The guidelines do not recommend the use of blood purification therapies including ECAT, since the underlying evidence does not suffice to provide a recommendation [2].

The latest German sepsis guideline was issued by the AWMF and Deutsche Sepsis Gesellschaft in 2010 [34]. The level of evidence for the optimal management of sepsis is constantly updated. Many therapeutic options only have weak recommendations due to a low quality of evidence and trials to determine their effectiveness are currently ongoing [2, 35].

SIRS: Symptombehandlung und Stabilisierung der PatientInnen

Since SIRS is a syndrome rather than a disease, the treatment and management of a patient with SIRS depends on the inciting cause. Symptomatic management and stabilisation of the patient is essential and similar to the supportive management of sepsis [8].

Target population

A0007 – What is the target population in this assessment?

2 Patientenpopulationen für CytoSorb®

Two target populations arise from the main fields of application:

- Patients with sepsis and septic shock

  therapeutische Anwendung bei Pts, die mit Standardtherapie allein nicht stabilisiert werden können (vgl. ins. Risikopopulationen)

  The therapeutic use of CytoSorb® in patients with sepsis is indicated in patients that cannot be clinically stabilised with standard medical treatment, have clinical signs of hyperinflammation, develop organ dysfunction, or have systemic markers of infection.

  The target patient groups include postsurgical patients with on setting sepsis, acute kidney failure, or patients with therapy refractory septic shock. Furthermore, patients with impaired immune competence due to a chronic disease (chronic liver disease, dialysis patients), and elderly patients belong to the potential patient population.

- Development of SIRS during or following cardiac surgery with CPB

  intraoperative präventive Anwendung bei Pts, die sich einer Kardio-OP mit CPB unterziehen sowie Risiken (Alter, Gesundheitsstatus, Invasivität des Eingriffs) aufweisen

  The preventive use of CytoSorb® during cardiac surgery with CPB is proposed for patients with the following risk factors:

  - Age >75
  - Preoperative status with endocarditis, cardiac failure, leukocytosis or organ dysfunctions
  - High-risk procedures: Combination of procedures (valve repair and cardiac bypass graft), re-operation, aortic surgery with hypothermic arrest, left ventricular assist device (LVAD) implantation

Furthermore, its use is suggested for patients with intraoperative development of SIRS, prolongation of the anticipated CPB time, or complication where postoperative onset of SIRS is likely.

A0023 – How many people belong to the target population?

A0011 – How much is ECAT utilised?

Schätzungen für Österreich: 6.700 bis 9.500 Sepsis Pts p.a.

For Austria, the estimated number of patients with 'severe' sepsis ranges from 6,700 to 9,500 per year [30]. Another study estimated 54-116 sepsis cases per year per 100,000 inhabitants. These data stem from 2002 and 2004 [31], however, since the overall number of sepsis patients is increasing, it can be assumed that this number is still equally high or higher today.

Keine Zahlen für kardiale Eingriffe mit CPB aus Österreich

Data on the numbers of cardiac procedure requiring CPB to estimate the use of ECAT during cardio-pulmonary bypass surgery were not available for Austria. Several surgical procedures apply CPB, such as coronary artery bypass graft surgery, valve replacement, heart or lung transplantation, LVAD procedures for heart failure and operations on the aortic arch.

5 Clinical effectiveness

5.1 Outcomes

Within the scope of both applications of ECAT as preventive and therapeutic treatment, the following outcomes were defined as crucial to derive a recommendation:

wichtige klinische Endpunkte für Empfehlung:

- Improved survival
- Improved clinical outcomes: organ functions (MODS or SOFA score)
- Days in ICU
- Days of hospitalization

besseres Überleben
verbesserte Organfunktion
Tage in ICU
Tage im Spital

Since sepsis is a life-threatening disease, the ultimate aim of the treatment with ECAT is to improve mortality. Improved survival and improved organ function, measured with the SOFA score were consequently regarded as crucial for a recommendation of CytoSorb® as supportive treatment of sepsis. The SOFA score was endorsed by the 2016 sepsis-3 guideline as most sensitive tool to predict mortality and poor outcomes in patients with suspected sepsis. Furthermore, it was suggested to be used as entry criterion for clinical trials [1]. It is applied by many ongoing trials on sepsis and SIRS.

Sepsis:
SOFA Score als valider Prädikator für Mortalität

The preventive treatment with ECAT during cardiac surgery aims to reduce the number of sustained post-surgical SIRS. In this regard, while survival is equally important, it is not as relevant, since only 10% (generously estimated) of patients develop sustained SIRS during CPB. Consequently, the most crucial patient relevant outcomes were improved clinical outcomes, such as improved organ functions, and a decrease of days spent in the ICU and total days of hospitalization. This is in line with outcome measures recommended for clinical trials on extracorporeal blood treatment in SIRS and sepsis [36]

SIRS: verbesserte Organfunktion;
Tage in ICU;
Tage im Spital

Additionally, the following parameters were considered relevant to assess effectiveness of the therapy:

weitere relevante, aber nicht entscheidende Endpunkte: Surrogate

- Ventilator free days
- Decrease in dose of vasopressor drugs and catecholamines
- Reduction of cytokine levels in the blood

beatmungs-freie Tage

Reduktion der Katecholamnine

The claimed benefit of ECAT is the reduction of cytokine levels in the blood to restore a balanced immune response. Accordingly, in order to assess the efficacy of the technology to remove cytokines, the reduction in the cytokine concentration was also analysed. However, there is no clear evidence whether and how the general reduction of cytokines in the blood directly influences patient outcomes in sepsis and SIRS. Thus, while qualitatively described in the results part of this assessment, this outcome was not designated as *crucial* for the recommendation.

Reduktion des Zytokin-Levels

5.2 Included studies

nur Studien mit Vergleichsgruppe

To evaluate efficacy-related outcomes, we considered all published studies that included a comparison group.

