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**CARRERA PROFESIONAL DE MEDICINA HUMANA**

**“Hemoadsorción de citoquinas con Cytosorb en sepsis. Una  
revisión sistemática y metanálisis”**

Tesis para optar el grado académico de:

**MAESTRO EN EPIDEMIOLOGÍA CLÍNICA Y  
BIOESTADÍSTICA**

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### ACTA DE SUSTENTACIÓN

Lima, 04 de agosto de 2023.

Los integrantes del Jurado de tesis:

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Miembro: <b>Magister Fernando Miguel Runzer Colmenares</b>
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Se reúnen para evaluar la tesis titulada: **“Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metanálisis”**

Presentada por **Jiovany Jhan Carlos Saldaña Gastulo**.

Para optar por el Grado de **Maestro en Epidemiología Clínica y Bioestadística**.

Con la asesoría de: **Dra. Leda Yamilée Hurtado Roca**.

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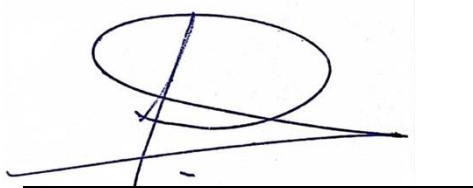
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Yo: Jiovany Jhan Carlos Saldaña Gastulo, egresado de la Maestría en Epidemiología Clínica y Bioestadística de la Universidad Científica del Sur, en conjunto con la asesora de tesis Leda Yamilée Hurtado Roca, declaramos que este informe final de tesis titulado: “Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metanálisis”, sustentado para obtener el grado de Maestro en Epidemiología Clínica y Bioestadística es original.

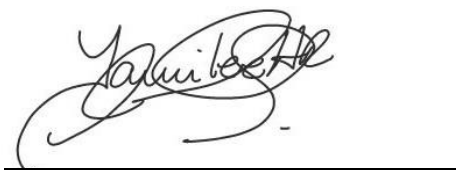
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## INFORME DE REVISIÓN DE ORIGINALIDAD

**Título del documento evaluado.** Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metanálisis

**Autores.** Jiovany Jhan Carlos Saldaña Gastulo.

**Mecanismo de revisión de originalidad.** Evaluación con Turnitin (ID 2149198989).

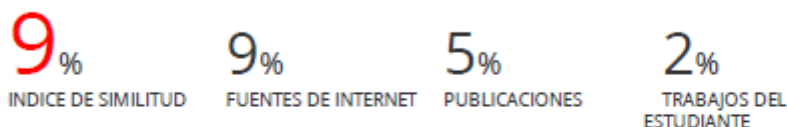
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### Hemoadsorción de citoquinas

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**Dedicatoria.**

A mi familia, en especial a mis padres, quienes han sido mi mayor inspiración y mi apoyo incondicional en cada etapa de mi vida. Su amor y dedicación han sido fundamentales para alcanzar mis metas y este logro no habría sido posible sin su constante aliento.

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## “Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metanálisis”

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### RESUMEN

**Antecedentes y objetivos:** Las terapias de purificación de la sangre se han utilizado en diferentes escenarios inflamatorios agudos; sin embargo, su uso es controvertido. Realizamos una revisión sistemática y un metanálisis para analizar el uso del efecto Cytosorb en la mortalidad, los niveles de interleucinas, el uso de vasopresores y los eventos adversos en pacientes con sepsis.

**Métodos:** Se realizaron búsquedas en MEDLINE, Embase y Cochrane Library de ensayos controlados aleatorios y estudios de cohortes que informaron el uso de Cytosorb entre pacientes sépticos. El resultado primario fue la mortalidad, y los resultados secundarios incluyeron el uso de vasopresores, los niveles de marcadores inflamatorios, la mortalidad prevista frente a la observada, la duración de la estancia en la UCI y los eventos adversos.

**Resultados:** Incluimos 6 estudios que reclutaron a 413 pacientes, la evaluación del riesgo de sesgo indicó variaciones en la calidad del estudio de alta a moderada. La mortalidad global fue del 45 % y no se encontró ningún efecto significativo sobre la mortalidad a los 28-30 días RR 0,98 [0,12-8,25] para el ECA y RR 0,74 [0,49-1,13] para los estudios de cohortes. No realizamos metanálisis para otros resultados debido al pequeño número de estudios encontrados o la falta de datos.

**Conclusiones:** Nuestro estudio encontró evidencia de certeza muy baja que no muestra ningún beneficio del uso de Cytosorb en la mortalidad a los 28-30 días. Sobre la base de la evidencia existente, no se pueden sacar conclusiones definitivas sobre el impacto de Cytosorb en la mortalidad de pacientes con sepsis o shock séptico. Por lo tanto, en este momento, no podemos recomendar el uso de Cytosorb en pacientes sépticos o con shock séptico fuera de los ensayos clínicos. Se necesitan más ensayos aleatorios de alta calidad con un brazo de intervención común para evaluar la influencia de Cytosorb en esta población.

Registro de protocolo: (CRD 42021262219).

Palabras clave: Hemoperfusión, Mortalidad, Sepsis, Cytosorb, Cytosorbentes.

## “Cytokine hemoadsorption with CytoSorb® in patients with sepsis: a systematic review and meta-analysis”

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### ABSTRACT

**Objective:** To analyze the effect of CytoSorb® on mortality, interleukin levels, vasopressor use and adverse events in patients with sepsis.

**Methods:** We searched MEDLINE®, Embase and the Cochrane Library for randomized controlled trials and cohort studies that reported the use of CytoSorb® among septic patients. The primary outcome was mortality, and secondary outcomes included the use of vasopressors, levels of inflammatory markers, predicted versus observed mortality, length of stay in the intensive care unit, and adverse events.

**Results:** We included 6 studies enrolling 413 patients, and assessment for risk of bias indicated variations in study quality from high to moderate. The overall mortality rate was 45%, and no significant effect on mortality was found at 28 - 30 days (RR 0.98 [0.12 - 8.25] for the randomized clinical trial and RR0.74 [0.49 - 1.13] for cohort studies). We did not perform a metanalysis for other outcomes due to the small number of studies found or the lack of data.

**Conclusion:** Our study found very low certainty evidence, due to imprecision, risk of bias, and heterogeneity, thereby showing no benefit of CytoSorb® use in terms of mortality at 28 - 30 days. We cannot recommend the use of CytoSorb® in septic or septic shock patients outside clinical trials. Further high-quality randomized trials with a common intervention arm are needed to evaluate the influence of CytoSorb® in this population.

PROSPERO register: CRD42021262219

Keywords: Cytokine; Hemoperfusion; Mortality; Sepsis; Septic shock

## VERSIÓN APROBADA PARA PUBLICAR.

### INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1) and its most severe state, septic shock, represents a highly lethal condition that causes substantial morbidity and mortality among critically ill patients (2). The pathophysiology of sepsis is very complex, involving many factors, such as proinflammatory and anti-inflammatory cytokines, pathogen-associated molecular patterns (PAMPs), bacterial exotoxins and endotoxins, mycotoxins, damage-associated molecular patterns (DAMPs) released by injured cells and host-specific factors such as activated complement and procalcitonin (3). Inflammation generated, can lead to severe immune system dysfunction ranging from destructive maladaptive systemic inflammatory response syndrome (SIRS) to advanced immunosuppression, which could lead to multisystem organ dysfunction and death (3,4).

Despite early treatment and multiple efforts to reduce mortality in sepsis and septic shock, such as the surviving sepsis campaign, which provides treatment guidelines (5), mortality is still high, around 20-40 % for severe sepsis and 40-60% in septic shock (1,6,7), without significant variations in this figure in recent years; that is why adjuvant therapies have been described, such as blood purification techniques, including extracorporeal removal of cytokines by Hemoadsorption(2,8–10).

There are currently multiple blood purification techniques, with different results, at the level of cytokines removal, decrease in vasopressors and even decrease in mortality, these include high-volume dialysis, high-cut membranes, adsorption by filtration coupled plasma and special adsorption filters (such as Oxiris, Cytosorb, HA 330 and Polymyxin B filters)(8,11). Blood purification therapies have been used in different acute inflammatory scenarios such as sepsis, cardiac surgery, and autoimmune diseases, however, their use is controversial, and despite a theoretical justification, the use of blood purification methods cannot yet be recommended for patients with sepsis due to lack of evidence (12).

The cytosorb is a cartridge composed of polystyrene-divinyl-benzene polymer beads with a highly porous and biocompatible polyvinylpyrrolidone cover. Its estimated size is 300 to

800  $\mu\text{m}$  with a total surface area of more than 40,000  $\text{m}^2$ . The elimination of substances from the blood is based on the capture of substances in the pores and surface adsorption. The typical duration of therapy is up to 24 hours per session, daily for 2 to 7 consecutive days (8,13). The physiological reason for using Cytosorb in the setting of sepsis is to restore a balanced response of pro-inflammatory and anti-inflammatory mediators. Elevated circulating concentrations of several cytokines, including  $\text{TNF-}\alpha$ ,  $\text{IL-1}\beta$ ,  $\text{IL-6}$ ,  $\text{IL-8}$ , and  $\text{IL-10}$ , have been reported to be associated with morbidity and mortality in patients with sepsis, so their removal would be useful for the treatment (3,11).

We performed a systematic review and meta-analysis with the aim to analyze the use of Cytosorb in mortality, interleukin levels, the use of vasopressors and adverse events in patients with sepsis, and septic shock since the available evidence is still controversial.

## **METHODS**

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(14), a research protocol was developed and registered in the International prospective register of systematic reviews PROSPERO database (CRD 42021262219) (15).

### **Information sources and search strategy**

We conducted a systematic search in the databases of PubMed, Embase, and Cochrane Library. Medical Subject Headings (MeSH) or equivalent terms were used. Articles in English and Spanish were included. A preliminary search strategy was created for MEDLINE/PUBMED, the other searches were tailored to individual databases (Supplement Table 1), and the search was performed from the inception to November 2022. Additionally, the bibliographic references of the selected articles were reviewed to identify other references relevant to the topic. The medline search strategy was developed as follows:

("Cytosorb"[tiab] OR "Cytokine adsor\*"[tiab]) AND (Sepsis [Mesh] OR Sepsis [tiab] OR sept\* [tiab]).

For the Embase and The Cochrane Library databases, the search strategy was developed with the terms: “Cytosorb”, “Cytokine adsorption”, “hemadsorption”, “Septic shock” and “Sepsis”.

### **Study selection**

Relevant studies were identified by 2 reviewers (ML and JS), who independently assessed using the research objectives and question (PICO), when an agreement was not reached, a third reviewer (YH) member of the investigator group was included and resolved any discrepancies. The articles selected in each database were exported to the Zotero software where the elimination of duplicates was carried out.

We included studies that met the following criteria: 1) Adult patients with sepsis or septic shock, 2) RCT (randomized clinical trial) studies, propensity score-matched cohort studies (prospective or retrospective), or studies with historical control, 3) Patients who received at least one Hemoadsorption therapy with cytosorb, 4) Studies that reported on mortality at 28-30 days, requirement for the use of vasopressors, inflammatory markers levels and adverse effects of Cytosorb (CS) treatment. The exclusion criteria were the following 1) Use of CS in contexts other than sepsis and septic shock (such as pancreatitis, cardiac surgery, endocarditis, transplant, trauma or in COVID-19), 2) Type of study or publication of type reports of cases or letters to the editor, we also do not include abstracts from conferences, or before and after studies without a comparator group, 3) Studies in neonates or pediatric patients, 4) Studies that do not report mortality data. It was deemed appropriate to include non-randomized studies of interventions (NRSI), due to the low number of clinical trials found according to the research question.

### **Data Extraction and Risk of Bias Assessment**

A standardized data extraction sheet was used, two independent reviewers (JS and LC) extracted the data and disagreements were resolved by discussion and consensus in case no agreement was reached a third reviewer (YH) was included who resolved discrepancies.

The following information was extracted: name of the main author, year of publication, journal of publication, place of study, inclusion and exclusion criteria, patient population,

time of initiation of intervention use, Cytosorb dose used, mean age, number of patients, general mortality rate and by groups, predicted mortality for the groups. Additionally, data on pre- and post-treatment changes in inflammatory markers and vasopressor levels were collected, if available.

Two authors (JS and LC) performed the risk of bias assessment, we used the risk of bias tool (ROB) for the RCTs(16) and the Review Manager 5.4 program (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark), the risk of bias assessment tool for non-randomized interventions (ROBINS I) (17) was used for the cohort studies, as recommended by the Cochrane collaboration. Importantly, ROBINS-I bias assessments are made based on the comparison between a given study and a theoretical randomized-controlled trial with an ideal design for the study question, which represents the standard for a “low risk study”. (Supplemental table 2 and 3)

### **Data Synthesis and Analysis**

The outcomes were analyzed using the Mantel-Hansel statistical method and the Der Simonian-Laird random effects models, in relation to the high heterogeneity between the studies, since the studies were not equivalent, they differed in the starting time, the duration of therapy, type of administration, and the source of sepsis, among other characteristics, that could have affected the results and therefore a common effect size should not be assumed. Relative Risks (RR) for overall mortality, with 95% CI, were calculated for the conventional treatment and CS treatment groups. Quantitative synthesis was not performed when only one study per outcome was identified or the studies were of a different type of design, or when the studies did not report the necessary statistics, in that scenario were limited to a qualitative description.

The Review Manager 5.4 program (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark) was used for the analysis, and a p value < 0.05 was considered significant.

Publication bias was not assessed due to the number of included studies

## **RESULTS**

## Search Results and Study Characteristics

Our search strategy identified 332 citations, of which 32 were judged to be potentially eligible based on titles or abstracts, or both, and the full texts were obtained. We excluded 26 articles after reviewing the full text, 14 for not having a comparator group, 7 for a different outcome or mixed population, 3 for being in process, 1 for a different type of article, and 1 for being a secondary publication. Finally, 6 studies were included (2 RCT and 4 Cohort studies) including 413 patients (9–11,18–20). **Figure 1** shows our flow chart of study selection.

Patients in the included studies had different causes of sepsis and septic shock. In addition, they differed in the mode, starting time and number of CS treatment sessions. **Table 1** summarizes the characteristics of the included studies.

### Risk of bias in included studies

RCTs presented a high risk of bias, in none of them was it possible to blind the intervention for the outcome assessors. Cohort studies presented a moderate to severe risk. The risk of bias assessment is shown in **Figure 2**.

### Effect on mortality at 28-30 days

Overall mortality was 45% (42% intervention group and 48% control group) (9–11,18–20), and only one study showed mortality greater than 70% (9). A quantitative review was carried out, finding no significant effect on mortality at 28-30 days RR 0.98 [0.12-8.25] for the RCT and RR 0.74 [0.49-1.13] for NRSI. The results are shown in **Figure 3**, and summary of findings table is shown in **Figure 4**.

### Effect on the use of vasopressors

Two studies, one RCT (10) and one cohort study (18) reported the use of vasopressors as an outcome; both reported a significant decrease in vasopressor levels in the intervention group, however this reduction was also shown in the control group. **Table 2**.

### Effect on levels of inflammatory markers

Only one study reported a 5-18% decrease in IL-6 (interleukin-6) levels(20), however no statistical significance was found.

Two studies, one RCT(10) and one cohort study(18), reported results for CRP (c-reactive protein). In the RCT, CRP levels did not show statistical difference, however in the other study, a significant difference was found in the CS group. These results are shown in **Table 2**.

Regarding the PCT (procalcitonin) levels, two studies, one RCT(10) and one cohort study(18) reported a significant decrease in PCT levels compared to the baseline level, nevertheless, this significant reduction was not found in the control group. These results are shown in **Table 2**.

### **Effect on Predicted vs. Observed Mortality**

Two NRSI-type (11,19) studies reported a decrease in observed mortality over predicted mortality. Brouwer et al.(19) 75% vs 52.2% and Rugg et al. (11) 85.1% vs 21.4%. In both studies, predicted mortality was calculated by the SOFA score; nevertheless, the reduction in predicted vs observed mortality was also found in the control group. **Table 2** summarizes the findings.

### **Effect on length of stay in the ICU**

Five studies reported the effect on length of stay in the ICU(9–11,18,19), however, only two of them(10,18) (one RCT and one NRSI) reported SD so a quantitative synthesis was not performed. Only one NRSI (18) found significant differences that favored the use of Cytosorb.

### **Effect on adverse events**

Three studies reported this outcome(10,18,20), two reported no adverse effects (10,18), and the other reported one serious adverse event (20), which was identified as probably related to the use of Cytosorb, it was a decrease in platelet count. In this same study, 3 treatment discontinuations were reported in 3 patients during the study due to adverse events likely related to therapy.

## **DISCUSSION**



To our knowledge, this is the first meta-analysis evaluating the use of Cytosorb, a hemadsorption device, in the setting of sepsis and septic shock, including clinical trials and cohort studies. Our study did not demonstrate a benefit of the use of cytosorb on mortality, however it should be noted that the studies were heterogeneous and the evidence for the RCTs was of high risk of bias and for the NRSIs it was of moderate to severe risk, therefore that future research, of higher quality, could change, or modify the direction of the effect.

Moderate heterogeneity was found in the RCTs ( $I^2=57\%$ ) and high among the NRSIs ( $I^2=70\%$ ), this could be explained by the different etiologies of sepsis, the severity of the disease, different kinds of interventions like ECMO or CRRT and the mode of use of the therapy. This heterogeneity makes it difficult to interpret a meta-analysis of these studies.

Two previous meta-analyses have evaluated the use of extracorporeal blood purification in sepsis (21,22), unlike our study, they did not focus on the use of Cytosorb hemadsorption, and also did not include cohort studies, however, they included the same RCT (10,20), finding similar results. There is a recently published meta-analysis that evaluated the use of Cytosorb in critically ill patients, this study found a low-certainty evidence that shows that the use of Cytosorb might increase mortality, however, it did not find differences in adverse events.(23)

We found a significant decrease in the use of vasopressors in two studies(10,18), but we did not carry out a quantitative synthesis because they were of a different type. These findings are consistent with multiple quasi-experimental before and after studies that indicate that the use of Cytosorb therapy resulted in decreased doses of vasopressors, hemodynamic stabilization, and improvement in metabolic parameters (2,24–27). Some studies report that early use (within the first 24-48 hours), filtered blood volume, and prolonged duration of Cytosorb therapy were associated with lower mortality (2,20,26,28–30), unfortunately, not all studies reported these variables.

Regarding the levels of inflammatory markers, it has been described that Cytosorb is effective in vitro for the elimination of both inflammatory and proinflammatory cytokines, as well as for the decrease of CRP and procalcitonin levels(3,31); and that the levels of cytokines correlate with both the severity of the disease and mortality(32,33). In this revision, only one study reported a non-significant decrease in IL-6 (20) and two studies reported a decrease in levels of CRP and procalcitonin(10,18), these findings coincide with

before and after studies, not included in this review, where Cytosorb was shown to reduce the levels of inflammatory markers(26,27,34,35).

The predicted mortality based on the SOFA score was calculated in two studies, unfortunately, these findings could not be meta-analyzed due to a lack of data in one of the studies(11). A reduction between the observed vs predicted mortality was found in both studies. These findings are similar to those reported in other studies not included.(30,36)

Cytosorb is considered to be a biocompatible and hemocompatible device (37), studies in cardiac surgery and sepsis suggest that Cytosorb does not induce coagulopathy, hemolysis, or clinically relevant side effects (26,38,39), this seems to coincide with the findings of the present review, where only one serious adverse event related to therapy was reported, however it is worth mentioning that the use of Cytosorb in the setting of sepsis is generally longer and that Cytosorb may influence the elimination or decrease in serum concentrations of some drugs, and most of the time it requires interventions that included ECMO and renal replacement therapy to be carried out, therefore, as in other studies, we suspect that the adverse effects were underreported and not systematically evaluated. (23)

An important limitation is that meta-analysis was only carried out for the main outcome, we did not perform it for secondary outcomes due to the small number of studies found or the lack of data. Studies were at moderate to high risk of bias, mainly due to confounding and study participant selection bias; It should be noted that, actually, the number of studies evaluating the use of Cytosorb in sepsis and septic shock is limited.

Our review has other limitations. First, we did not include unpublished studies, nor did we conduct a search of the gray literature, nor did we include conference abstracts or non-original articles. Second, studies without a control group were not included, since our main objective was to assess mortality. Third, the starting time, the duration of therapy, the volume of blood filtered, and the number of cartridges used for it, were different or were not described in some studies, which could have affected the result. Fourth, only one study did not use renal replacement therapy (RRT) and two of them used it according to the patient's needs, as it is known that acute renal failure can amplify the septic cascade induced by endotoxins, so the use of RRT could have affected the result. Fifth, our study has focused only on short-term mortality.

## CONCLUSIONS

Our study found very low certainty evidence that shows no benefit of Cytosorb use in mortality at 28-30 days. We cannot recommend the use of Cytosorb in septic or septic shock patients outside clinical trials. Further high-quality randomized trials with a common intervention arm are needed to evaluate the influence of Cytosorb in this population

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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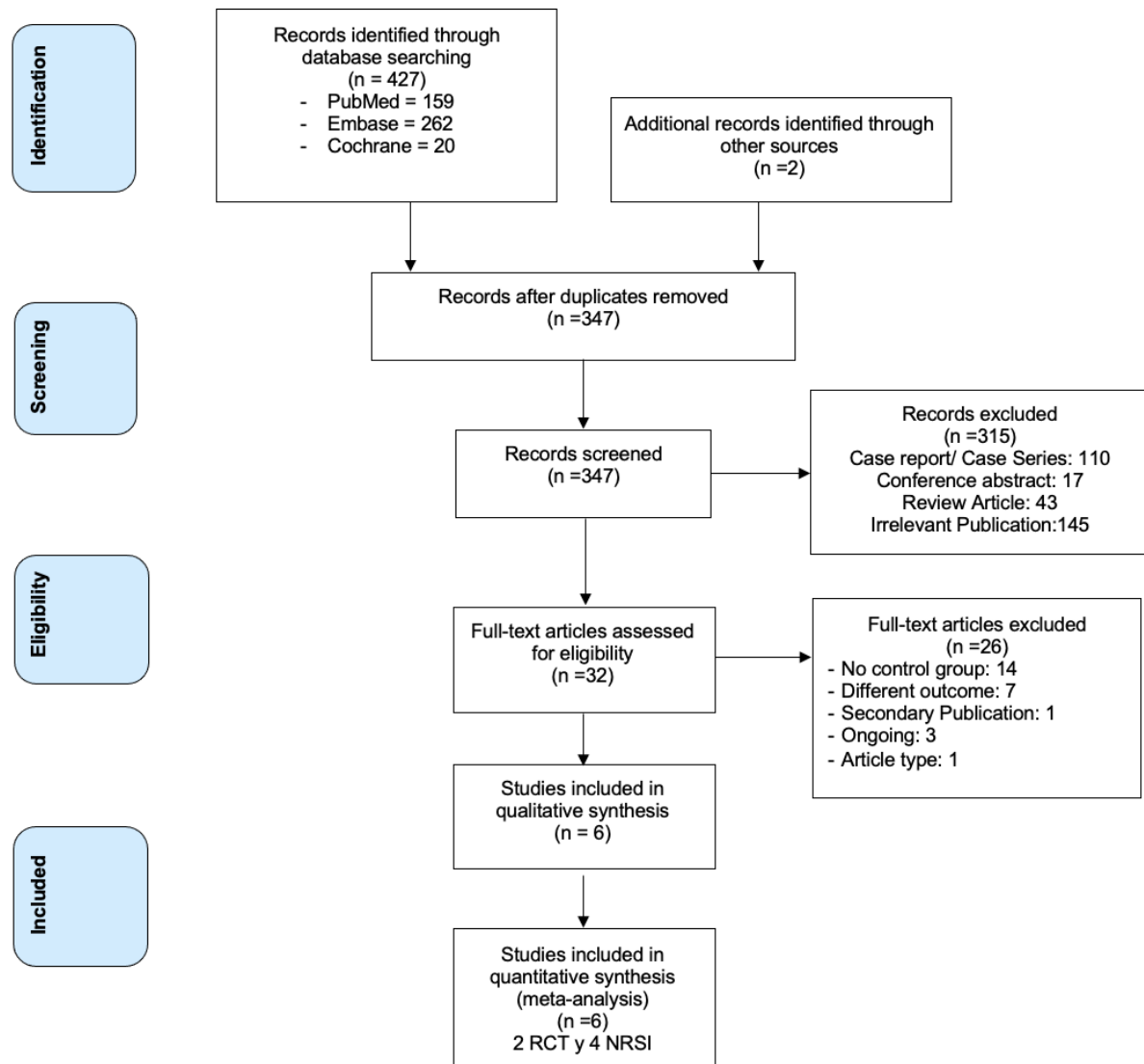
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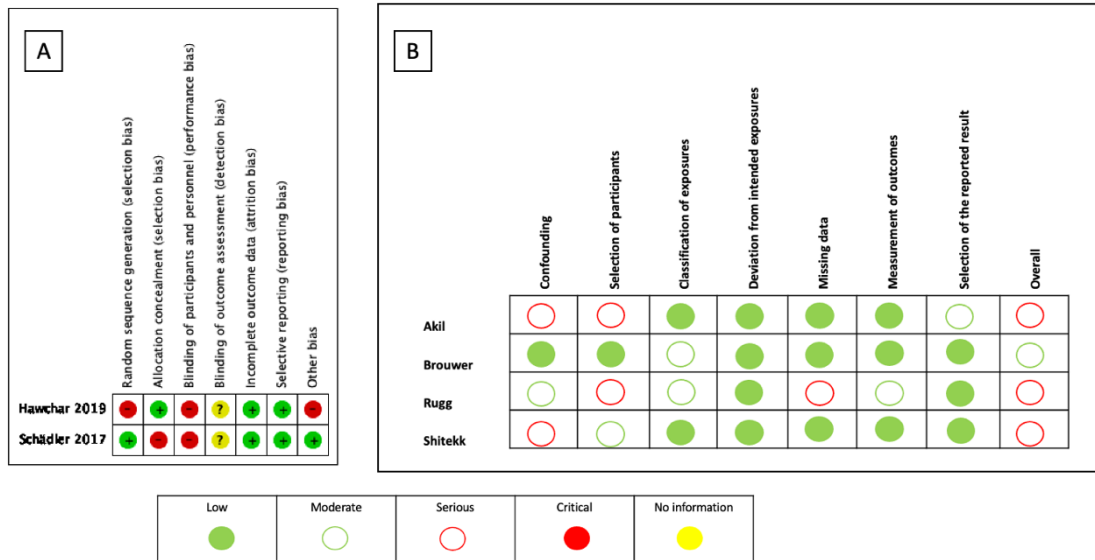
**Figure 1.-** Flowchart of study selection.



RCT (Randomized control trial)

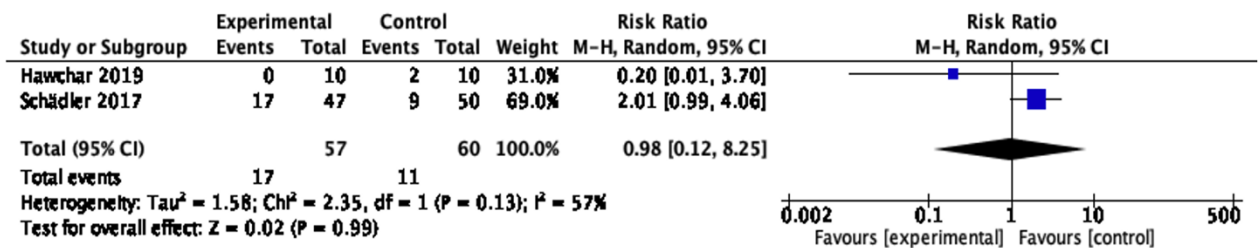
NRSI (Non randomized studies of interventions)

**Figure 2.-** Risk of bias assessment of eligible studies. A. Randomized Control Trial (RCT) B. Non-randomized studies of interventions (NRSI)

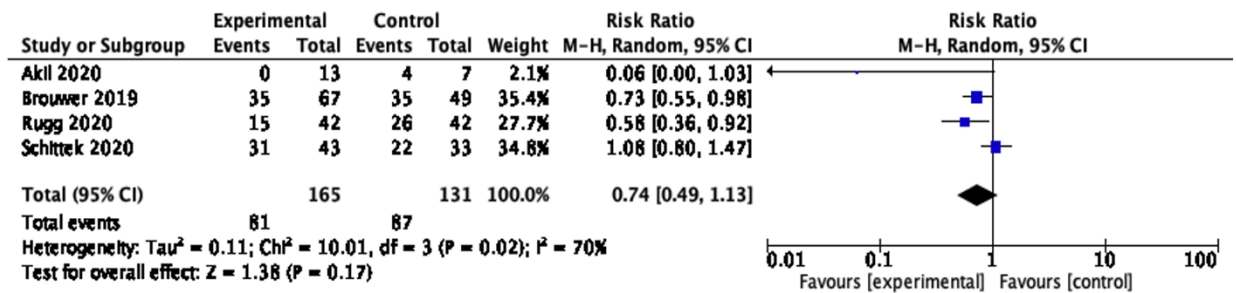


**Figure 3.-** Forest Plot effect of Cytosorb in mortality at 28-30 days. A. Randomized Control Trial (RCT) B. Nonrandomized studies of interventions (NRSI)

A. Randomized control trial



B. Non Randomized Studies of Interventions



**Figure 4.-** Summary of findings for the main comparison



### Cytosorb compared to placebo for Sepsis and Septic Shock

**Patient or population:** Sepsis and Septic Shock  
**Setting:** ICUs Germany, Hungary, The Netherlands, and Austria  
**Intervention:** Cytosorb  
**Comparison:** Conventional therapy

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Cytosorb
MORTALITY-RCT	117 (2 RCTs)	⊕○○○ Very low <sup>a,b,c</sup>	<b>RR 0.98</b> (0.12 to 8.25)	183 per 1,000	<b>4 fewer per 1,000</b> (161 fewer to 1,329 more)
MORTALITY-OBSERVATIONAL STUDIES	296 (4 observational studies)	⊕○○○ Very low <sup>d,e</sup>	<b>RR 0.74</b> (0.49 to 1.13)	664 per 1,000	<b>173 fewer per 1,000</b> (339 fewer to 86 more)

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

#### Explanations

- a. It was decided to decrease two levels due to the high risk of bias
- b. It was decided to decrease one level due to the different results.
- c. It was decided to decrease two levels due to the wide CI
- d. It was decided to decrease two levels due to the different results
- e. It was decided to decrease two levels due to the wide CI

**Table 1** - Characteristics of included studies

Study	Study design	Country	Specific population	Control group	Time of First CS Initiation	Duration of CS therapy	Mortality in CS group
<b>Hawchar, 2019</b>	RCT	Hungary	Septic Shock	Patients with septic shock of medical origin, on mechanical ventilation, norepinephrine > 10 µg/min, procalcitonin (PCT) > 3 ng/mL without the need for renal replacement therapy.	Started within 24 h after ICU admission	24 hrs	0%
<b>Schadler, 2017</b>	RCT	Germany	Severe Sepsis or Septic Shock within 72 hours of ARDS or acute lung injury	Mechanically ventilated patients with severe sepsis or septic shock in the setting of acute lung injury (ALI) or acute respiratory distress syndrome established within the last 72 hours.	Enrolment within 72hrs of diagnosis of sepsis with ARDS/ALI	max 7x6hrs 24hrs apart	36%
<b>Akil, 2020</b>	Cohort historic control	Germany	Pneumogenic sepsis and ECMO	Historical cohort. Patients with pneumogenic septic shock accompanying acute respiratory failure, invasive hemodynamic monitoring, and demand for norepinephrine 0.3 µg/min; elevated lactate concentrations 2.0 mmol/L; and procalcitonin (PCT) serum level 1 ng/mL were eligible.	Within 6 hours after admission to our intensive care unit (ICU).	Min 2 x24 hrs without interruption	0%
<b>Brouwer, 2019</b>	Propensity-score-weighted retrospective study	The Netherlands	Septic Shock	Patients with septic shock treated with CRRT without Cytosorb. Stabilized inverse probability treatment weight was applied.	CS was initiated at the discretion of the treating intensive care physician.	24 hrs, mean duration of 2.34 ± 0.16 days	52.20%
<b>Rough, 2020</b>	Propensity-score-weighted retrospective study	Austria	Primary or Secondary Sepsis	Matched controls were treated for septic shock and required RRT, but did not receive Cytosorb therapy. A generalized propensity score and Mahalanobis distance matching method ('genetic' matching) was applied.	Initiation of CS therapy varied from 0.5 to 719 h after ICU admission, but most patients received treatment within the first days.	1-6 x 24 hrs without interruption	21.40%