1 RCT
1 retrospektive Fallserie

In total, two studies were included to analyse the clinical effectiveness of ECAT [37, 38], of which only one met the initial inclusion criteria. The studies comprised one randomised controlled trial published in 2016 (n=37, 19 receiving ECAT), and one retrospective case series from 2014 (n=40, 20 receiving ECAT).

beide Studien zur Indikation Prävention von SIRS bei Kardio-OP mit CPM

Both studies evaluated the preventive use of CytoSorb® during CPB surgery. Inclusion criteria for the RCT were elective cardiac surgery with an expected CPB duration of more than 120 minutes. The case series investigated the use of CytoSorb® in CPB surgery and hypothermic arrest with antegrad cerebral perfusion, specifically.

keine Studie zum therapeutischen Einsatz bei Sepsis

We could not identify data from any randomised or non-randomised controlled trial assessing the effectiveness of CytoSorb® in patients with sepsis or septic shock.

Patientencharakteristika nur in 1 Studie berichtet

Patient characteristics were missing for one of the two studies [38]. The mean age of patients in the RCT was 67 years. 29.7% of the patients in the intervention group were female, as compared to 22.2% in the control group. The follow-up of the RCT was 30 days, the case series only had a follow-up of four days post-surgery [37, 38].

Follow-up: 30 Tage

loss-to-follow-up

The loss to follow-up was only reported by Bernardi et al. (RCT), with a percentage of 30% loss to follow-up [37]. Both studies shared their primary outcome measure, a decrease the cytokine IL-6.

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 7-1.

5.3 Results

Mortality

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

Preventive use of CytoSorb® to reduce SIRS during elective CPB surgery

RCT: 30-Tage Mortalität
1 Todesfall in IG
keiner in KG

Bernardi et al. (RCT) assessed 30 day mortality as secondary outcome measure in 37 patients [37]. One out of 19 patients in the intervention group died on the 22nd postoperative day. All 18 patients in the control group survived the 30 days.

Born et al. did not report on improvements in mortality [38].

Therapeutic use of CytoSorb® in patients with sepsis or septic shock

keine vergleichende Studie/Evidenz zu ECAT bei Sepsis

None of the studies reported on sepsis mortality.

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 in the SOFA score.

keine Studie erhob/berichtete SOFA oder MODS

Neither SOFA score, nor MODS score, nor any other score measure to assess organ failure was reported by the two studies.

Regading the surrogate outcome of a change in the cytokine concentration in the blood, both studies assessed changes in the serum level of the cytokine IL-6. Born et al. reported a siginifact decrease in IL-6 levels until the forth post-operative day [38]. Conversely, this decrease was not found in Bernardi et al., who found no significant differences between both groups, measured until the fifth post-operative day [39].

Reduktion von Zytokin IL-6: widersprüchliche Ergebnisse

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

In order to answer this research question, lengths of ICU stay, days of hospitalization, mechanical ventilation and need of catecholamine medication were applied as indicators for disease progression.

Bernardi et al. (RCT) found no significant difference in the length of stay in intensive care units between the intervention group (2.3 days, +/- 2) and the control group (2.4 days, +/- 1.9) [37].

RCT: kein Unterschied bei Tage in ICU

Differences in the total length of hospitalisation follow up of the patients after hospital discharge and re-admission to hospital were not assessed by any of the studies.

Dauer der Hospitalisierung: nicht erhoben/berichtet

Bernardi et al. (RCT) reported no significant difference in the days of mechanical ventilation (p=0.19), and no difference in the need of catecholamines (p value not claculated) in patients with SIRS [39].

RCT: kein Unterschied bei Beatmung und Medikamentierung (Katecholamine)

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, nor 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

6 Safety

6.1 Outcomes

Interventions-bezogene Endpunkte:

Blutgerinnsel, Blutverlust durch Leck oder Trennung, Luftembolie

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

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 [19]. Air entering the bloodlines and the circuit can result in serious injury and even death, as this could cause air embolism.

Hypersensibilitäts-Reaktionen, Hypotension, Temperaturveränderung, Muskelkrämpfe, Übelkeit

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 [19].

Additional potential side effects are hypotension, change of the body temperature, muscle cramping, headache, nausea, vomiting, fever and pruritus.

wichtige klinische Endpunkte für Empfehlung: Peri- und postoperative AE

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

- Perioperative (serious) adverse events and complications
- Postoperative (serious) adverse events and complications

EC-Guidelines zu Definitionen von Nebenwirkungen und Komplikationen bei Medizinprodukten

In accordance with the European Commission guidelines for medical devices on serious adverse event reporting, the following definitions were applied[5]:

Adverse Event (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).

Differenzierung AE, SAE, SADE

Serious Adverse Event (SAE) is an adverse event that led i) to death, ii) to a serious deterioration in 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 life threatening illness or injury.

Serious Adverse Device Effect (SADE) 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.

[5] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

6.2 Included Studies

Studien mit > 10 Pts.

In order to assess safety-related outcomes, we accepted all published evidence with more than 10 patients.

keine Studien, die insb. Sicherheitsendpunkte im Fokus hatten

We could not identify any randomised controlled trial or non-randomised trial that specifically described safety outcomes, or reported adverse events as their primary or secondary outcomes.

3 Studien: 1 RCT + 2 retrospektive Fallserien

Three studies were included to analyse the safety of ECAT [31-33]. The studies comprised one randomised controlled trial published in 2016 (n=37, 19 receiving ECAT) and two retrospective case series from 2016 (n=16) and 2014 (n=40, 20 receiving ECAT) respectively.

2 Studien zur Indikation Prävention von SIRS bei Kardio-OP mit CPM, 1 Studie post-Kardio-OP mit CPM

One study, a retrospective case series including 16 patients, assessed the use of CytoSorb® as an additive therapeutic option in the treatment of post-cardiopulmonary bypass SIRS [40]. The two other studies assessed the preventive use of CytoSorb® during cardiopulmonary bypass surgery to reduce the occurrence of SIRS post-surgery.

Patientencharakteristika Ø Alter 67-70 28-30 Tage Follow-up

Bernardi et al. (RCT) and Born et al. (case-series) included patients undergoing cardiac surgery with CPB, as afore described [37, 38]. Conversely, Träger et al. (case-series) included patients post- CPB surgery that developed post-CPB SIRS over the course of the first postoperative 24-hours [40]. The mean age in the studies was around 70 years, 71 in Träger et al. and 67 in Bernardi et al. The latter two studies included similar follow-up, with 28 and 30 days following surgery. Exclusion criteria are only reported by Bernardi et al. and can be found in the data extraction tables in the Appendix.

keine Studie zum therapeutischen Einsatz bei Sepsis

We could not identify any study that reported data on the safety of CytoSorb® as therapeutic option in the treatment of sepsis or septic shock.