<b>Schittek, 2020</b>	Retrospective control group and prospective intervention group	Germany	Patients in severe septic shock with sepsis-associated acute kidney injury (SA-AKI)	Retrospective controls with septic shock (rising noradrenaline dose above 20 µg/min.) with sepsis associated acute kidney injury in CVVHDF	No information	No information overall. Survivors, approximately one cartridge per patient was utilized as the median (IQR 1, 2) for 35.5 h (17-47).	76.70%
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CS(Cytosorb)

RCT (Randomized control trial)

ICU (Intensive care unit)

ARDS (Acute respiratory distress syndrome)

ALI (Acute lung injury)

ECMO (Extracorporeal membrane oxygenation)

**Table 2.** Effect of Cytosorb on secondaries outcomes.

**Norepinephrine (NE) levels (ug/kg/min)**

Study	NE T0-CG	NE 48hrs-CG	p	NE T0-CS	NE 48hrs-CS	p
Hawchar	0.43[0.19–0.64]	0.25[0.08–0.65]	NR	0.54 [0.20-1.22]	0.16 [0.07-0.48]	0.016
Akil	0.83 +-0.16	0.38 +- 0.11	0.05	0.603 +-0.08	0.009+- 0.005	0.0001

**C reactive protein (CRP) levels (mg/L)**

Study	CRP T0-CG	CRP 48hrs-CG	p	PCR T0-CS	PCR 48 hr-CS	p
Hawchar	307.4 +-116.7	189.9 +-48.5	NS	238.1 +- 95.5	169.54 +-86.4	NS
Akil	27.2+-2.9	22.6+-3.1	0.31	35+-5	12+-3	0.002

**Procalcitonin (PCT) levels(ng/mL)**

Study	PCT T0-CG	PCT 48 hr-CG	p	PCT T0-CS	PCT 48 hr-CS	p
Hawchar	13.2 [7.6-47.8]	9.2 [3.8-44.2]	NR	20.6 [6.5-144.5]	5.6 [1.9-54.4]	0.004
Akil	13.14 +- 9.7	8.14 +-5.9	0.68	15.6 +-5.4	2.71+-1.5	0.03

**Predicted vs. Observed Mortality**

Study	Observed Mortality CG	Predicted Mortality CG	p	Observed Mortality CS	Predicted Mortality CS	p
Brouwer	51%	67,9%	0,035	47,8%	74,5%	<0,001
Rugg	47,6%	65,7%	NR	21,4%	85,7%	NR

CG (control group)

CS (Cytosorb group)

## SUPPLEMENTARY MATERIAL

**Supplemental Table 1.** Search Strategy

<b>Search Strategy Embase</b>		
#1	hemadsorption'/exp OR <b>hemadsorption</b>	1875
#2	'blood filter'/exp OR ' <b>blood filter</b> '	1845
#3	('sepsis'/exp OR <b>sepsis</b> ) AND ('septic shock'/exp OR ' <b>septic shock</b> ')	72608
#4	#1 OR #2	3488
#5	#4 AND #3	262
<b>Search Strategy Pubmed</b>		
#1	("Cytosorb"[tiab] OR "Cytokine adsor*"[tiab])	367
#2	(Sepsis [Mesh] OR Sepsis [tiab] OR sept* [tiab])	51303
#3	#1 AND #2	159
<b>Search Strategy Cochrane library</b>		
	cytosorb in Title Abstract Keyword AND sepsis in Title Abstract Keyword	20

**Supplemental Table 2. ROB Score Consensus by Domain for Included Studies**

<b>Hawchar, 2019, J Crit Care</b>	
<b>Bias</b>	<b>Consensus</b>
Random Sequence Generation	<b>High Risk.</b> Block randomization by study author who was also involved in recruitment
Allocation Concealment	<b>Low Risk.</b> Sealed envelopes
Blinding of participants & Personnel	<b>High Risk.</b> No sham machine
Blinding of outcome assessment	<b>Unclear Risk.</b> Not described
Incomplete outcome data	<b>Low Risk.</b> No data loss reported
Selective reporting	<b>Low Risk.</b> Outcomes reported
Other bias	<b>High Risk.</b> Dialysis performed on patients in control group

<b>Schadler, 2017 PLOS One</b>	
<b>Bias</b>	<b>Consensus</b>
Random Sequence Generation	<b>Low Risk.</b> Block randomization
Allocation Concealment	<b>High Risk.</b> Sealed envelopes but multiple violations
Blinding of participants & Personnel	<b>High Risk.</b> No sham machine
Blinding of outcome assessment	<b>Unclear Risk.</b> Not described
Incomplete outcome data	<b>Low Risk.</b> Exclusions accounted for
Selective reporting	<b>Low Risk.</b> Outcomes reported
Other bias	<b>Low Risk.</b> No described

**Supplemental Table 3. ROBIN-I Score Consensus by Domain for Included Studies**

Akil et al., 2020	
Domain	Consensus
<p><b>Bias Due to Confounding:</b> Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline.</p>	<p><b>Serious Risk.</b> It's mentioned that one "Indication for ECMO therapy was the clinical deterioration due to acute respiratory failure", In addition, the participant characteristics table shows that those included in the CytoSorb group had a higher SAPS II score. Other factors were evaluated.</p>
<p><b>Bias in selection of participants into the study:</b> When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical.</p>	<p><b>Serious Risk.</b> It's mentioned that the authors "collected clinical parameters and outcome data from a historical cohort at our institution with acute respiratory failure due to pneumogenic sepsis, which were treated with ECMO and standard of care therapy at the period before January 2018". The period of time prior to January 2018, in which the search for control cases was carried out, is not mentioned.</p>
<p><b>Bias in classification of interventions:</b> Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.</p>	<p><b>Low Risk.</b> It was well defined the intervention</p>
<p><b>Bias due to deviations from intended interventions:</b> Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).</p>	<p><b>Low Risk.</b> Authors mentioned that all the patients "were treated following the sepsis treatment guidelines".</p>
<p><b>Bias due to missing data:</b> Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.</p>	<p><b>Low Risk.</b> Any patient was excluded due to lack of data</p>
<p><b>Bias in measurement of outcomes:</b> Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.</p>	<p><b>Low Risk.</b> There was no difference in the measurement of outcomes in both groups.</p>
<p><b>Bias in selection of the reported result:</b> Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis).</p>	<p><b>Moderate Risk.</b> The most important clinical and laboratory outcomes were reported in the study. However they did not make comparison between groups</p>
<p><b>Overall risk of bias judgement</b></p>	<p><b>Serious Risk.</b> Two domains are rated as serious.</p>

<b>Brouwer et al., 2019</b>	
<b>Domain</b>	<b>Consensus</b>
<p><b>Bias Due to Confounding:</b> Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline.</p>	<p><b>Low Risk.</b> Authors carried out an analysis using the inverse probability of treatment weights (IPTW) to avoid bias.</p>
<p><b>Bias in selection of participants into the study:</b> When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical.</p>	<p><b>Low Risk.</b> Patients were only excluded from the study, in case the primary diagnosis of the patient was not septic shock.</p>
<p><b>Bias in classification of interventions:</b> Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.</p>	<p><b>Moderate Risk.</b> Some patients that initiated on CytoSorb subsequent to CRRT where included in the CytoSorb Group</p>
<p><b>Bias due to deviations from intended interventions:</b> Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).</p>	<p><b>Low Risk.</b> Patients were treated per protocol as part of standard of care, i.e. no interventions were applied for the purpose of this study</p>
<p><b>Bias due to missing data:</b> Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.</p>	<p><b>Low Risk.</b> Any patient was excluded due to lack of data</p>
<p><b>Bias in measurement of outcomes:</b> Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.</p>	<p><b>Low risk.</b> The end points were clearly defined "All-cause mortality was measured from ICU admission until 28 days after admission (irrespective of ICU, in-hospital or out of hospital mortality)</p>
<p><b>Bias in selection of the reported result:</b> Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis).</p>	<p><b>Low Risk.</b> The outcome of interest was reported without any obvious bias.</p>
<p><b>Overall risk of bias judgement</b></p>	<p><b>Moderate Risk.</b> Only one domain was rated as moderate risk</p>



Rugg et al., 2020	
Domain	Consensus
<p><b>Bias Due to Confounding:</b> Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline.</p>	<p><b>Moderate Risk.</b> Initiation of CytoSorb therapy varied from 0.5 to 719 h after ICU admission, many patients probably were indicated to start with cytosorb due to a torpid evolution, however the authors made a “genetic matching” to minimize risk of bias.</p>
<p><b>Bias in selection of participants into the study:</b> When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical.</p>	<p><b>Serious Risk.</b> Proof of matching took place manually primarily due to missing data on admission diagnoses and RRT requirements and general definition of baseline differed between the groups.</p>
<p><b>Bias in classification of interventions:</b> Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.</p>	<p><b>Moderate Risk.</b> It was well defined the intervention, however some patients were included in the cytosorb group after being only with RRT.</p>
<p><b>Bias due to deviations from intended interventions:</b> Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).</p>	<p><b>Low Risk.</b> Patients were treated per protocol as part of standard of care, however, in the control group were included patients treated since 2011 (the protocol of standard care)</p>
<p><b>Bias due to missing data:</b> Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.</p>	<p><b>Serious risk.</b> Due to missing data, it was necessary to include patients in a huge period of time</p>
<p><b>Bias in measurement of outcomes:</b> Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.</p>	<p><b>Low Risk.</b> The primary end point where clearly defined</p>
<p><b>Bias in selection of the reported result:</b> Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis).</p>	<p><b>Low Risk.</b> There was no selective reporting of the results.</p>
<p><b>Overall risk of bias judgement</b></p>	<p><b>Serious Risk.</b> Two domains are rated has a serious risk</p>

Schittek et al., 2020	
Domain	Consensus
<p><b>Bias Due to Confounding:</b> Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline.</p>	<p><b>Serious Risk.</b> Some patients received more than one session of Hemoadsorption and there was a significantly higher severity of illness as depicted by APACHE II and catecholamine dependency in patients treated with Hemoadsorption</p>
<p><b>Bias in selection of participants into the study:</b> When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical.</p>	<p><b>Moderate Risk.</b> It was clearly defined since each group where from different periods of time, however, the inclusion criteria differed from both groups</p>
<p><b>Bias in classification of interventions:</b> Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.</p>	<p><b>Low Risk.</b> It was well defined the intervention.</p>
<p><b>Bias due to deviations from intended interventions:</b> Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).</p>	<p><b>Low Risk.</b> Authors said that all patients were treated in accordance with the local sepsis treatment protocol.</p>
<p><b>Bias due to missing data:</b> Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.</p>	<p><b>Low Risk.</b> Missing data regarded only laboratory test result, and therefore did not influence the interpretation of primary or secondary results.</p>
<p><b>Bias in measurement of outcomes:</b> Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.</p>	<p><b>Low Risk.</b> The primary end point where clearly defined</p>
<p><b>Bias in selection of the reported result:</b> Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis).</p>	<p><b>Low Risk.</b> There is no evidence of selective reporting.</p>
<p><b>Overall risk of bias judgement</b></p>	<p><b>Serious Risk.</b> One domain was rated as a serious risk</p>

## PRIMER MANUSCRITO ENVIADO A LA REVISTA

### **Cytokine Hemoadsorption with Cytosorb in Sepsis: A Systematic Review and Meta-Analysis.**

#### **ABSTRACT**

*Background and Aims:* Blood purification therapies have been used in different acute inflammatory scenarios; however, their use is controversial. We performed a systematic review and meta-analysis with the aim to analyze the use of Cytosorb effect in mortality, interleukin levels, the use of vasopressors and adverse events in patients with sepsis.

*Methods:* We searched MEDLINE, Embase and Cochrane Library for randomized controlled trials and cohort studies that reported the use of Cytosorb among septic patients. The primary outcome was mortality. Secondary outcomes included use of vasopressors, levels of inflammatory markers, predicted vs. observed Mortality, length of stay in the ICU, and adverse events.

*Results:* We included 6 studies enrolling 413 patients, assessment for risk of bias indicated variations in study quality from high to moderate. Overall mortality was 45%, no significant effect was found on mortality at 28-30 days RR 0.98 [0.12-8.25] for the RCT and RR 0.74 [0.49-1.13] for NRSI. Disease severity subgroup meta-analysis revealed a significant reduction of mortality in the intermediate risk of death presented a RR of 0.69 [0.54, 0.88]  $p < 0.05$ . We did not perform metanalysis for other outcomes due to the small number of studies found or the lack of data.

*Conclusions:* Our study found no benefit of Cytosorb use in mortality at 28-30 days, however it suggests that the group of patients with intermediate risk of death could have

a greater benefit, we also found that Cytosorb could be useful to reduce the use of vasopressors. *Protocol registration:* (CRD42021262219).

Keyword: Hemoperfusion, Mortality, Sepsis, Cytosorb, Cytosorbent

## INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1) and its most severe state, septic shock, represents a highly lethal condition that causes substantial morbidity and mortality among critically ill patients (2). The pathophysiology of sepsis is very complex, involving many factors, such as pro-inflammatory and anti-inflammatory cytokines, pathogen-associated molecular patterns (PAMPs), bacterial exotoxins and endotoxins, mycotoxins, damage-associated molecular patterns (DAMPs) released by injured cells and host-specific factors such as activated complement and procalcitonin (3). Inflammation generated by upregulation of proinflammatory cytokines activated complement, and other mediators can lead to severe immune system dysfunction ranging from destructive maladaptive systemic inflammatory response syndrome (SIRS) to advanced immunosuppression, which could lead to multisystem organ dysfunction and death (3,4).

Despite early treatment and multiple efforts to reduce mortality in sepsis and septic shock, such as the surviving sepsis campaign, which provides treatment guidelines (5), mortality is still high, around 20-40 % for severe sepsis and 40-60% in septic shock (1,6,7), without significant variations in this figure in recent years; that is why adjuvant therapies have

been described, such as blood purification techniques, including extracorporeal removal of cytokines by Hemoadsorption(2,8–10).

There are currently multiple blood purification techniques, with different results, at the level of cytokines removal, decrease in vasopressors and even decrease in mortality, these include high-volume dialysis, high-cut membranes, adsorption by filtration coupled plasma and special adsorption filters (such as Oxiris, Cytosorb, HA 330 and Polymyxin B filters)(8,11). Blood purification therapies have been used in different acute inflammatory scenarios such as sepsis, cardiac surgery, and autoimmune diseases, however, their use is controversial, and despite a theoretical justification, the use of blood purification methods cannot yet be recommended for patients with sepsis due to lack of evidence (12).

The Cytosorb is a cartridge composed of polystyrene-divinyl-benzene polymer beads with a highly porous and biocompatible polyvinylpyrrolidone cover. Its estimated size is 300 to 800  $\mu\text{m}$  with a total surface area of more than 40,000  $\text{m}^2$ . The elimination of substances from the blood is based on the capture of substances in the pores and surface adsorption. The typical duration of therapy is up to 24 hours per session, daily for 2 to 7 consecutive days (8,13). The physiological reason for using Cytosorb in the setting of sepsis is to restore a balanced response of pro-inflammatory and anti-inflammatory mediators. Elevated circulating concentrations of several cytokines, including  $\text{TNF-}\alpha$ ,  $\text{IL-1}\beta$ ,  $\text{IL-6}$ ,  $\text{IL-8}$ , and  $\text{IL-10}$ , have been reported to be associated with morbidity and mortality in patients with sepsis, so their removal would be useful for the treatment (3,11).