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 7-1.

6.3 Results

Patient safety

C0008 – How safe is ECAT in comparison to the comparator(s)?

keine Evidenz zu AE aus vergleichenden Studien

There is no direct comparator to ECAT.

keine Studie berichtete AE zu den insgesamt 55 Pts.

None of the studies reported adverse or serious adverse events for the use of CytoSorb® either during CPB surgery or post-operative [37, 38, 40]. In total, the technology was used in 55 patients. Furthermore, no adverse device effects were described.

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?

None of the studies reported results on how 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**

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Scheme [5] for each endpoint individually. Each study was rated by two independent researchers (KH, CW). In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [5].

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.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Stärke der Evidenz: sehr niedrig

Overall, the strength of evidence for the effectiveness and safety of ECAT is very low.

Table 7-1: Evidence profile: efficacy and safety of extracorporeal haemadsorption therapy

No of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
28-day mortality							
1/37	RCT	Int: 1/19 vs Co: 0/18	Serious limitations (-1)[1]	Only one study	direct	Imprecise data (-1)[2]	low
1/16	Case series	6/16	Serious limitations (-1)[3]	Only one study	direct	-	Very low
Improved organ function (SOFA score)							
1/37	RCT	NR	0	0	0	0	
Days in ICU							
1/37	RCT	Int: 2.3 (+/- 2) Co: 2.4 (+/-1) p= 0.87	Serious limitations (-1)[1]	Only one study	Direct	Imprecise data (-1)[2]	low
Days of hospitalisation							
No data							
Safety							
Treatment-related mortality in % (Int vs Co)*							
No data							
Serious AE							
None reported							

[1] *Unclear allocation concealment, outcome assessors not blinded, 30% loss to follow-up*

[2] *Low power of the study (few patients)*

[3] *No control group*

NR = not reported

* *unclear if 28-day mortality is treatment related*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

8 Discussion

„emerging technology", frühes Stadium der Erprobung

55 PatientInnen in Studien > 5 Pts.

ECAT is an emerging technology with very limited clinical evidence available to date. We could retrieve evidence from three studies, one technical feasibility RCT and two retrospective observational studies; however only one study met our initial inclusion criteria for both efficacy and safety. In total, 93 patients were enrolled in the studies, of which 55 patients were treated with CytoSorb®. We did not limit our search to a specific study design, language or period and included all studies that provided clinical data of more than five patients.

zusätzlich 17Einzelfallstudien mit heterogenen Indiktationen

In addition to the included studies, we could identify 17 case reports as presented in Appendix A, Table A–5. The case reports, all published between 2013 and 2016, present examples of first-time use of CytoSorb® in several different conditions reflecting the early stage of the technology in clinical use. Case reports represent a very low level of evidence and due to the lacking control and comparison groups, evidently, no conclusions for the clinical effectiveness of the technology can be drawn. Furthermore, there is large heterogeneity in between the assessed conditions and patient groups of the case reports on CytoSorb®. Additionally, we found several unpublished studies where only abstracts or conference posters were available. A recent technology briefing conducted by NICE, and presented in Appendix A Table A-6 provides an overview of this preliminary study material.

Aussagen zur Wirksamkeit aus 2 kontrollierten Studien zu CytoSorb® als präventive Anwendung gegen SIRS; widersprüchliche Ergebnisse zu IL-6 Reduktion; Patientenrelevanz unklar

In terms of clinical effectiveness, we could only identify two controlled studies to investigate the potential effects of CytoSorb® therapy during CPB surgery, one RCT and one retrospective case series [37, 38]. While both studies presented results on the same indication and intervention, the comparability of the patient groups could not be fully assessed, since only Bernardi et al. (RCT) reported patient characteristics. Both studies assessed a change in the level of cytokines as primary outcome measures, with IL-6 as principal investigated cytokine. Born et al. suggested a significant reduction of the level of IL-6 in the blood; Bernardi et al. reported no significant differences in IL-6 levels between the control and the intervention group. The relevance of this outcome regarding the clinical benefit for patients is unclear [41, 42].

patientenrelevante Endpunkte (SOFA) nicht gemessen; kein Unterschied bei Tagen in ICU

Patient-relevant outcomes, such as data on 30-day mortality, lengths of ICU stay and days of mechanical intervention, were provided by Bernardi et al., yet only as secondary outcome measure [37]. In this regard, no significant differences between the intervention group and the study group were found. Both studies failed to report changes in the SOFA or other scores assessing organ dysfunction in sepsis or SIRS [1].

keine einzige Studie (abseits von Einzelfallstudien) zur Therapie der Sepsis

There was no evidence on the effect of ECAT in patients with sepsis and septic shock. Moreover, no data on CytoSorb® use in patients with sepsis was available, other than from case reports. One single RCT comparing ECAT with standard of care was identified, however, it is only available in abstract form [43, 44], and thus, data and quality of the study could not be assessed. This preliminary study material has been described in the NICE briefing mentioned above and depicted in Table A-6 [20].

Sepsis and septic shock represents the principal and original indication for CytoSorb® use. The lacking data on effectiveness for this indication underlines the imperative need for adequate efficacy studies prior to its introduction to everyday clinical practice [41].

keine Daten zu AE oder SAE berichtet, wenngleich aufgrund der Erkrankungen schwierig zu erheben

As regards to safety of the intervention, none of the three included studies provided sufficient data on the existence or non-existence of adverse and serious adverse events [37, 38, 40]. Safety outcomes were only discussed as part of the discussion and conclusion. Out of the nature of sepsis, it is evident that potential adverse events are difficult to relate to the procedure, as not enough knowledge on the underlying pathophysiologic mechanisms of sepsis exists.

Patienten Register zur Kontrolle von SAEs und AEs eingerichtet

However, the more important it is for future studies to note potentially non-related adverse events. In this regard, a registry has been established to track and record potential adverse events occurring during or following the use of CytoSorb®. Although voluntary, this was regarded as first step towards increased transparency and improved data on safety outcomes [41].