We performed a systematic review and meta-analysis with the aim to analyze the use of Cytosorb in mortality, interleukin levels, the use of vasopressors and adverse events in patients with sepsis and septic shock since the available evidence is still controversial.

## **METHODS**

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(14), a research protocol was developed and registered in the International prospective register of systematic reviews PROSPERO database (CRD42021262219) (15).

### **Information sources and search strategy**

We reviewed PubMed/MEDLINE, Embase, and The Cochrane Library databases, using Medical Subject Headings (MeSH) or equivalent terms. Articles in English and Spanish were included. A preliminary search strategy was created for MEDLINE/PUBMED, the other searches were tailored to individual databases (Supplement Table 1), and the search was performed from the incept to May 2022. Additionally, the bibliographic references of the selected articles were reviewed to identify other references relevant to the topic. MEDLINE search strategy was developed as follows:

("Cytosorb"[tiab] OR "Cytokine adsor\*"[tiab]) AND (Sepsis [Mesh] OR Sepsis [tiab] OR sept\* [tiab]).

For the Embase and The Cochrane Library databases, the search strategy was developed with the terms: "Cytosorb", "Cytokine adsorption", "hemadsorption", "Septic shock" and "Sepsis".

### **Study selection**

Relevant studies were identified by 2 reviewers (ML and JS), who independently assessed using the research objectives and question (PICO), when the agreement was not reached, a third reviewer (YH) member of the investigator group was included and resolved any

discrepancies. The articles selected in each database were exported to the Zotero software where the elimination of duplicates was carried out.

We included studies that met the following criteria: 1) Adult patients with sepsis or septic shock, 2) RCT (randomized clinical trial) studies, propensity score-matched cohort studies (prospective or retrospective), or studies with historical control, 3) Patients who received at least one Hemoadsorption therapy with cytosorb, 4) Studies that reported on mortality, the requirement for the use of vasopressors, interleukin levels and adverse effects of CS treatment. The exclusion criteria were the following 1) Use of CS in contexts other than sepsis and septic shock (such as pancreatitis, cardiac surgery, endocarditis, transplant, trauma or in COVID-19), 2) Type of study or publication of type reports of cases or letters to the editor, we also do not include abstracts from conferences, or before and after studies without a comparator group, 3) Studies in neonates or pediatric patients, 4) Studies that do not report mortality data.

According to the search criteria in the different pre-selected databases, the references of each database that met the search criteria were exported to the Zotero software. Duplicates were eliminated and the required information (description of the methodology, results, and conclusions) was extracted independently.

### **Data Extraction and Quality Assessment**

A standardized data extraction sheet was used, two independent reviewers (JS and LC) extracted the data and disagreements were resolved by discussion and consensus, in case no agreement was reached a third reviewer (YH) was included who solved discrepancies.

The following information was extracted: name of the main author, year of publication, journal of publication, place of study, inclusion and exclusion criteria, patient population,

time of initiation of intervention use, Cytosorb dose used, mean age, number of patients, general mortality rate and by groups, predicted mortality for the groups. Additionally, if available, data on pre- and post-treatment changes in interleukin levels and vasopressor levels were collected.

Two authors (JS and LC) performed the quality assessment and the risk of bias analysis, the risk of bias tool (ROB2) was used for the RCTs(16) and the Review Manager 5.4 program was used (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark), the risk of a bias assessment tool for non-randomized interventions (ROBINS I) (17) was used for the cohort studies, as recommended by the Cochrane collaboration.

### **Data Synthesis and Analysis**

The outcomes were analyzed using the Mantel-Hansel statistical method and the Der Simonian-Laird random effects models, about the high heterogeneity between the studies since the studies were not equivalent, they differed in the starting time, the duration of therapy, type of administration, and the source of sepsis, among other characteristics, that could have affected the results and therefore a common effect size should not be assumed. Relative Risks (RR) for overall mortality, with 95% CI, were calculated for the conventional treatment and CS treatment groups. Quantitative synthesis was not performed when only one study per outcome was identified or the studies were of a different type of design, or when the studies did not report the necessary statistics, in that scenario we were limited to a qualitative description.

A subgroup analysis was performed for mortality according to disease severity. Included studies were stratified into three groups according to overall mortality rates: low-risk group (mortality rate  $<0.3$ ), intermediate-risk group ( $0.3-0.6$ ), and high-risk group ( $>0.6$ ),



the Review Manager 5.4 program (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark) was used for the analysis, a  $p < 0.05$  was considered significant.

Publication bias was not assessed due to the number of included studies.

## **RESULTS**

### **Search Results and Study Characteristics**

Our search strategy identified 332 citations, of which 31 were judged to be potentially eligible based on titles or abstracts, or both, and the full texts were obtained. We excluded 25 articles after reviewing the full text, 13 for not having a comparator group, 7 for a different outcome or mixed population, 3 for being in process, 1 for a different type of article and 1 for being a secondary publication. Finally, 6 studies were included (2 RCT and 4 Cohort studies) including 413 patients (9–11,18–20). **Figure 1** shows our flow chart of study selection.

Patients in the included studies had different causes of sepsis and septic shock. In addition, they differed in the mode, starting time and number of CS treatment sessions.

**Table 1** summarizes the characteristics of the included studies.

### **Risk of bias in included studies**

RCTs presented a high risk of bias, in none of them was it possible to blind the intervention for the outcome assessors. Cohort studies presented a moderate to severe risk. The risk of bias assessment is shown in **Figure 2**.

### **Effect on mortality at 28-30 days**

Overall mortality was 45% (42% intervention group and 48% control group) (9–11,18–20), only one study showed mortality greater than 70% (9). When performing the quantitative synthesis, no significant effect was found on mortality at 28-30 days RR 0.98 [0.12-8.25] for the RCT and RR 0.74 [0.49-1.13] for NRSI (**Figure 3**).

The RCTs presented overall mortality of less than 30%, so analysis by subgroups was not performed. When evaluating the NRSI, it was found that the studies with an intermediate risk of death presented a RR of 0.69 [ 0.54, 0.88]  $p < 0.05$ , favouring the CS group (**Figure 4**).

#### **Effect on the use of vasopressors**

Two studies, one RCT (10) and one cohort study (18) reported the use of vasopressors as an outcome. Hawchar et al. (10) found that vasopressor requirements decreased significantly after Cytosorb use at 48 hrs (norepinephrine: CytoSorb: T0 = 0.54[IQR:0.20–1.22], T48=0.16[IQR:0.07 –0.48],  $p=0.016$ , Controls: T0=0.43[IQR:0.19–0.64], T48=0.25[IQR:0.08–0.65]  $\mu\text{g}/\text{kg}/\text{min}$ ); Akil et al. also found that vasopressor use decreased significantly at 48 hrs (norepinephrine: CytoSorb: T0 = 0.603 +/- 0.08, T48=0.009 +/- 0.005  $p=0.0001$ ; Controls: T0=0.83 +/- 0.16, T48=0.38 +/- 0.11  $\mu\text{g}/\text{kg}/\text{min}$ ),  $p=0.05$ .

#### **Effect on levels of inflammatory markers**

Only one study reported a 5-18% decrease in IL-6 levels (20), however, no statistical significance was found.

Two studies, one RCT(10) and one cohort study (18), reported results for CRP and PCT, CRP levels did not differ significantly at 48 hrs. in both studies, however, PCT levels did show a reduction significant at 48 hrs. These results are shown in **Table 2**.

### **Effect on Predicted vs. Observed Mortality**

Two NRSI-type (11,19) studies reported a decrease in predicted mortality over observed mortality. Brouwer et al.(19) 75% vs 52.2% and Rugg et al. (11) 85.1% vs 21.4%. In both studies, predicted mortality was calculated by the SOFA score. **Table 3** summarizes the findings.

### **Effect on length of stay in the ICU**

Five studies reported the effect on length of stay in the ICU(9–11,18,19), however, only two of them (10,18) (one RCT and one NRSI) reported SD, so a quantitative synthesis was not performed. Only one NRSI (18) found significant differences that the use of Cytosorb.

### **Effect on adverse events**

Three studies reported this outcome(10,18,20), two reported no adverse effects (10,18), and a single study reported a serious adverse (20), which was identified as probably related to the use of Cytosorb, which was a decrease in platelet count. In this same study, 3 treatment discontinuations were reported in 3 patients during the study due to adverse events likely related to therapy.

## DISCUSSION

To our knowledge, this is the first meta-analysis evaluating the use of Cytosorb, a hemadsorption device, in the setting of sepsis and septic shock, including clinical trials and cohort studies. Our study did not demonstrate a benefit of the use of cytosorb on mortality, however, it should be noted that the studies were heterogeneous and the quality of the evidence for the RCTs was of high risk of bias and for the NRSIs it was of moderate to severe risk, therefore that future research, of higher quality, could change, or modify the direction of the effect.

Moderate heterogeneity was found in the RCTs ( $I^2=57\%$ ) and high among the NRIs ( $I^2=70\%$ ), this could be explained by the different etiologies of sepsis, the severity of the disease and the mode of use of the therapy. An analysis by subgroups was performed to evaluate heterogeneity, although this was not contemplated in the protocol, we found that in NRSI-type studies, Cytosorb was shown to reduce mortality in patients with an intermediate risk of dying.

Two previous meta-analyses have evaluated the use of extracorporeal blood purification in sepsis (21,22), unlike our study, they did not focus on the use of Cytosorb hemadsorption, and also did not include cohort studies, however, they included the same RCT (10,20), finding similar results.

We found a significant decrease in the use of vasopressors in two studies camp (10,18), but we did not carry out a quantitative synthesis because they were of different types. These findings are consistent with multiple quasi-experimental before and after studies that indicate that the use of vasopressor therapy Cytosorb resulted in decreased doses of vasopressors, hemodynamic stabilization, and improvement in metabolic parameters

(2,23–26), some studies report that early use (within the first 24-48 hours), Filtered blood volume and prolonged duration of Cytosorb therapy were associated with lower mortality (2,20,25,27–29), unfortunately not all studies reported these variables.

Regarding the levels of inflammatory markers, it has been described that Cytosorb is effective in vitro for the elimination of both inflammatory and proinflammatory cytokines, as well as for the decrease of CRP and procalcitonin levels (3,30); and that the levels of cytokines correlate with both the severity of the disease and mortality(31,32). In this SR, only one study reported a non-significant decrease in IL-6 (20) and two studies reported a decrease in levels of CRP and procalcitonin(10,18), these findings coincide with before and after studies, not included in this review, where Cytosorb was shown to reduce the levels of inflammatory markers(25,26,33,34).

The predicted mortality based on the SOFA score was calculated in two studies, unfortunately, these findings could not be meta-analysed due to a lack of data in one of the studies (11). A reduction in the observed vs predicted mortality was found in both studies. These findings are similar to those reported in other studies not included.(29,35)

Cytosorb is considered to be a biocompatible and hemocompatible device (36), studies in cardiac surgery and sepsis suggest that Cytosorb does not induce coagulopathy, hemolysis or clinically relevant side effects (25,37,38), this seems to coincide with the findings of the present review, where only one serious adverse event related to therapy was reported, however, it is worth mentioning that the use of Cytosorb in the setting of sepsis is generally longer and that Cytosorb may influence the elimination or decrease in serum concentrations of some drugs, for so its use must be assessed risk-benefit.

An important limitation is that meta-analysis was only carried out for the main outcome, we did not perform it for secondary outcomes due to the small number of studies found or the lack of data. Studies were at moderate to high risk of bias, mainly due to confounding and study participant selection bias; It should be noted that the number of studies evaluating the use of Cytosorb in sepsis and septic shock is limited.

Additionally, our review has other limitations. First, we did not include unpublished studies, conduct a search of the grey literature or include conference abstracts or non-original articles. Second, studies without a control group were not included, since our main objective was to assess mortality. Third, the starting time, the duration of therapy, the volume of blood filtered, and the number of cartridges used for it, were different or were not described in some studies, which could have affected the result. Fourth, only one study did not use renal replacement therapy (RRT) and two of them used it according to the patient's needs, as it is known that acute renal failure can amplify the septic cascade induced by endotoxins, so the use of RRT could have affected the result. Finally, our study has focused only on short-term mortality.

## **Conclusions**

Our study found no benefit of Cytosorb use in mortality at 28-30 days, however, it suggests that the group of patients with intermediate risk of death could have a greater benefit, we also found that Cytosorb could be useful to reduce the use of vasopressors. We believe that proper patient selection and early use of therapy are essential to improve patient survival. We recommend further RCTs focused on early and high-dose use of Cytosorb therapy.

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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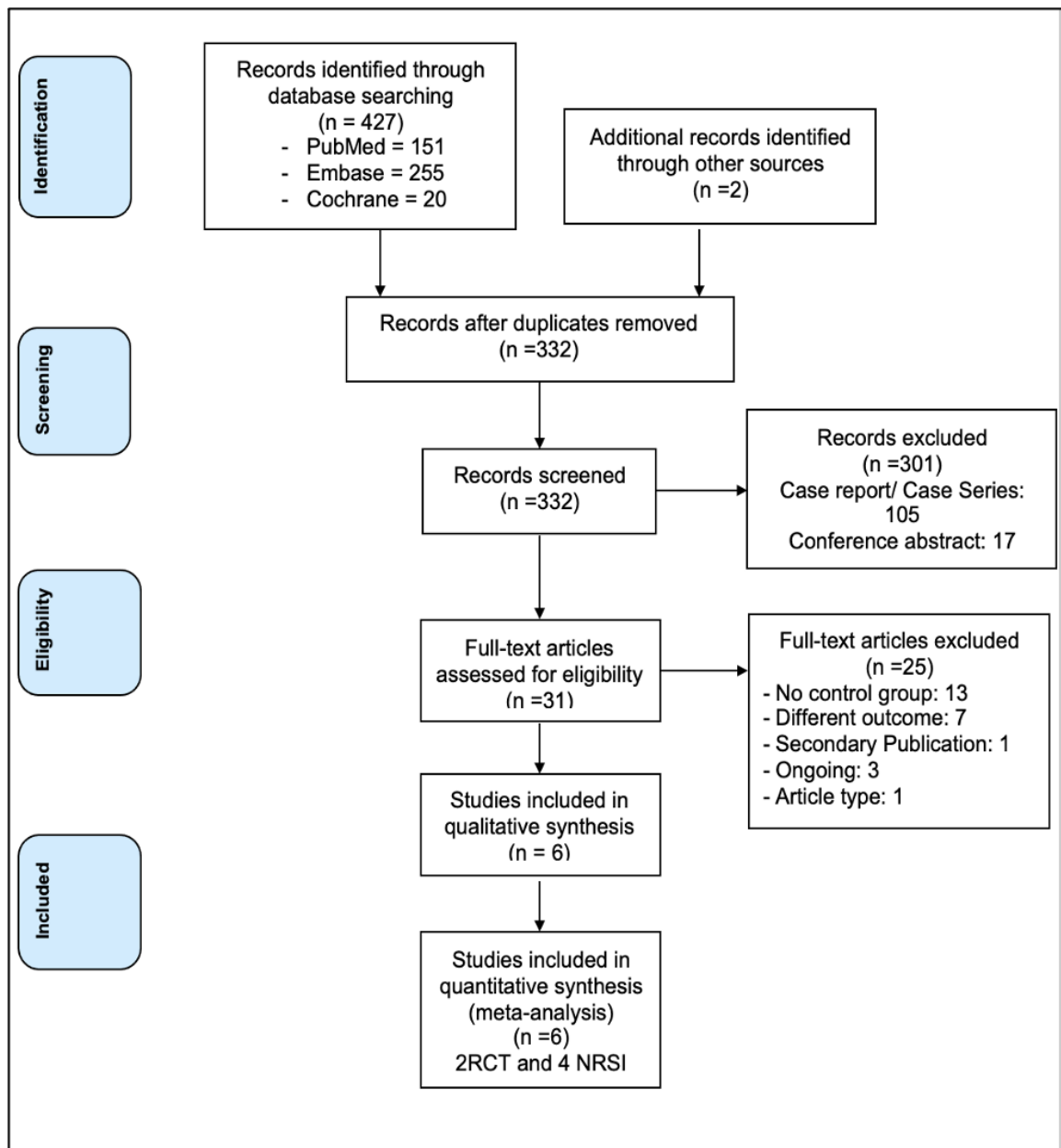
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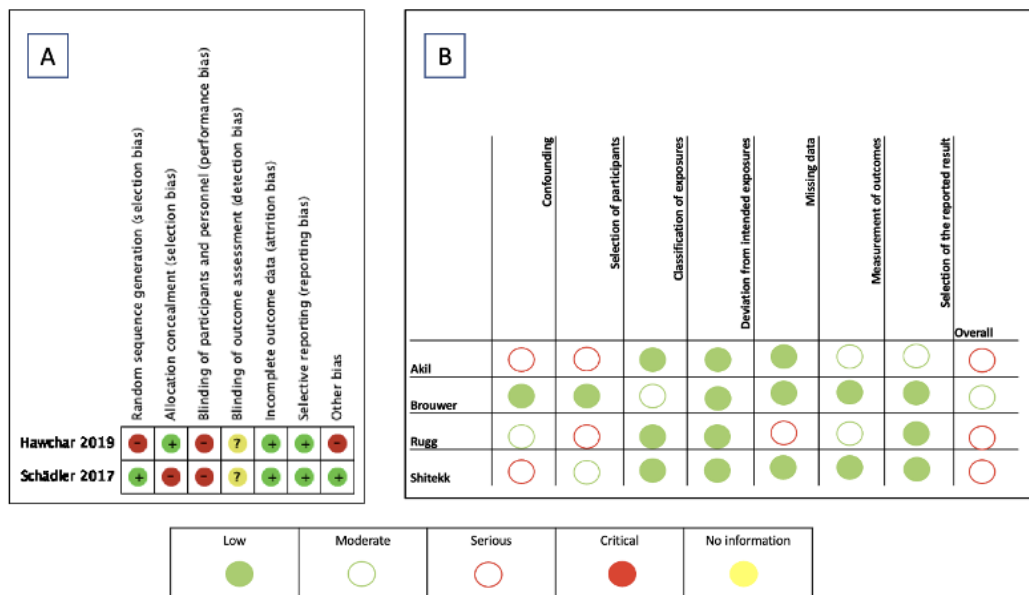
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**Figure 1.** Flowchart of study selection.

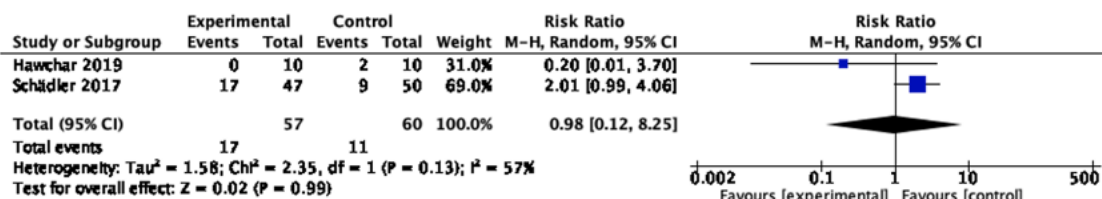


**Figure 2.** Quality assessment of eligible trials. A. Randomized Control Trial (RCT) B. Non-randomized studies of interventions (NRSI)

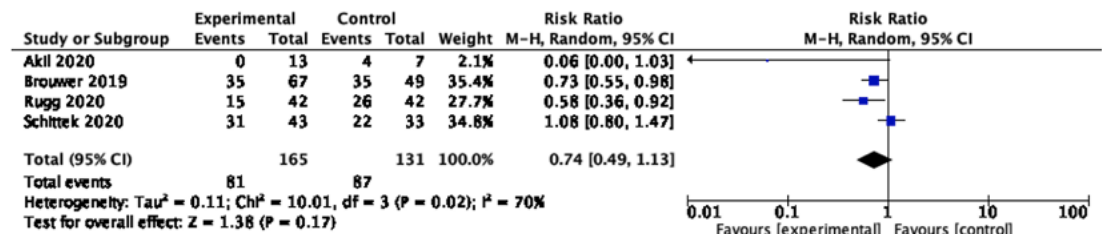


**Figure 3.** Forest Plot effect of Cytosorb in mortality at 28-30 days. A. Randomized Control Trial (RCT) B. Nonrandomized studies of interventions (NRSI)

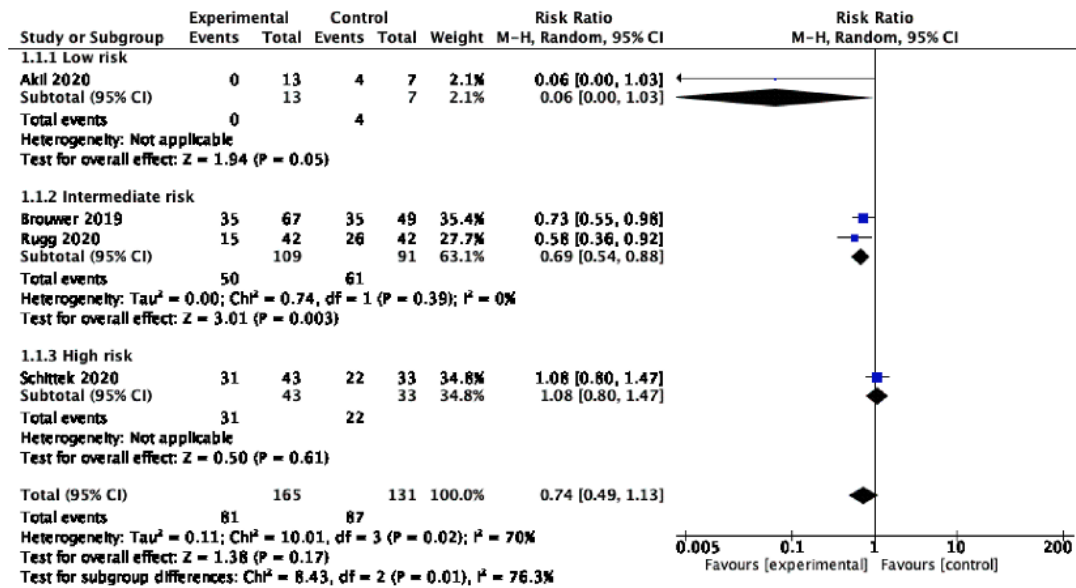
A. Randomized control trial



B. Non Randomized Interventions



**Figure 4.** Mortality in Non-randomized studies of interventions (NRSI) by disease severity subgroup meta-analysis.



**Table 1.** Characteristics of included studies

Study	Study design	Country	Specific population	Time of First CS Initiation	Duration of CS therapy	Mortality in CS group
<b>Hawchar, 2019</b>	RCT	Hungary	Septic Shock	Started within 24 h after ICU administration	24 hrs	0%
<b>Schadler, 2017</b>	RCT	Germany	Severe Sepsis or Septic Shock within 72hours of ARDS or acute lung injury	Enrolment within 72hrs of diagnosis of sepsis with ARDS/ALI	max 7x6hrs 24hrs apart	36%
<b>Akil, 2020</b>	Cohort historic control	Germany	Pneumogenic sepsis and ECMO	Within 6 hours after admission to our intensive care unit (ICU).	Min 2 x24 hrs without interruption	0%
<b>Brouwer, 2019</b>	Propensity-score-weighted retrospective study	The Netherlands	Septic Shock	Cytosorb was initiated at the discretion of the treating intensive care physician.	24 hrs, mean duration of 2.34 +- 0.16 days	52.20%
<b>Rough, 2020</b>	Propensity-score-weighted retrospective study	Austria	Primary or Secondary Sepsis	Initiation of Cytosorb therapy varied from 0.5 to 719 h after ICU admission, but most patients received treatment within the first days.	1-6 x 24 hrs without interruption	21.40%
<b>Schitteck, 2020</b>	Retrospective control group and prospective intervention group	Germany	Patients in severe septic shock with sepsis-associated acute kidney injury (SA-AKI)	No information	No information overall. Survivors, approximately one cartridge	76.70%



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perpatient was  
utilised as the  
median (IQR  
1, 2) for 35.5 h  
(17- 47).

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**Table 2.** Effect of studies on CRP and PCT levels

Study	Inicial CS	PCR	PCR 48 hr-CS	p value	Inicial PCT CS	PCT 48 hr-CS	p value
<b>Hawchar</b>	238.1 ± 95.5		169.54 ±86.4	>0.05	20.6 (6.5-144.5)	5.6 (1.9-54.4)	0.004
<b>Akil</b>	35±5		12±3	>0.05	15.6 ±5.4	2.71±1.5	0.03

**Table 3.** Effect of Studies on Predicted vs. Observed Mortality

Study	Observed Mortality CS	Predicted Mortality CS	p value	Observed Mortality CG	Predicted Mortality CG	p value
<b>Brouwer</b>	47,8%	74,5%	<0,001	51%	67,9%	0,035
<b>Rugg</b>	21,4%	85,7%	NR	47,6%	65,7%	NR

SUPPLEMENTARY MATERIAL

**Supplement Table 1. Search Strategy**

<b>Search Strategy Embase</b>		
#1	hemadsorption'/exp OR <b>hemadsorption</b>	1823
#2	'blood filter'/exp OR ' <b>blood filter</b> '	1782
#3	('sepsis'/exp OR <b>sepsis</b> ) AND ('septic shock'/exp OR ' <b>septic shock</b> ')	70839
#4	#1 OR #2	3399
#5	#4 AND #3	255
<b>Search Strategy Pubmed</b>		
#1	("Cytosorb"[tiab] OR "Cytokine adsor*"[tiab])	336
#2	(Sepsis [Mesh] OR Sepsis [tiab] OR sept* [tiab])	501952
#3	#1 AND #2	151
<b>Search Strategy Cochrane library</b>		
	cytosorb in Title Abstract Keyword AND sepsis in Title Abstract Keyword	20

## **CARTAS DE RESPUESTA A LAS OBSERVACIONES**

### **CARTA DE RESPUESTA 1 (RESPONSE LETTER-1)**

**Dear Sonia Elisabete Gaion Freitas**  
**Revista Brasileira de Terapia Intensiva Editorial Office**

Recently, we have received your decision on Manuscript ID RBTI-2022-0289, entitled "Cytokine Hemoadsorption with Cytosorb in Sepsis. A systematic Review and Meta-Analysis."

In relation to the comments made by two independent reviewers, we made some changes in our manuscripts. We have collected most of the observations and have substantially modified the conclusions, justification for the use of NRSI has been added and the risk of bias assessment process has been described, and the search has been updated.

We submit our new modified manuscript to get a new revision.

The reviewers comments were:

Reviewer 1-  
Major issues

1. The subgroup analysis based on "disease severity" has some major flaws and should be removed from the manuscript. First, the separation in three groups was done arbitrarily, without any previous reference in medical literature or physiological reason; Second, it is not possible to infer the disease severity based on observed mortality. Disease severity must be assessed by baseline data, including scores like APACHE or SAPS, or intensity of organ dysfunction. Observed mortality may be lower or higher than expected by baseline features, so, to assess whether severity of disease had an interaction with Cytosorb treatment, the authors would have to stratify patients according to baseline features (e.g., quartiles of SAP3), not by observed mortality. Third, this subgroup analysis included only two studies, both non-randomized, leading to a very high risk of bias. Considering these previous comments, I strongly suggest that authors remove this subgroup analysis from the entire manuscript.

Response: We think that it was a very good observation, so we remove severity subgroup metanalysis.

2. Although not mandatory, most medical journals suggest using the GRADE approach to rate the certainty of evidence in systematic reviews. I suggest that the authors include this framework in this review.

Response: We add a figure in relation to this topic, you can see it as figure 4, summary of finding for the main outcome.

3. One major limitation of this review was the high heterogeneity between studies regarding Cytosorb use, mainly in time to initiation, time of each session and number of sessions. This heterogeneity makes it difficult to interpret a meta-analysis of these studies, as we are aggregating different intervention schemes as if they were the same. Although the authors acknowledge this heterogeneity in the manuscript, I suggest that they elaborate further on this topic as a limitation of this review and as a suggestion for future studies (to deliver a common intervention schedule).

Response: We add some lines in the discussion related to this topic.

4. The authors should be cautious in the conclusion since the results of this review are

insufficient to support the use of Cytosorb in patients with sepsis outside clinical trials. There were only two RCTs, comprising only a quarter of the total sample of this study, all the included studies had high risk of bias and there was high heterogeneity. I believe that the major result of this systematic review was that there is insufficient data to support the use of Cytosorb in septic patients and that larger trials, with a common intervention arm are needed before adoption of this treatment. I suggest that authors modify the conclusion considering the comments above.

Response: We make the conclusion again.

#### Minor issues

1. I suggest that authors avoid the use of abbreviations in the abstract.

Response: We avoid the use of abbreviations in the abstract

2. In the methods, give more details about the time point in which mortality was assessed (30 days, 90 days, hospital discharge?).

Response: We add in methods the time point in which mortality was evaluated, it was 28-30 days, and it depends of the study.

3. The description of risk of bias assessment is confused. Please review it.

Response: We add supplemental tables about this topic, and we describe how the risk of bias was development.

4. I am not a statistician, but I believe that the authors may be able to summarize changes in vasopressor use with mean/median differences, which could be used to aggregate data on this outcome. This would make this outcome more informative for readers.

Response: It was not possible, due to some studies did not report the necessary statistics measurements (e.g., some reported median and range, but not mean and SD) or they were different kind of studies.

5. When describing the effect of intervention on inflammatory markers, please make sure to name abbreviations when used for the first time.

Response: We make modifications in order to name abbreviations when used for the first time.

6. Regarding adverse events, I got really surprised by the low incidence of reported adverse outcomes. Considering the intervention delivered (which involves an extracorporeal circuit and a venous access) I believe there is a high risk of underreporting in the studies. I suggest that the authors comment on this topic.

Response: We comment this in the discussion, also we add a new reference that suspect that the adverse effects were underreported and not systematically evaluated

7. Regarding the analysis of observed vs predicted mortality, would be interesting to know the results of the same analysis in the controls groups. I suggest that authors include this information in the main text if available.

Response: We included the information of reduction in predicted vs observed mortality in both groups.

8. I suggest that authors include in studies characteristics the cointerventions used in the studies, including ECMO and renal replacement therapy, if available.

Response: We included it in table 1

9. In the review flow chart, the authors state that 301 papers were excluded, 105 because were

case reports and 17 because were conference abstracts. And the other 179 papers? Why were they excluded?

Response: We made it again.

Reviewer 2-

Major issues

Suggestions:

Major suggestions:

-I couldn't figure out the meaning of this paragraph:

“Two studies, one RCT(10) and one cohort study (18), reported results for CRP and PCT, CRP levels did not differ significantly at 48 hrs. in both studies, however, PCT levels did show a reduction significant at 48 hrs. These results are shown in Table 2.”

Did the PCT level show a significant reduction or not? The reduction was compared to the baseline or to the control group? I'd suggest having this paragraph rewritten for better comprehension.

Response: We made this paragraph again

-I strongly recommend rewriting the conclusion so that only outcomes investigated in this paper are stated.

Response: We change the conclusion

-It is stated in the methods that reporting on interleukin levels were an inclusion criteria, but the result of only one study is shown. If it was an inclusion criteria, I'd suggest including the result of the combined results, and not only stating the result of the only study with a positive result.