Stärke der Evidenz: sehr niedrig

viele relevante Wirksamkeits-Endpunkte nicht oder unvollständig berichtet

Sicherheitsendpunkt: nicht berichtet

Overall, there is no evidence for the efficacy and safety of therapeutic use of ECAT in patients with sepsis, and very low evidence for its preventive use. The quality of evidence is very low in both indications. Although we could identify one randomised study, the risk of bias of this study was high, due to a small sample size, unclear allocation concealment, insufficient blinding, and a high rate of loss to follow-up (30%), without intention to treat analysis. The study sample of the RCT was not powered to draw conclusions on mortality, or other patient-relevant benefits. Only one of the two observational studies included a control group, however, failed to state patient characteristics. Within the assessed studies, patient relevant outcomes were either not reported [38], or incompletely reported [40], or reported as secondary outcome measure [37]. Furthermore, safety endpoints were not adequately described by any of the studies. The number of patients included in the studies was small, and stemmed entirely from single centre studies.

sehr kurze Follow-ups

All studies included a follow-up of maximum 30 days, Born et al. only reported outcomes up until the 5th postoperative day [38]. To date, to the knowledge of the authors, neither a study nor an ongoing trial exists assessing the long-term benefits of the intervention. Since the long-term outcomes of patients with sepsis are poor, with frequent re-admission and an increased mortality rate following hospital discharge, a follow-up period of at least six months would be highly recommendable [21].

Ergebnisse nicht übertragbar auf SIRS und Sepsis PatientInnen

Considering the small study population and the two different indications, as preventive treatment during CPB and as therapeutic treatment in patients with sepsis or SIRS, the results of the studies cannot be generalised to a larger population. Furthermore, the currently available evidence is focused on the management of post-CPB SIRS, rather than sepsis or SIRS in general. Further details on the applicability of the comprised study evidence can be found in Appendix A, Table A-7.

In RCT starb 1 Patient in Interventionsgruppe wegen Komplikationen: Ursache unbekannt

Notably, one patient of the RCT intervention group died on the 22nd postoperative day due to major surgical complications. It is not possible to associate this event directly to the intervention itself, nor has this individual event informative value on efficacy or safety. However, since the indication of CytoSorb® as preventive therapy is to improve post-CPB outcomes and is particularly indicated in cases of surgical complications, it remains to be noted that this single event could not be prevented using CytoSorb® therapy, while no comparable event occurred in the control group [37].

Several authors expressed their concerns that the ECAT itself could also worsen the outcomes of patients with sepsis or SIRS due to a removal of anti-inflammatory cytokines besides pro-inflammatory ones [41, 42, 45]. It was raised that since the timing of the intervention within the phases of sepsis might play a pivotal role, too early or too late cytokine removal could be potentially harmful [42].

ECAT kann klinische Ergebnisse auch verschlechtern, wenn anti-inflammatorische Zytokine entfernt werden

The pathophysiological effects of a general cytokine reduction in the mortality of sepsis are not completely understood. While there have been studies indicating an association between the level of certain cytokines and the mortality of sepsis, such as IL-6 and TNF- α, there is no clear understanding of the actual underlying intracellular pathways [8, 9]. Several theories on the function of cytokines within sepsis were proposed as cytokinetic and cytotoxic model [46]. Yet, until today, the specific role of cytokines in the pathophysiology of sepsis remains controversial and unresolved [8].

grundlegendes Verständnis der Rolle der Zytokine für Sepsis und SIRS noch gering

Considering the lacking understanding of the clinical effect of a cytokine reduction, it becomes evident that there is a need to reduce these knowledge gaps before introducing ECAT as standard procedure, both in sepsis as well as during CPB surgery. A reduction of cytokines could improve the haemodynamic stability in patients with sepsis; however, it could also contribute to a deterioration of the disease. Evidence on cytokine reduction as primary outcome measure cannot replace efficacy and clinical benefit assessments. Clinical benefits in patient-relevant outcomes, and in particular improvement in mortality rates need to be demonstrated in order to introduce ECAT to clinical practice.

Reduktion von Zytokinen: hämodynamische Stabilisierung bei Sepsis, aber ev. auch Verschlechterung

daher: patientenrelevante Endpunkte umso wichtiger

Further evaluation of ECATs long- term clinical efficacy and complication rates is required.

9 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 the assessed technology extracorporeal haemadsorption with CytoSorb® in patients with sepsis and SIRS is effective and safe. The results from ongoing trials and the publication of the results from completed RCTs will potentially influence the effect estimate considerably.

Evidenz unzureichend: derzeit nicht empfohlen

In total, we identified seven relevant ongoing trials and one patient registry. Two of the ongoing trials assess the use of CytoSorb® in patients with sepsis, while the others focus on its preventive use during CPB surgery. Five of the studies use parallel assignments (including a control group); yet, only one of the studies has a double blind study design. Details on ongoing studies can be found in Appendix A Table A-8.

7 laufende Kontrollierte Studien, eine Registerstudie

nur zwei Studien zu Sepsis

A re-evaluation of the technology is recommended in 2019 to assess inclusion for the benefits catalogue 2020. A minimum level of evidence from at least one larger randomized controlled trial (n > 100 patients) and several prospective case-series (n > 20) for each indication should be available at the time of re-evaluation.

Re-Evaluierung 2019

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: ECAT during cardiopulmonary bypass surgery: Results from randomized controlled trials

Author, year	Bernardi, 2016 [37, 39]
Country	Austria
Sponsor	Medical University of Vienna; materials partially funded by Cytosorbents Europe GmbH
Intervention/Product	Haemoadsorption with CytoSorb® during CPB
Comparator	No intervention
Study design	Randomised, single-blinded, controlled, single centre, pilot, feasibility study
Number of pts	46 randomized, 9 drop out before intervention, 37 included (Int: 19 vs Co: 18), 2 loss to follow up (35 included for primary outcome analysis)
Inclusion criteria	elective cardiac surgical intervention with an expected CBP duration >120 minutes
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 patients (yrs)	Mean age: 67 yrs (30-81); Mean age Int: 64(30-81) vs mean age Co:69 (51-81); p=0,1737
Gender (% female)	Total: 11 (29.7%), Int: 7 (36.8%) vs Co:4 (22.2%)
Primary Outcome Measures	Differences in the evolution of cytokines IL-1β, IL-6, IL-18, TNF-α, IL-10 during cardiopulmonary bypass
Secondary Outcome Measures	✿ Serum CRP changes ✿ ex vivo LPS induced TNF-α production ✿ Drug treatment Vasopressor dose, Insulin dose ✿ 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
Follow-up (months)	30 days
Loss to follow-up, n (%)	14 (30%), Int:8 vs. Co:6
Mean CPB time/ treatment time	Int: 191 min. (range 112-288min), Co 170 min (83-274)