Response: Interleukin 6 levels were included in the data we collected, but the inclusion criteria was inflammatory biomarker levels, and only one study report levels of IL-6

-Although stated in the Abstract that the primary outcome was mortality at 28-30, it is not clearly stated in the main text. I'd suggest including a paragraph with the main outcome and others outcomes of interest.

Response: We included it in the methodology.

-I'd suggest including the meaning of the initials in all the figures and tables, even if it is already stated in the main text.

Response: We made it

-I'd suggest including a declaration of conflict of interests.

Response: There is a COI disclosure in the updated files in the main page of the RBTI

Minor suggestions:

-I'd suggest shortening the introduction. The first paragraph, for example, could be shortened while maintaining the paper quality.

Response: We reduce some words in the first paragraph.

-I'd suggest including a reference for the Zotero software.

Response: We see many articles, but in any Systematic Review and metanalysis they do cite Zotero, so we did not consider referencing it.

-The initials NRSI (nonrandomized studies of interventions) are used in the text without stating the meaning; the meaning is only stated in the legend of a figure. I'd suggest including the meaning in the text, also.

Response: We added the meaning the first time we use it

-I believe this phrase about the ICU length of stay is incomplete: “Only one NRSI (18) found significant differences that the use of Cytosorb.”.

Response: We made this line again.

-There is a word missing in this sentence: “Three studies reported this outcome(10,18,20), two reported no adverse effects (10,18), and a single study reported a serious adverse

EFFECT/EVENT(20),”.

Response: We made this line again

-In the discussion, I'd suggest removing the word vasopressor highlighted: “These findings are consistent with multiple quasi-experimental before and after studies that indicate that the use of vasopressor therapy Cytosorb resulted in decreased doses of vasopressors,”.

Response: We removed the mentioned word.

Sincerely,

**Jiovany Jhan Carlos Saldana Gastulo**

**Corresponding author**

## CARTA DE RESPUESTA 2 (RESPONSE LETTER-2)

Dear Sonia Elisabete Gaion Freitas  
Revista Brasileira de Terapia Intensiva Editorial Office

Recently, we have received your decision on Manuscript ID RBTI-2022-0289, entitled "Cytokine Hemoadsorption with Cytosorb in Sepsis. A systematic Review and Meta-Analysis.". In relation to the comments made by two independent reviewers, we made some changes in our manuscripts. We have collected the observations and have substantially modified our manuscript.

We submit our new modified manuscript to get a new revision.

The comments were:

- Associate Editor

1) Use of terminology:

- For example, in the conclusion you say "Our study found a low certain quality evidence" and it would be better stated "Our study found low certainty evidence that (...)". The term quality is to be avoided when using GRADE terminology. Risk of bias is only one domain for increasing or reducing certainty of evidence.
- The reasons for downgrading must be explicit, in your case it is very low certainty evidence, due to imprecision, risk of bias and heterogeneity.

We change the terminology and add reasons for downgrading

2) PICO specification: I didn't find early in the manuscript the PICO specification, more specifically the control group. Usually cytosorb is conducted in patients undergoing dialysis. How did you define the control group?

- Figure 4 states placebo comparison? Please revise to "control" only. It's not possible to have a placebo arm in a trial of an equipment.
- Please specify the control group of each study in Table 1.

We specified control group on our Prospero Registry CRD42021262219, control group was defined by patients who undergo conventional therapy.

We think there is a confusion because cytosorb is usually conducted in patients undergoing renal replacement therapy, that is needed in patients who have acute renal failure and require hemodialysis, hemofiltration or hemodiafiltration that could be continuous or intermittent, however cytosorb can be used alone as hemoperfusion treatment or in combination with other therapies such as ECMO (extracorporeal membrane oxygenation).

We changed figure 4, we change "placebo arm" to "conventional therapy"

We specify control group in Table 1

3) Risk of bias ascertainment: you rated one study at high risk of bias in other domains because the group was hemodialysis without cytosorb. I don't find this sensible. This probably occurred because of the confusion regarding the PICO. Also, regarding blinding, if mortality is the outcome then outcome assessors can be considered at low risk of bias even if the study is not blinded, since one cannot ascertain death differently, although bias due to performance bias can occur and should be scrutinised based on process measures within the trial.

- Please modify the terminology "quality" assessment to "risk of bias" assessment.

We rated the study as a high risk of bias in other domains because in Hawchar's study every patient (control and cytosorb group) used a dialysis treatment "CytoSorb" was placed in a blood pump circuit using a renal replacement device (MultiFiltrate, Fresenius Medical Care, BadHomburg von der Höhe, Germany), with heparin anticoagulation and a blood flow rate of



250-400”, and you can see it at table 1 in this study, number of dialysis treatment 2.6 in cytosorb group and 2.1 in control group. That was the reason.

Regarding to our primary outcome. We know that there is not possible ascertain death differently, however we cannot find any risk of bias in the evaluation of this outcome.

We modified the terminology you writing for.

- Reviewer 1

1) I suggest that the authors review the writing of results section. There are some points for improvement as in page 10, lines 9, 21 and 29.

We wrote this lines again

2) In page 10, line 47, the authors report “Two NRSI-type (11,19) studies reported a decrease in predicted mortality over observed mortality”. Wouldn't it be the other way around?

We wrote it again.

3) In page 10, lines 40 and 52 I suggest changing “funding” for “found”.

We made this change.

4) In page 12, line 5, I suggest that the authors include a dot or a between the two ideas being discussed.

We made this change.

5) In page 12, line 19, state the meaning of the abbreviation “SR”.

We changed this sentence.

6) In figure 3, in part B of the forest plot I suggest modifying “Non Randomized Intervention” to “Nonrandomized studies of interventions” to comply with the entire manuscript.

We made this change.

7) In tables 2 to 5, I suggest the authors include legends describing the meaning of the abbreviations used (CG, CS) and the units of parameters analyzed (e.g., mcg/kg/min).

We made this change.

8) The number of tables and figures is excessive (4 figures and 5 tables). I suggest that the authors put the less relevant ones in the supplement or join tables 2, 3 and 4 in a single table.

We made this change.

- Reviewer 2

Major:

-The meaning of the initials used in Tables 2-5 should be stated.

We specified the meaning of initials.

-I'd suggest merging Tables 2-5 in one single Table of secondary outcomes.

We made this change.

-The difference in predicted vs observed mortality was observed both in the control and the Cytosorb group. I'd suggest avoiding stating that the reduction was higher in the CS group, since it could lead to misinterpretation of the data.

We made this change.

Minor:

-I suggest changing the last line in the Conclusion (both Abstract and Main Text), from “Further high-quality randomized trials with a common intervention arm are needed to confirm the benefit or harmful of Cytosorb in this kind of population” to “to evaluate the influence of

Cytosorb in this population”, since there is a possibility that the use of Cytosorb will cause neither harm nor benefit.

We made this change

-The meaning of CRP is presented in the line after the initials are first used.

We made this change.

-I suggest a revision of the punctuation, especially the use of commas.

We reviewed all the article grammar and punctuation.

Sincerely,

**Jiovany Jhan Carlos Saldana Gastulo**

**Corresponding author**

## VERSIÓN EN ESPAÑOL

# “Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metanálisis”

## INTRODUCCIÓN

La sepsis se define como una disfunción orgánica potencialmente mortal causada por una respuesta desregulada del huésped a la infección (1) y su estado más grave, el shock séptico, representa una condición altamente letal que causa una morbilidad y mortalidad sustanciales entre los pacientes en estado crítico (2). La fisiopatología de la sepsis es muy compleja e involucra muchos factores, como citocinas proinflamatorias y antiinflamatorias, patrones moleculares asociados a patógenos (PAMP), exotoxinas y endotoxinas bacterianas, micotoxinas, patrones moleculares asociados al daño (DAMP) liberados por células lesionadas y factores específicos del huésped, como el complemento activado y la procalcitonina (3). La inflamación generada puede conducir a una disfunción grave del sistema inmunitario que va desde el síndrome de respuesta inflamatoria sistémica desadaptativa destructiva (SIRS) hasta la inmunosupresión avanzada, que podría conducir a la disfunción orgánica multisistémica y la muerte (3,4).

A pesar del tratamiento precoz y los múltiples esfuerzos para reducir la mortalidad en sepsis y shock séptico, como la campaña de supervivencia a la sepsis, que brinda pautas de tratamiento (5), la mortalidad sigue siendo alta, alrededor del 20-40 % para la sepsis y del 40-60 % para el choque séptico (1,6,7), sin variaciones significativas en esta cifra en los últimos años; es por lo que se han descrito terapias adyuvantes, como las técnicas de purificación sanguínea, incluyendo la remoción extracorpórea de citoquinas por hemoadsorción (2,8–10).

Actualmente existen múltiples técnicas de purificación sanguínea, con diferentes resultados, a nivel de remoción de citoquinas, disminución de vasopresores e incluso disminución de la mortalidad, estas incluyen diálisis de alto volumen, membranas de alto corte, adsorción por filtración acoplada al plasma y filtros especiales de adsorción (como filtros Oxiris, Cytosorb, HA 330 y Polimixina B)(8,11). Las terapias de purificación de sangre se han utilizado en diferentes escenarios inflamatorios agudos, como sepsis, cirugía cardíaca y enfermedades autoinmunes; sin embargo, su uso es controvertido debido a la evidencia limitada, los resultados de los estudios contradictorios y la falta de ensayos controlados aleatorios a gran escala (ECA). La evidencia existente sobre la

efectividad de Cytosorb para mejorar los resultados de los pacientes aún es limitada, con resultados mixtos informados en varios estudios. Sin evidencia sólida de ensayos bien diseñados, es difícil sacar conclusiones definitivas sobre su eficacia (12,13). A pesar de una justificación teórica, el uso de métodos de purificación de sangre aún no puede recomendarse para pacientes con sepsis por falta de evidencia (14).

El Cytosorb es un cartucho compuesto por perlas de polímero de poliestireno-divinilbenceno con una cubierta de polivinilpirrolidona altamente porosa y biocompatible. Su tamaño estimado es de 300 a 800  $\mu\text{m}$  con una superficie total de más de 40.000  $\text{m}^2$ . La eliminación de sustancias de la sangre se basa en la captación de sustancias en los poros y la adsorción superficial. La duración típica de la terapia es de hasta 24 horas por sesión, diariamente durante 2 a 7 días consecutivos (8,15). La razón fisiológica para usar Cytosorb en el contexto de la sepsis es restablecer una respuesta equilibrada de mediadores proinflamatorios y antiinflamatorios. Se ha informado que las concentraciones circulantes elevadas de varias citoquinas, incluidas TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8 e IL-10, están asociadas con morbilidad y mortalidad en pacientes con sepsis, por lo que sería útil su eliminación. para el tratamiento (3,11).

## MÉTODOS

Se realizó una revisión sistemática de acuerdo con la declaración Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(16), se desarrolló un protocolo de investigación y se registró en la base de datos del registro prospectivo internacional de revisiones sistemáticas PROSPERO (CRD 42021262219) (17).

### *Fuentes de información y estrategia de búsqueda*

Realizamos una búsqueda sistemática en las bases de datos de PubMed, Embase y Cochrane Library. Se utilizaron encabezamientos de temas médicos (MeSH) o términos equivalentes. Se incluyeron artículos en inglés y español. Se creó una estrategia de búsqueda preliminar para MEDLINE/PUBMED, las otras búsquedas se adaptaron a bases de datos individuales (Tabla complementaria 1) y la búsqueda se realizó desde el inicio hasta noviembre de 2022. Además, se revisaron las referencias bibliográficas de los artículos seleccionados para identificar otras referencias relacionadas con el tema. La estrategia de búsqueda en medline se desarrolló de la siguiente manera:

("Cytosorb"[tiab] O "Cytokine adsor\*"[tiab]) Y (Sepsis [Mesh] O Sepsis [tiab] O sept\* [tiab]).

Para las bases de datos de Embase y The Cochrane Library se desarrolló la estrategia de búsqueda con los términos: “Cytosorb”, “Cytokine adsorción”, “hemadsorción”, “Septic shock” y “Sepsis”.

No incluimos ningún término relacionado con el resultado porque queríamos hacer una búsqueda amplia.

#### *Selección de estudios*

Los estudios relevantes fueron identificados por 2 revisores (ML y JS), quienes evaluaron de forma independiente utilizando los objetivos y la pregunta de la investigación (PICO), cuando no se llegó a un acuerdo, se incluyó a un tercer revisor (YH) miembro del grupo de investigadores y resolvió cualquier discrepancia. Los artículos seleccionados en cada base de datos fueron exportados al software Zotero donde se realizó la eliminación de duplicados.

Se incluyeron estudios que cumplieron con los siguientes criterios: 1) Pacientes adultos con sepsis o shock séptico, 2) Estudios de ECA (ensayo clínico aleatorizado), estudios de cohortes emparejados por puntaje de propensión (prospectivo o retrospectivo) o estudios con control histórico, 3) Pacientes que recibieron al menos una terapia de hemoadsorción con Cytosorb, además del tratamiento estándar, 4) Estudios que informaron sobre mortalidad a los 28-30 días, requerimiento para el uso de vasopresores, niveles de marcadores inflamatorios como IL-6, PCR y PCT y reacciones adversas. efectos del tratamiento con Cytosorb (CS). Los criterios de exclusión fueron los siguientes 1) Uso de CS en contextos distintos a sepsis y shock séptico (como pancreatitis, cirugía cardíaca, endocarditis, trasplante, trauma o en COVID-19), 2) Tipo de estudio o publicación de tipo informes de casos o cartas al editor, tampoco incluimos resúmenes de congresos, ni estudios antes y después sin grupo de comparación, 3) Estudios en neonatos o pacientes pediátricos, 4) Estudios que no reportan datos de mortalidad. Se consideró apropiado incluir estudios de intervenciones no aleatorizados (NRSI), debido al bajo número de ensayos clínicos encontrados según la pregunta de investigación.

#### *Extracción de datos y evaluación del riesgo de sesgo*

Se utilizó una hoja de extracción de datos estandarizada, dos revisores independientes (JS y LC) extrajeron los datos y los desacuerdos se resolvieron mediante discusión y consenso en caso de que no se llegara a un acuerdo se incluyó un tercer revisor (YH) que resolvió las discrepancias.

Se extrajo la siguiente información: nombre del autor principal, año de publicación, revista de publicación, lugar de estudio, criterios de inclusión y exclusión, población de

pacientes, tiempo de inicio de uso de la intervención, dosis de Cytosorb utilizada, edad media, número de pacientes, tasa de mortalidad general y por grupos, mortalidad prevista para los grupos. Además, se recopilaron datos sobre los cambios previos y posteriores al tratamiento en los marcadores inflamatorios y los niveles de vasopresores, si estaban disponibles.

Dos autores (JS y LC) realizaron la evaluación del riesgo de sesgo, utilizamos la herramienta de riesgo de sesgo (ROB) para los ECA(18) y el programa Review Manager 5.4 (Review Manager; The Nordic Cochrane Centre, Copenhagen, Dinamarca), Se utilizó la herramienta de evaluación del riesgo de sesgo para intervenciones no aleatorias (ROBINS I) (19) para los estudios de cohortes, según lo recomendado por la colaboración Cochrane. Es importante destacar que las evaluaciones de sesgo de ROBINS-I se realizan en función de la comparación entre un estudio dado y un ensayo teórico controlado aleatorizado con un diseño ideal para la pregunta del estudio, que representa el estándar para un "estudio de bajo riesgo". (Tabla complementaria 2 y 3)

#### *Síntesis y análisis de datos*

Los resultados se analizaron mediante el método estadístico de Mantel-Hansel y los modelos de efectos aleatorios de Der Simonian-Laird, en relación a la alta heterogeneidad entre los estudios, ya que los estudios no eran equivalentes, diferían en el tiempo de inicio, la duración de la terapia, el tipo de administración y el origen de la sepsis, entre otras características, que podrían haber afectado los resultados y por lo tanto no se debe asumir un tamaño del efecto común. Se calcularon los riesgos relativos (RR) para la mortalidad general, con un IC del 95 %, para los grupos de tratamiento convencional y de tratamiento con CS. La síntesis cuantitativa no se realizó cuando solo se identificó un estudio por desenlace o los estudios tenían un tipo de diseño diferente, o cuando los estudios no reportaron las estadísticas necesarias, en ese escenario se limitaron a una descripción cualitativa.