Author, year	Bernardi, 2016 [37, 39]
Outcomes	
Efficacy	
Overall survival, n (%)	36/37 (97,2%); Int: 18/19; Co: 18/18
MODS score	NR
SOFA score	NR.
Days in ICU Days in ICU	Int 2.3 (+/-2) vs. Co 2.4 (+/-1.9), p=0.87
Days of hospitalisation	NR
Days of ventilator therapy	Int 0.7 (+/- 1.6) vs Co 0.2 (+/- 0.4); p=0.19
Reduction of catecholamine support; Reduction of vasopressor therapy	No difference between Int and Co group
Reduction in IL 6 Levels	IL-6 pg/ml: after CBP:Median Int: 62.9 vs Co: 63.6, p= 0.326 2 h: Int: 120.8 vs Co: 118.7, p=0.6781 24h: Int: 111.6 vs. Co: 120.9, p= 0.9837 48h: Int: 89.0 vs Co 120.9, p= 0.3809
Safety	
Overall complications, n (%)	None reported[1]
Major AE, n (%)	Int 0/19, co: 0/18
Minor AE, n (%)	Int 0/19, co: 0/18

[1] *One patient of the intervention group died on the 22nd postoperative day due to multiple surgical complications*

AE = Adverse effect, CPB = Cardiopulmonary bypass, Co = Control- group, CRP = C-reactive protein, ICU = Intensive care Unit, Int = Intervention- group, NR = not reported, PO = primary outcomes, yrs = years

Table A-2: ECAT during and after CPB surgery: Results from observational studies

Author, year	Träger, 2016 [40]	Born, 2014 [38]
Country	Germany	Germany
Sponsor	University hospital Ulm	NR
Intervention/Product	Therapeutic haemoadsorption therapy with CytoSorb® post-CPB	Preventive haemadsorption therapy with CytoSorb® during CPB
Comparator	none	Conventional cardio-pulmonary bypass
Study design	Single-center retrospective case series Datacollection: 05/2013- 10/2014	Single-center retrospective case series Datacollection: Int:02/2013- 11/2013 Co: 01/2012- 12/2012
Number of pts	16	40 (20 Int; 20 Co)
Inclusion criteria	Pts post-CPB SIRS within 24h after surgery AKIN criteria met, CRRT treatment necessary	Pts undergoing complex heart surgery with hypothermic arrest and antegrade cerebral perfusion
Exclusion criteria	NR	NR
Age of patients (yrs)	Mean: 71 (range 53- 84)	NR
Gender (% female)	4 (25%)	NR

Author, year	Träger, 2016 [40]	Born, 2014 [38]
Outcome Measures	✿ IL-6 ✿ IL-8 ✿ Lactate ✿ Base excess ✿ Cardiac index ✿ MAP ✿ Epinephrine dose (catecholamine dose) ✿ Norepinephrine dose (catecholamine dose) ✿ Days in ICU ✿ 28-day survival	✿ IL-6 ✿ CRP ✿ Procalcitonin ✿ Leukocytes ✿ Fibrinogen
Follow-up (days)	28 days	4 days post surgery
Loss to follow-up, n (%)	n.a	n.a.
Mean treatment time with CytoSorb®	34 h (range 5-50h)[1]	NR
No. of CytoSorb® treatments	1-3/pts	1/pts
Outcomes		
Efficacy		
Overall survival, n (%)	10/16 (62%)	NR
MODS score	NR	NR
SOFA score	NR[2]	NR
Days in ICU Days in ICU	NR	NR
Days of hospitalisation	NR	NR
Days of ventilator therapy	NR	NR
Reduction of catecholamine support; Reduction of vasopressor therapy	Not reported for all patients (only individual data entries)	NR
Reduction in IL 6 Levels	Not reported for all patients (only individual data entries)	Int vs Co Day 1: 200 ng/l vs 300 ng/l Day 2: 110ng/l vs 320 ng/l Day 3: 90 ng/l vs 400 ng/l Day4: 80ng/l vs 420 ng/l
Outcomes		
Safety		
Overall complications, n (%)	NR	NR
Major AE, n (%)	None reported	NR
Minor AE, n (%)	None reported	NR

[1] *Mean treatment time for the first treatment with cytosorb*

[2] *SOFA score measured but not reported*

AE = Adverse Event, yrs = years, CRRT = Continuous Renal Replacement Therapy ICU = Intensive Care Unit, Pts = Patients, MAP = Mean Arterial Pressure, NR = not reported, n.a. = not applicable, No = number, SIRS = Systemic Inflammatory Response Syndrome,

Risk of bias tables

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 Guidelines of EUnetHTA [47, 48].

Table A-3: Risk of bias – study level (randomised studies), Cochrane Risk of bias tool

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 [37]	Yes	Unclear	Yes	No	No	No[1]	high

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

Table A-4: Risk of bias – study level (case series), IHE Risk of Bias checklist

Study reference/ID	Träger, 2016 [40]	Born, 2014 [38]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	No
2. Are the characteristics of the participants included in the study described?	Yes	No
3. Were the cases collected in more than one centre?	No	Yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	No
5. Were participants recruited consecutively?	Yes	No[1]
6. Did participants enter the study at similar point in the disease?	Yes	Yes
7. Was the intervention clearly described in the study?	Yes	No
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	No
11. Were outcomes measured before and after intervention?	No	No
12. Were the statistical tests used to assess the relevant outcomes appropriate?	No	No
13. Was the length of follow-up reported?	Yes	No
14. Was the loss to follow-up reported?	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	No
16. Are adverse events reported?	Yes	No
17. Are the conclusions of the study supported by results?	Yes	No
18. Are both competing interest and source of support for the study reported?	Yes	No
Overall Risk of bias	Moderate	Very high

[1] *Recruitment was not reported*

Table A–5: List of case reports of the application of haemadsorption therapy with CytoSorb®