Para el análisis se utilizó el programa Review Manager 5.4 (Review Manager; The Nordic Cochrane Centre, Copenhagen, Dinamarca) y se consideró significativo un valor de  $p < 0,05$ .

No se evaluó el sesgo de publicación debido al número de estudios incluidos.

## **RESULTADOS**

#### *Resultados de la búsqueda y características del estudio*

Nuestra estrategia de búsqueda identificó 332 citas, de las cuales 32 se consideraron potencialmente elegibles según los títulos o los resúmenes, o ambos, y se obtuvieron

los textos completos. Se excluyeron 26 artículos después de revisar el texto completo, 14 por no tener un grupo de comparación, 7 por un resultado diferente o población mixta, 3 por estar en proceso, 1 por un tipo diferente de artículo y 1 por ser una publicación secundaria. Finalmente, se incluyeron 6 estudios (2 ECA y 4 estudios de Cohorte) con 413 pacientes (9–11,20–22). La Figura 1 muestra nuestro diagrama de flujo de selección de estudios.

Los pacientes en los estudios incluidos tenían diferentes causas de sepsis y shock séptico. Además, diferían en la modalidad, hora de inicio y número de sesiones de tratamiento de CS. La Tabla 1 resume las características de los estudios incluidos.

#### *Riesgo de sesgo en los estudios incluidos*

Los ECA presentaron alto riesgo de sesgo, en ninguno de ellos fue posible cegar la intervención para los evaluadores de resultado. Los estudios de cohortes presentaron un riesgo moderado a severo. La evaluación del riesgo de sesgo se muestra en la Figura 2.

#### *Efecto sobre la mortalidad a los 28-30 días*

La mortalidad global fue del 45 % (42 % del grupo de intervención y 48 % del grupo de control) (9–11,20–22), y solo un estudio mostró una mortalidad superior al 70 % (9). Se realizó una revisión cuantitativa, no encontrando efecto significativo sobre la mortalidad a los 28-30 días RR 0,98 [0,12-8,25] para el ECA y RR 0,74 [0,49-1,13] para NRSI. Los resultados se muestran en la Figura 3, y la tabla de resumen de hallazgos se muestra en la Figura 4.

#### *Efecto sobre el uso de vasopresores*

Dos estudios, un ECA (10) y un estudio de cohortes (20) informaron el uso de vasopresores como resultado; ambos informaron una disminución significativa en los niveles de vasopresores en el grupo de intervención, sin embargo, esta reducción también se mostró en el grupo de control. Tabla 2.

#### *Efecto sobre los niveles de marcadores inflamatorios*

Solo un estudio informó una disminución del 5-18% en los niveles de IL-6 (interleucina-6) (22), sin embargo, no se encontró significación estadística.

Dos estudios, un ECA(10) y un estudio de cohorte(20), informaron resultados para PCR (proteína c reactiva). En el ECA, los niveles de PCR no mostraron diferencia estadística, sin embargo, en el otro estudio, se encontró una diferencia significativa en el grupo CS. Estos resultados se muestran en la Tabla 2.

Con respecto a los niveles de PCT (procalcitonina), dos estudios, un ECA(10) y un estudio de cohorte(20) reportaron una disminución significativa en los niveles de PCT en comparación con el nivel basal, sin embargo, esta reducción significativa no se encontró en el grupo control. Estos resultados se muestran en la Tabla 2.

#### *Efecto sobre la mortalidad prevista frente a la observada*

Dos estudios tipo NRSI (11,21) informaron una disminución en la mortalidad observada sobre la mortalidad prevista. Brouwer et al.(21) 75% vs 52,2% y Rugg et al. (11) 85,1% frente a 21,4%. En ambos estudios, la mortalidad prevista se calculó mediante la puntuación SOFA; sin embargo, la reducción de la mortalidad predicha vs observada también se encontró en el grupo control. La Tabla 2 resume los hallazgos.

#### *Efecto sobre la duración de la estancia en la UCI*

Cinco estudios informaron el efecto sobre la estancia en la UCI (9–11,20,21), sin embargo, solo dos de ellos(10,20) (un RCT y un NRSI) informaron SD, por lo que no se realizó una síntesis cuantitativa. Solo un NRSI (20) encontró diferencias significativas a favor del uso de Cytosorb.

#### *Efecto sobre los eventos adversos*

Tres estudios informaron este resultado (10,20,22), dos no informaron efectos adversos (10,20) y el otro informó un evento adverso grave (22), que se identificó como probablemente relacionado con el uso de Cytosorb, fue una disminución en el recuento de plaquetas. En este mismo estudio, se informaron 3 interrupciones del tratamiento en 3 pacientes durante el estudio debido a eventos adversos probablemente relacionados con la terapia.

## **DISCUSIÓN**

Hasta donde sabemos, esta es la primera revisión sistemática que evalúa el uso de Cytosorb, un dispositivo de hemoadsorción, en el contexto de sepsis y shock séptico, que incluye ensayos clínicos y estudios de cohorte. Nuestro estudio encontró evidencia heterogénea y de muy baja calidad en la que no se demuestra beneficio del uso de Cytosorb sobre la mortalidad. El riesgo de sesgo para los ECA fue alto y para los NRSI fue de riesgo moderado a grave. Además, los intervalos de confianza en los ECA fueron amplios debido probablemente a la heterogeneidad, por lo que investigaciones futuras de mayor calidad podrían cambiar o modificar los resultados encontrados.

Se encontró una heterogeneidad moderada en los ECA ( $I^2=57\%$ ) y alta entre los NRSI



(I<sup>2</sup>=70%), esto podría explicarse por las diferentes etiologías de la sepsis, la gravedad de la enfermedad, diferentes tipos de intervenciones como ECMO o CRRT y el modo de uso de la terapia. Esta heterogeneidad dificulta la interpretación de un metaanálisis de estos estudios. Asimismo, se ha descrito que el I<sup>2</sup> podría subestimar la heterogeneidad hasta en 28 puntos porcentuales cuando el número de estudios es limitado (21). Teniendo en cuenta que en nuestro estudio encontramos una alta heterogeneidad clínica y pocos estudios, suponemos que la heterogeneidad medida con este estadístico podría estar subestimada.

Dos metanálisis previos han evaluado el uso de purificación de sangre extracorpórea en sepsis (24,25), a diferencia de nuestro estudio, no se centraron en el uso de hemadsorción de Cytosorb, y tampoco incluyeron estudios de cohortes, sin embargo, incluyeron los mismos ECA (10,22), encontrando resultados similares. Existe un metaanálisis publicado recientemente que evaluó el uso de Cytosorb en pacientes críticos, este estudio encontró evidencia de certeza baja que muestra que el uso de Cytosorb podría aumentar la mortalidad, sin embargo, no encontró diferencias en los eventos adversos. (25)

Encontramos una disminución significativa en el uso de vasopresores en dos estudios (10,20), pero no realizamos una síntesis cuantitativa por ser de diferente tipo. Estos hallazgos son consistentes con múltiples estudios cuasiexperimentales de antes y después que indican que el uso de la terapia con Cytosorb resultó en una disminución de las dosis de vasopresores, estabilización hemodinámica y mejoría en los parámetros metabólicos (2,27–30). Algunos estudios informan que el uso temprano (dentro de las primeras 24 a 48 horas), el volumen de sangre filtrado y la duración prolongada de la terapia con Cytosorb se asociaron con una mortalidad más baja (2,22,29,31–33), desafortunadamente, no todos los estudios informaron estas variables

En cuanto a los niveles de marcadores inflamatorios, se ha descrito que Cytosorb es eficaz *in vitro* para la eliminación de citocinas tanto inflamatorias como proinflamatorias, así como para la disminución de los niveles de PCR y procalcitonina (3,34); y que los niveles de citocinas se correlacionan tanto con la gravedad de la enfermedad como con la mortalidad (35,36). En esta revisión, solo un estudio reportó una disminución no significativa de IL-6 (22) y dos estudios reportaron una disminución en los niveles de PCR y procalcitonina (10,20), estos hallazgos coinciden con estudios antes y después, no incluidos en esta revisión, donde se demostró que Cytosorb reduce los niveles de marcadores inflamatorios (29,30,37,38).

La mortalidad predicha basada en la puntuación SOFA se calculó en dos estudios; desafortunadamente, estos hallazgos no pudieron metaanalizarse debido a la falta de datos en uno de los estudios (11). En ambos estudios se encontró una reducción entre

la mortalidad observada y la predicha. Estos hallazgos son similares a los reportados en otros estudios no incluidos (33,39).

Cytosorb se considera un dispositivo biocompatible y hemo compatible (13), los estudios en cirugía cardíaca y sepsis sugieren que Cytosorb no induce coagulopatía, hemólisis o efectos secundarios clínicamente relevantes (29,40,41), esto parece coincidir con los hallazgos de la presente revisión, donde solo se informó un evento adverso grave relacionado con la terapia, sin embargo, vale la pena mencionar que el uso de Cytosorb en el contexto de la sepsis generalmente es más prolongado y que Cytosorb puede influir en la eliminación o disminución de las concentraciones séricas de algunos medicamentos, y la mayoría de las veces requiere la realización de intervenciones que incluyeron ECMO y terapia de reemplazo renal, por lo que, al igual que en otros estudios, sospechamos que los efectos adversos fueron subreportados y no evaluados sistemáticamente. (26)

Una limitación importante es que el metanálisis solo se realizó para el desenlace principal, no lo realizamos para los desenlaces secundarios debido al pequeño número de estudios encontrados, la poca cantidad de pacientes incluidos y la falta de datos estadísticos como la DS. Los estudios tuvieron un riesgo de sesgo de moderado a alto, principalmente debido a la confusión y al sesgo de selección de los participantes del estudio. Cabe señalar que, en realidad, el número de estudios que evalúan el uso de Cytosorb en sepsis y shock séptico es limitado. Además, el número de pacientes incluidos en cada estudio también fue bajo, lo que disminuye el poder estadístico individual de cada estudio y afecta los resultados globales.

Nuestra revisión tiene otras limitaciones. En primer lugar, no incluimos estudios no publicados, ni realizamos una búsqueda en la literatura gris, ni incluimos resúmenes de congresos o artículos no originales. Además, no incluimos otras bases de datos como WOS y Scopus. En segundo lugar, no se incluyeron estudios sin grupo control, ya que nuestro principal objetivo era evaluar la mortalidad. En tercer lugar, el tiempo de inicio, la duración de la terapia, el volumen de sangre filtrada y la cantidad de cartuchos utilizados para la misma fueron diferentes o no se describieron en algunos estudios, lo que podría haber afectado el resultado. En cuarto lugar, solo un estudio no utilizó terapia de reemplazo renal (TRS) y dos de ellos la usaron de acuerdo con las necesidades del paciente, ya que se sabe que la insuficiencia renal aguda puede amplificar la cascada séptica inducida por las endotoxinas, por lo que el uso de TRS podría tener afectado el resultado. En quinto lugar, nuestro estudio se ha centrado únicamente en la mortalidad a corto plazo.

## CONCLUSIONES

Nuestro estudio encontró evidencia de certeza muy baja que no muestra ningún beneficio del uso de Cytosorb en la mortalidad a los 28-30 días. Sobre la base de la evidencia existente, no se pueden sacar conclusiones definitivas sobre el impacto de Cytosorb en la mortalidad de pacientes con sepsis o shock séptico. Por lo tanto, en este momento, no podemos recomendar el uso de Cytosorb en pacientes sépticos o con shock séptico fuera de los ensayos clínicos. Se necesitan más ensayos aleatorios de alta calidad con un brazo de intervención común para evaluar la influencia de Cytosorb en esta población.

## Declaración de conflicto de intereses

Los autores declaran que no existe conflicto de intereses.

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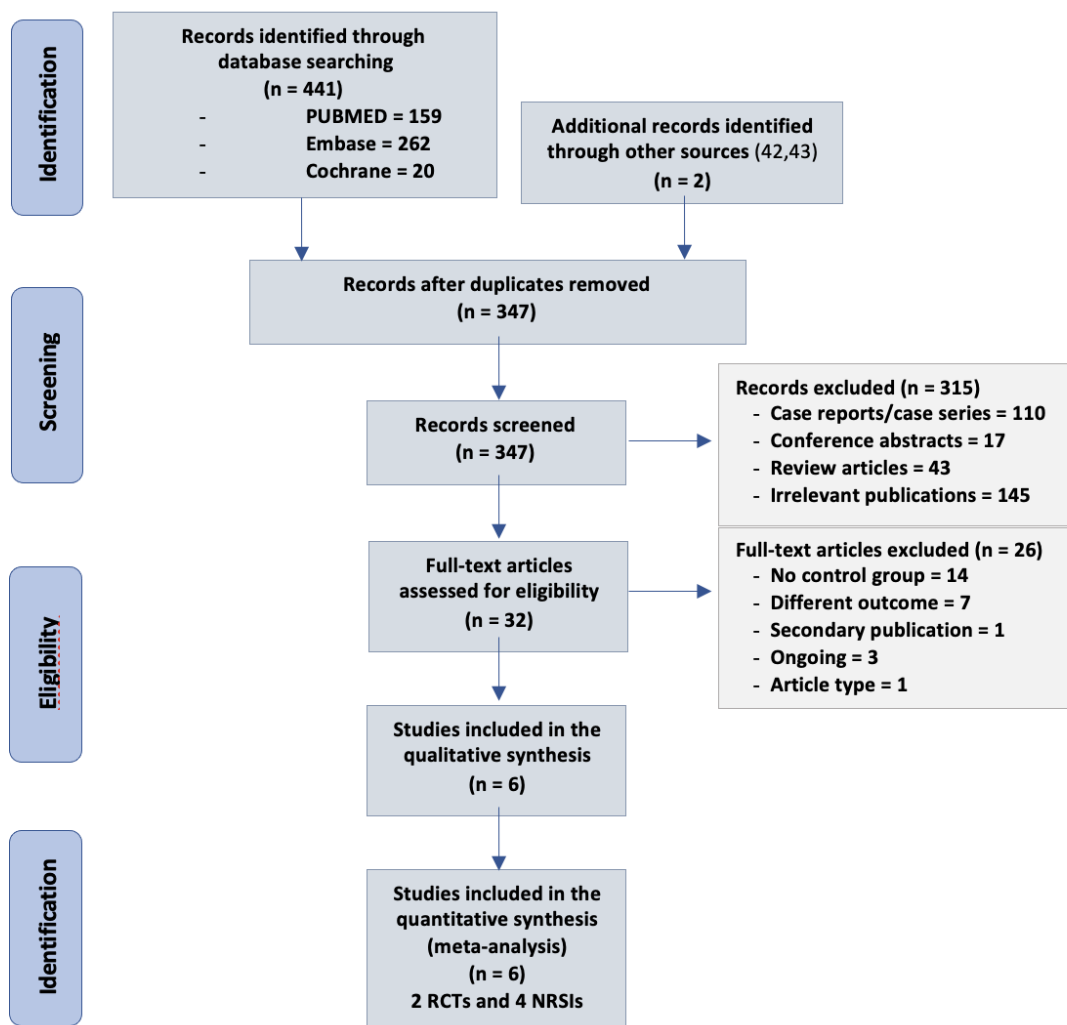
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**FIGURA 1. Diagrama de flujo de la selección de estudios.**



RCT (Randomized control trial)  
NRSI (Non randomized studies of interventions)

FIGURA 2.- Evaluación del riesgo de sesgo de los estudios elegibles. A. Ensayo de control aleatorizado (ECA) B. Estudios de intervenciones no aleatorizados (NRSI)