Title	Author, Year
Use of a novel haemoadsorption device for cytokine removal as adjuvant therapy in a patient with septic shock with multi-organ dysfunction: A case study	Basu, 2014 [49]
First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: a case report	Bruenger, 2015 [50]
First description of single-pass albumin dialysis combined with cytokine adsorption in fulminant liver failure and hemophagocytic syndrome resulting from generalized herpes simplex virus 1 infection	Frimmel, 2014 [51]
Hemoadsorption using CytoSorb® beads (Cytosorbents) in a cirrhotic patient with septic multiorgan failure	Gruber, 2013 [52]
Septic shock secondary to beta-hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy	Hetz, 2014 [53]
CytoSorb, a novel therapeutic approach for patients with septic shock: a case report	Hinz, 2015 [54]
The Use of a Cytokine Adsorber (CytoSorb) in a Patient with Septic Shock and Multi-Organ Dysfunction (MODS) after a Severe Burn Injury	Houschyar, 2016 [55]
Combination of ECMO and cytokine adsorption therapy for severe sepsis with cardiogenic shock and ARDS due to Panton-Valentine leukocidin-positive Staphylococcus aureus pneumonia and H1N1	Lees, 2016 [56]
Improvement of hemodynamic and inflammatory parameters by combined hemoadsorption and hemodiafiltration in septic shock: a case report	Mitzner, 2013 [57]
Early report: The use of cytosorbTM haemabsorption column as an adjunct in managing severe sepsis: Initial experiences, review and recommendations	Morris, 2015 [58]
Hemoadsorption in Infection-Associated Rhabdomyolysis	Suefke, 2016 [59]
First use of a hemoadsorption device (CytoSorb®) during continous venovenous hemofiltration (CVVH) in a patient undergoing retransplantation with ABO incompatible graft for acute graft dysfunction	Tomescu, 2014 [60]
First report of cytokine removal using CytoSorb® in severe noninfectious inflammatory syndrome after liver transplantation	Tomescu, 2016 [61]
Cytokine Reduction in the Setting of an ARDS-Associated Inflammatory Response with Multiple Organ Failure	Trager, 2016 [62]
First case of toxic shock treated with haemoadsorption by CytoSorb® in the Netherlands	van der Linde, 2016 [63]
CytoSorb® in a patient with Legionella pneumonia-associated rhabdomyolysis: a case report	Wiegele, 2015 [64]
Can cytokine adsorber treatment affect antibiotic concentrations? A case report	Zoller, 2015 [65]

Table A-6: Medtech innovation brieifing MIB87, NICE, Summary of evidence (2016) [20]

Study size,design and location	Intervention and comparator	Outcomes	Strengths and limitations
Schädler et al (2013a); Schädleret al.(2013b) 43 patients, Randomised, controlled trial Multicentre study Germany	Haemoperfusion treatment for cytokine removal (CytoSorb) and standard care. Standard care (control).	There were no serious devicerelated adverse events. There were no differences in 28-day or 60-day Mortality between CytoSorb® and the control. CytoSorb® significantly reduced blood concentrations of cytokines.	Unable to assess the trial quality because it has only been published as an abstract in aposter.There was no between-group comparison ofreduction in cytokines. Unclear duration of follow-up. Minimal details of the patients. Funded by the manufacturer. The authors noted the limitation that further research is needed to assess the device on clinical outcomes.
Kogelmann et al. (2015) 8 patients Case series Singlecentre study Germany	CytoSorb® as adjunctive therapy.	Overall survival was 62.5%. Slight decrease in SOFA score and SAPS II.	Small case series only reported as an abstract, so unable to assess study quality.Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported. May include patients from Kogelmann et al (2016) study.
Kogelmann et al. (2016) 14 patients Case series Singlecentre study Germany	CytoSorb® as adjunctive therapy.	Overall survival was 35.7%.Survival increased if treatment started within 48 hours.	Small case series only reported as an abstract, so unable to assess study quality. Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported. May include patients from Kogelmann et al. (2015) study.
Laddomada et al. (2016) 8 patients Case series Singlecentre study Italy	CytoSorb® as adjunctivetherapy in combination with continuous renal replacement therapy.	Six of 8 patients survived. In survivors, procalcitonin levels decreased and renal function improved.	Small case series only reported as an abstract, so unable to assess study quality. Unclear if data collection was prospective or retrospective. No comparator group. Minimal details of the patients. Unclearduration of follow-up. Limited outcomes reported. Funding source not reported.
Sathe et al. (2015) 19 patients Case series Single centre study India	CytoSorb® as an adjuvant therapy with standard care.	Four of 19 patients with predicted high mortality survived. Three of the 4 survivors had CytoSorb® in less than 24 hours of admission. Almost half of those who died were given CytoSorb® more than 24 hours after admission.	Small retrospective case series only reported as an abstract, so unable to assess study quality. No comparator group. Minimal details of the patients. Unclear duration of follow-up. Limited outcomes reported. Funding source not reported.

SOFA = Sepsis-related Organ Failure Assessment; SAPS = Simplified Acute Physiology Score.

Applicability table

Table A-7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Prevention of SIRS and sepsis The main body of evidence assessed haemadsorption treatment as a preventive measure for patients undergoing elective heart surgery with CPB. This presents only a small fraction of patients that are at risk of developing SIRS and sepsis. The mean age of these patients is above 70, a patient population at higher risk of developing SIRS and sepsis. Minimal invasive heart surgery and off-pump procedures are becoming more frequently used, which might also negatively affect the potential of haemadsorption therapy during open heart surgery. Treatment of SIRS sepsis and septic shock. Only one observational study (n=16) covered this patient population, and only assssed patients with SIRS. The study included patients following complex heart surgery with SIRS symptomatic and the need of continuous renal replacement therapy. Since sepsis and septic shock stem from a wide variety of causes, the presented population does not reflect the spectrum of the disease, and differences in treatment courses and outcomes.
Intervention	The studies included CytoSorb® as a preventive intervention during CPB heart surgery or following CPB. Only very limited information is available on extracorporeal haemadsorption treatment as a standalone therapy for the treatment of sepsis. While all studies use the same technology (CytoSorb®), the interventions and procedures are highly heterogeneous between studies and cannot be directly compared to each other.
Comparators	Only two of the studies included a comparison group, of which one comparison group was historic.The comparator was standard of care for the treatment of sepsis and conventional surgery, as there is no causal sepsis therapy available to date. Efficacy could not be sufficiently assessed due to the limited number of patients included in the studies, and the lack of comparability between studies.
Outcomes	The most frequently reported outcome were changes in IL-6 levels, and inflammatory markers in the blood (CRP, Lactate, Procalcitonin). Critical patient related outcomes such as mortality, organ function, days in the ICU and days of hospitalisation were presented as secondary outcomes, and not statistically tested. Long- term patient benefit was not assessed in any study. Potential harms of the technology were only addressed in the discussion and not in the results part of the studies.
Setting	All of the studies were single-center studies based in Europe, two of them were based in Germany. The geographical focus of the published literature and of many ongoing trials is Germany and German-speaking countries, such as Austria. The procedures took place in hospital ICUs and in operating rooms, which reflects the clinical setting where the technology is deployed. Clinical expertise with extracorporeal circuits, such as haemodialysis devices, is needed.

List of ongoing randomised controlled trials

Table A-8: List of ongoing controlled trials of haemadsorption therapy

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date, current status	Sponsor
NCT00559130 Efficacy Study of CytoSorb® Hemoperfusion Device on IL-6 Removal in ARDS/ALI Patients With Sepsis	ICU patients with septic shock of medical origin. Acute Respiratory Distress Syndrome, Acute Lung Injury, Sepsis	Daily haemoperfusion for 6 hours with CytoSorb® device	Routine ICU care.	Relative IL-6 levels as a percent (%) of baseline Ventilator Free Days, Reduction cytokines TNF-Î±, IL-1b, IL-10, CRP, 28-day all cause mortality, Oxygen Index (OI), P/F ratios, MODS scores	June 2011, Completed, no results available	MedaSorb Technologies, Inc
NCT02566525 CytoSorb® Reduction of Free Hemoglobin During Cardiac Surgery (REFRESH)	Elective, cardiac surgery requiring cardio-pulmonary bypass with anticipated duration of >180 minutes	Standard of care plus treatment with CytSorb device installed on the CPB machine	Standard of care, Conventional cardio-pulmonary bypass	Change in plasma free haemoglobin, Assessment of serious device related adverse events	August 2016, recruiting	CytoSorbents, Inc
NCT02588794 Cytokine Adsorption in Sepsis and Acute Kidney Injury (CASAKI)	Renal Insufficiency or Renal Failure &or End-stage Renal Disease; Patients > 18, severe sepsis or septic shock according to ESICM guidelines not older than 24 h	Standart CVVHD plus CytoSorb® 300 ml device	Standart CVVHD	RIFLE stadium L or E after acute kidney injury related to sepsis	December 2017, recruiting	Technische Universität München
NCT02775123 Cytokine Clearance With Cytoabsorbant Device During Cardiac Bypass (CCCC)	Myocardial Ischemia Heart Valve Diseases, Patients planned for elective cardiac surgery requiring CPB	Standard of care plus treatment with CytSorb device installed on the CPB machine	Standard of care, Conventional cardiopulmonary bypass	Change in Cytokine levels	December 2017, recruiting	Centre Hospitalier Universitaire Vaudois
NCT02265419 Use of Extracorporeal Treatment With the Cytosorb-Adsorber for the Reduction of SIRS in Heart Surgery Patients (CASHSP)	Multiple Organ Failure	Extracorporeal treatment with the CytoSorb® adsorber for 24 hours after heart surgical operation.	Historic control group	Significant difference in the mean-SOFA (Sequential Organ Failure Assessment)-score between the Cytosorb-group and the historic control group after 7 days	March 2017, recruiting	University of Rostock

NCT02297334 Removal of Cytokines During Extracorporeal Circulation in Cardiac Surgery	Coronary Artery Disease, Heart Valve Diseases	CytoSorb device, installed into the heart lung machine in a parallel stream to the main circulation.	No Intervention: Patients randomised to this arm are treated without the CytoSorb device during bypass	Change of levels of cytokines during procedure compared to baseline parameters to be measured are: interleukin (IL) 1, interleukin 6, interleukin 8, interleukin 10, tumor necrosis factor-alpha	October 2015 Ongoing, not recruiting	Universitätsklinikum Hamburg-Eppendorf
DRKS00007928 Removal of cytokines during cardiac surgery, RECCAS	Elective, cardiac surgery requiring cardiopulmonary bypass with anticipated duration of >90 minutes	Standard of care plus treatment with CytSorb device installed on the CPB machine	Standard of care, Conventional cardio-pulmonary bypass	Reduction of IL-6 in patient serum	26.01.2015*	Universitätsklinikum Köln
NCT02312024 International Registry on the Use of the CytoSorb®-Adsorber in ICU Patients	Sepsis; Need of Cardiac Surgery	Device: Use of CytoSorb® adsorber	Observational study design	Difference between mortality predicted by scoring systems (APACHE II/SAPS II, EuroSCORE II) and actual mortality within 30 days after intervention	December 2020 Recruiting	Jena University Hospital University Hospital Goettingen

* *enrolment date of the first patient*

Literature search strategies

Search strategy for Medline via OVID

Database: Ovid MEDLINE(R) Epub Ahead of Print <December 22, 2016>, Ovid MEDLINE(R)Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 22, 2016>, Ovid MEDLINE(R) Daily Update <December 07, 2016>	
Search Strategy:	
1	exp Sepsis/(116433)
2	Severe Sepsis*.mp. (7987)
3	exp Shock, Septic/(21930)
4	Septic Shock*.mp. (19195)
5	Abdominal septic*.mp. (129)
6	Septic Arthrit*.mp. (5176)
7	exp Systemic Inflammatory Response Syndrome/(120203)
8	SIRS.ti,ab. (4786)
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (136554)
10	exp Cytokines/(696951)
11	exp Adsorption/(56264)
12	10 and 11 (598)
13	(Cytokine* adj5 (Adsorption* or Adsorb*)).mp. (161)
14	exp Hemadsorption/(1016)
15	H?em?adsor*.mp. (1843)
16	Extra?corporeal blood purif*.mp. (157)
17	(Cytokine* adj5 filt*).mp. (122)
18	Cyto?Sorb*.mp. (25)
19	(Cytokine* adj5 Remov*).mp. (586)
20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3252)
21	9 and 20 (249)
22	remove duplicates from 21 (227)
Search date: 23th December 2016	

Search strategy for Embase

No.	Query Results	Results	Date
#30	'sepsis'/exp OR 'severe sepsis*':ti,ab OR 'septic shock'/exp OR 'septic shock*':ti,ab OR 'abdominal septic':ti,ab OR 'septic arthrit*':ti,ab OR 'systemic inflammatory response syndrome'/exp ORsirs:ti,ab AND ('cytokine'/exp AND 'adsorption'/exp OR (cytokine* NEAR/5 (adsorption* OR adsorb*)):ab,ti OR 'hemadsorption'/exp OR hemadsor*:ti,ab OR hemaadsor*:ti,ab OR hemoadsor*:ti,ab OR 'hemo adsor*':ti,ab OR 'haemoadsor*':ti,ab OR 'haemadsor*':ti,ab OR 'haemo-adsor*':ti,ab OR 'extracorporeal blood purif*':ti,ab OR 'extra-corporeal blood purif*':ti,ab OR (cytokine* NEAR/5 filt*):ti,ab OR cytosorb:tn,dn OR 'cyto sorb*' OR cytosorb* OR (cytokine* NEAR/5 remov*):ti,ab)	400	23 Dec 2016
#29.	'cytokine'/exp AND 'adsorption'/exp OR (cytokine*NEAR/5 (adsorption* OR adsorb*)):ab,ti OR'hemadsorption'/exp OR hemadsor*:ti,ab OR hemaadsor*:ti,ab OR hemoadsor*:ti,ab OR 'hemo adsor*':ti,ab OR 'haemoadsor*':ti,ab OR 'haemadsor*':ti,ab OR 'haemo-adsor*':ti,ab OR'extracorporeal blood purif*':ti,ab OR 'extra-corporeal blood purif*':ti,ab OR (cytokine* NEAR/5 filt*):ti,ab OR cytosorb:tn,dn OR 'cyto sorb*' OR cytosorb* OR (cytokine* NEAR/5 remov*):ti,ab	3,493	23 Dec 2016
#28.	(cytokine* NEAR/5 remov*):ti,ab	669	23 Dec 2016
#27.	cytosorb*	66	23 Dec 2016
#26.	'cyto sorb*'	3	23 Dec 2016
#25	cytosorb:tn,dn	26	23 Dec 2016
#24.	(cytokine* NEAR/5 filt*):ti,ab	133	23 Dec 2016
#23.	'extra-corporeal blood purif*':ti,ab	6	23 Dec 2016
#22.	'extracorporeal blood purif*':ti,ab	196	23 Dec 2016
#21.	'haemo-adsor*':ti,ab	1	23 Dec 2016
#20.	'haemadsor*':ti,ab	201	23 Dec 2016
#19.	haemoadsor*':ti,ab	12	23 Dec 2016
#18.	'hemo adsor*':ti,ab	3	23 Dec 2016
#17.	hemoadsor*:ti,ab	106	23 Dec 2016
#16.	hemaadsor*:ti,ab	0	23 Dec 2016
#15.	hemadsor*:ti,ab	720	23 Dec 2016
#14.	'hemadsorption'/exp	913	23 Dec 2016
#13.	(cytokine* NEAR/5 (adsorption* OR adsorb*)):ab,ti	191	23 Dec 2016
#12.	'cytokine'/exp AND 'adsorption'/exp	1,019	23 Dec 2016
#11.	'adsorption'/exp	74,050	23 Dec 2016
#10.	'cranial nerve'/exp	89,666	23 Dec 2016
#9.	'sepsis'/exp OR 'severe sepsis*':ti,ab OR 'septic shock'/exp OR 'septic shock*':ti,ab OR 'abdominal septic':ti,ab OR 'septic arthrit*':ti,ab OR 'systemic inflammatory response syndrome'/exp OR sirs:ti,ab	225,193	23 Dec 2016
#8.	sirs:ti,ab	6,826	23 Dec 2016
#7.	systemic inflammatory response syndrome'/exp	213,783	23 Dec 2016
#6.	'septic arthrit*':ti,ab	5,723	23 Dec 2016
#5.	'abdominal septic':ti,ab	151	23 Dec 2016
#4.	'septic shock*':ti,ab	25,893	23 Dec 2016
#3.	'septic shock'/exp	40,246	23 Dec 2016
#2.	'severe sepsis*':ti,ab	11,603	23 Dec 2016
#1.	'sepsis'/exp	208,559	23 Dec 2016

Search strategy for CRD

#### Cytokine Adsorption in Septic Patients	
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	(SIRS)
20	#14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#13 AND #20
31 Hits	
Search date: 23th December 2016	

Search strategy for Cochrane

Search Name: Cytokine Adsorption in Septic Patients	
Search Date: 23/12/2016 22:13:21.858	
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	SIRS:ti,ab,kw (Word variations have been searched)
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [Cytokines] explode all trees
#11	MeSH descriptor: [Adsorption] explode all trees
#12	#10 and #11
#13	Cytokine* near (Adsorption* or Adsorb*):ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Hemadsorption] explode all trees
#15	Haemadsor* (Word variations have been searched)

#16	Haemadsor* (Word variations have been searched)
#17	Hemo-adsor* (Word variations have been searched)
#18	Haemo-adsor* (Word variations have been searched)
#19	Hemadsor* (Word variations have been searched)
#20	blood near purif*:ti,ab,kw (Word variations have been searched)
#21	Cytokine* near filt*:ti,ab,kw (Word variations have been searched)
#22	CytoSorb* (Word variations have been searched)
#23	Cyto-Sorb* (Word variations have been searched)
#24	Cytokine* near Remov*:ti,ab,kw (Word variations have been searched)
#25	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#9 and #25
Total: 41 Hits	

Search strategy for PubMed

PubMed Suchstring:
(((Sepsis OR Severe Sepsis[tiab] OR Septic Shock OR Abdominal sepsis[tiab] OR Septic Arthritis[tiab] OR Systemic Inflammatory Response Syndrome OR SIRS[tiab]))) AND ((Cytokine Adsorption[tiab] OR Hemadsorption OR Extracorporeal blood purification[tiab] OR Cytokine Filter[tiab] OR Cytokine Filtration[tiab] OR Cytokine Removal[tiab] OR CytoSorb[tiab] OR cytosorbent[tiab]))
261 Hits
Search date: 23st December 2016

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Health Technology Assessment