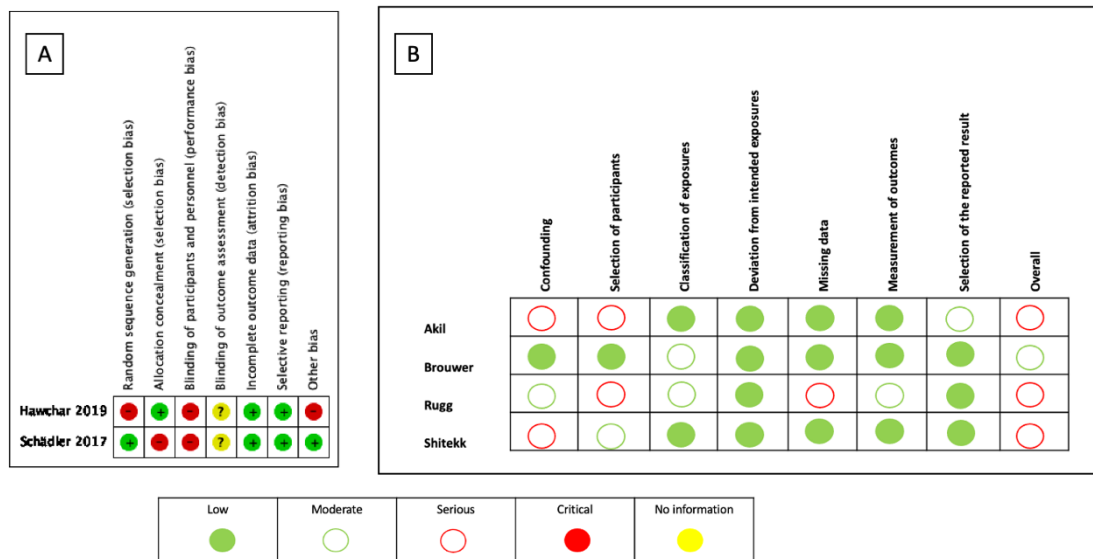
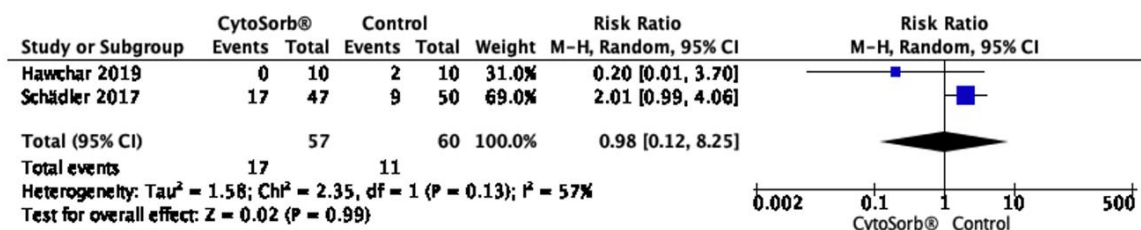
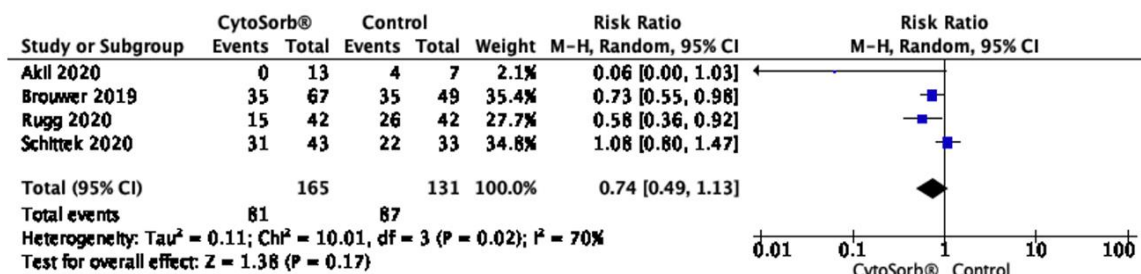


FIGURA 3.- Forest Plot. Efecto de Cytosorb en la mortalidad a los 28-30 días. A. Ensayo controlado aleatorizado (ECA) B. Estudios no aleatorizados de intervenciones (NRSI)

A. Randomized control trial



B. Non Randomized Studies of Interventions



**FIGURA 4.- Resumen de resultados de la comparación principal**

<b>Cytosorb compared to placebo for sepsis and septic shock</b>					
<b>Patient or population:</b> Sepsis and septic shock					
<b>Setting:</b> Intensive care units Germany, Hungary, The Netherlands, and Austria					
<b>Intervention:</b> CytoSorb					
<b>Comparison:</b> Conventional therapy					
Outcomes	Participants in studies (n) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Cytosorb
Mortality-RCT	117 (2 RCTs)	⊕○○○ Very low*†‡	<b>RR 0.98</b> (0.12 to 8.25)	183 per 1,000	<b>4 fewer per 1,000</b> (161 fewer to 1,329 more)
Mortality-observational studies	296 (4 observational studies)	⊕○○○ Very low§¶	<b>RR 0.74</b> (0.49 to 1.13)	664 per 1,000	<b>173 fewer per 1,000</b> (339 fewer to 86 more)
The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).					
<b>GRADE Working Group grades of evidence</b>					
<b>High certainty:</b> we are very confident that the true effect lies close to that of the estimate of the effect.					
<b>Moderate certainty:</b> 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.					
<b>Low certainty:</b> our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.					
<b>Very low certainty:</b> we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.					

\* Se decidió disminuir dos niveles por el alto riesgo de sesgo; † se decidió disminuir un nivel debido a los diferentes resultados; ‡ se decidió disminuir dos niveles debido al amplio intervalo de confianza; § se decidió disminuir dos niveles debido a los diferentes resultados; ¶ se decidió disminuir dos niveles debido al amplio intervalo de confianza. GRADE - Graduación de Evaluación de Recomendaciones, Desarrollo y Evaluación; IC del 95 %: intervalo de confianza del 95 %; ECA - ensayo controlado aleatorizado; RR - relación de riesgo.



**Tabla 1 - Características de los estudios incluidos**

Estudio	Diseño del estudio	País	Población específica	Grupo control	Tiempo de inicio 1era terapia CS	Duración de la terapia CS	Mortalidad en grupo CS
<b>Hawchar, 2019</b>	ECA	Hungría	Choque séptico	Pacientes con shock séptico de origen médico, en ventilación mecánica, noradrenalina > 10 µg/min, procalcitonina (PCT) > 3 ng/mL sin necesidad de terapia renal sustitutiva.	Comenzó dentro de las 24 h posteriores a la admisión en la UCI	24 hrs	0%
<b>Schadler, 2017</b>	ECA	Alemania	Sepsis grave o choque séptico dentro de las 72 horas posteriores al SDRA y la lesión pulmonar aguda	Pacientes ventilados mecánicamente con sepsis grave o shock séptico en el contexto de lesión pulmonar aguda (LPA) o síndrome de dificultad respiratoria aguda establecido en las últimas 72 horas.	Inscripción dentro de las 72 horas del diagnóstico de sepsis con ARDS/ALI	max 7x6hrs cada 24hrs	36%
<b>Akil, 2020</b>	Cohorte con control histórico	Alemania	Sepsis neumónica y ECMO	Cohorte histórica. Pacientes con shock séptico neumogénico que acompaña a insuficiencia respiratoria aguda, monitorización hemodinámica invasiva y demanda de norepinefrina 0,3 µg/min; concentraciones elevadas de lactato 2,0 mmol/L; y un nivel sérico de procalcitonina (PCT) de 1 ng/mL fueron elegibles.	Dentro de las 6 horas posteriores al ingreso en nuestra unidad de cuidados intensivos (UCI).	Min 2 x24 hrs sin interrupción	0%
<b>Brouwer, 2019</b>	Estudio retrospectivo Ponderado por puntaje de propensión	Países bajos	Choque séptico	Pacientes con shock séptico tratados con CRRT sin Cytosorb. Se aplicó el peso del tratamiento de probabilidad inversa estabilizado.	CS se inició a criterio del médico intensivista tratante.	24 hrs, duración media de 2.34 +- 0.16 días	52.20%

<b>Rough, 2020</b>	Estudio retrospectivo Ponderado por puntaje de propensión	Austria	Sepsis Primaria o Secundaria	Los controles emparejados fueron tratados por shock séptico y requirieron TSR, pero no recibieron terapia con Cytosorb. Se aplicó una puntuación de propensión generalizada y el método de coincidencia de distancia de Mahalanobis (coincidencia 'genética').	El inicio de la terapia con CS varió de 0,5 a 719 h después de la admisión en la UCI, pero la mayoría de los pacientes recibieron tratamiento dentro de los primeros días.	1-6 x 24 hrs sin interrupción	21.40%
<b>Schittek, 2020</b>	Grupo de control retrospectivo y grupo de intervención prospectivo	Alemania	Pacientes en shock séptico severo con lesión renal aguda asociada a sepsis	Controles retrospectivos con choque séptico (ascendente dosis de noradrenalina superior a 20 µg/min.) con lesión renal aguda asociada a sepsis en CVVHDF	No información	No hay información en general. Sobrevivientes, se utilizó aproximadamente un cartucho por paciente como mediana (IQR 1, 2) durante 35,5 h (17-47).	76.70%

**Tabla 2. Efecto de Cytosorb en los outcomes secundarios**

<b>Niveles de Norepinefrina (NE) en ug/kg/min</b>						
Estudio	NE T0-CG	NE 48hrs-CG	p	NE T0-CS	NE 48hrs-CS	p
Hawchar	0.43[0.19–0.64]	0.25[0.08–0.65]	NR	0.54 [0.20-1.22]	0.16 [0.07-0.48]	0.016
Akil	0.83 +-0.16	0.38 +- 0.11	0.05	0.603 +-0.08	0.009+- 0.005	0.0001
<b>Niveles de proteína C reactiva (PCR) en mg/L</b>						
Study	PCR T0-CG	PCR 48hrs-CG	p	PCR T0-CS	PCR 48 hr-CS	p
Hawchar	307.4 +-116.7	189.9 +-48.5	NS	238.1 +- 95.5	169.54 +-86.4	NS
Akil	27.2+-2.9	22.6+-3.1	0.31	35+-5	12+-3	0.002
<b>Niveles de Procalcitonina (PCT) en ng/mL</b>						
Study	PCT T0-CG	PCT 48 hr-CG	p	PCT T0-CS	PCT 48 hr-CS	p
Hawchar	13.2 [7.6-47.8]	9.2 [3.8-44.2]	NR	20.6 [6.5-144.5]	5.6 [1.9-54.4]	0.004
Akil	13.14 +- 9.7	8.14 +-5.9	0.68	15.6 +-5.4	2.71+-1.5	0.03
<b>Predicted vs. Observed Mortality</b>						
Study	Mortalidad observada CG	Mortalidad predicha CG	p	Mortalidad observada CS	Mortalidad predicha CS	p
Brouwer	51%	67,9%	0,035	47,8%	74,5%	<0,001
Rugg	47,6%	65,7%	NR	21,4%	85,7%	NR

\*CG (grupo control) †CS (grupo Cytosorb) ‡ Rango §Desviación estándar

## MATERIAL SUPLEMENTARIO

### Tabla complementaria 1. Estrategia de búsqueda

<b>Estrategia de búsqueda en Embase</b>		
#1	hemadsorption'/exp OR <b>hemadsorption</b>	1875
#2	'blood filter'/exp OR ' <b>blood filter</b> '	1845
#3	('sepsis'/exp OR <b>sepsis</b> ) AND ('septic shock'/exp OR ' <b>septic shock</b> ')	72608
#4	#1 OR #2	3488
#5	#4 AND #3	262
<b>Estrategia de búsqueda en Pubmed</b>		
#1	("Cytosorb"[tiab] OR "Cytokine adsor*"[tiab])	367
#2	(Sepsis [Mesh] OR Sepsis [tiab] OR sept* [tiab])	51303
#3	#1 AND #2	159
<b>Estrategia de búsqueda en Cochrane library</b>		
	cytosorb in Title Abstract Keyword AND sepsis in Title Abstract Keyword	20

**Tabla complementaria 2. Consenso de puntuación ROB por dominio para los estudios incluidos (25)**

<b>Hawchar, 2019, J Crit Care</b>	
<b>Sesgo</b>	<b>Consenso</b>
Generación de secuencia aleatoria	<b>Alto riesgo.</b> Asignación al azar en bloque por el autor del estudio que también participó en el reclutamiento
Ocultamiento de asignación	<b>Riesgo bajo.</b> Sobres sellados
Cegamiento de participantes y Personal	<b>Alto riesgo.</b> No procedimiento falso
Cegamiento de la evaluación de resultados	<b>Riesgo poco claro.</b> No descrito
Datos de resultados incompletos	<b>Riesgo bajo.</b> No se ha informado de pérdida de datos
Informes selectivos	<b>Riesgo bajo.</b> Resultados informados
Otro sesgo	<b>Alto riesgo.</b> Diálisis realizada en pacientes del grupo control

<b>Schadler, 2017 PLOS One</b>	
<b>Sesgo</b>	<b>Consenso</b>
Generación de secuencia aleatoria	<b>Riesgo bajo.</b> Aleatorización de bloques
Ocultamiento de asignación	<b>Alto riesgo.</b> Sobres cerrados pero múltiples infracciones
Cegamiento de participantes y Personal	<b>Alto riesgo.</b> Sin procedimiento falsa
Cegamiento de la evaluación de resultados	<b>Riesgo poco claro.</b> No descrito
Datos de resultados incompletos	<b>Riesgo bajo.</b> Exclusiones contabilizadas
Informes selectivos	<b>Riesgo bajo.</b> Resultados informados
Otro sesgo	<b>Riesgo bajo.</b> Sin descripción

**Tabla complementaria 3. Consenso de puntuación de ROBIN-I por dominio para los estudios incluidos**

Akil et al., 2020	
Dominio	Consensus
<p><b>Sesgo debido a la confusión:</b> La confusión inicial ocurre cuando una o más variables pronósticas (factores que predicen el resultado de interés) también predicen la intervención recibida al inicio.</p>	<p><b>Riesgo grave.</b> Se menciona que una "Indicación para la terapia ECMO fue el deterioro clínico por insuficiencia respiratoria aguda". Además, la tabla de características de los participantes muestra que los incluidos en el grupo CytoSorb tenían una puntuación SAPS II más alta.</p>
<p><b>Sesgo en la selección de participantes en el estudio:</b> Cuando la exclusión de algunos participantes elegibles, o el tiempo de seguimiento inicial de algunos participantes, o algunos eventos de resultado están relacionados tanto con la intervención como con el resultado, habrá una asociación entre las intervenciones y el resultado incluso si los efectos de las intervenciones son idénticos.</p>	<p><b>Riesgo grave.</b> Se menciona que los autores "recolectaron parámetros clínicos y datos de resultados de una cohorte histórica en nuestra institución con insuficiencia respiratoria aguda debido a sepsis neumógena, que fueron tratados con ECMO y terapia de atención estándar en el período anterior a enero de 2018". No se menciona el período de tiempo anterior a enero de 2018, en el que se realizó la búsqueda de casos de control..</p>
<p><b>Sesgo en la clasificación de las intervenciones:</b> Sesgo introducido por la clasificación errónea diferencial o no diferencial del estado de la intervención. La clasificación errónea no diferencial no está relacionada con el resultado y, por lo general, sesgará el efecto estimado de la intervención hacia el valor nulo. La clasificación errónea diferencial ocurre cuando la clasificación errónea del estado de la intervención está relacionada con el resultado o el riesgo del resultado, y es probable que conduzca a un sesgo.</p>	<p><b>Riesgo bajo.</b> Intervención bien definida</p>
<p><b>Sesgo debido a desviaciones de las intervenciones previstas:</b> Sesgo que surge cuando existen diferencias sistemáticas entre la intervención experimental y los grupos de comparación en la atención brindada, que representan una desviación de la(s) intervención(es) prevista(s). La evaluación del sesgo en este dominio dependerá del tipo de efecto de interés (ya sea el efecto de la asignación a la intervención o el efecto de comenzar y adherirse a la intervención).</p>	<p><b>Riesgo bajo.</b> Los autores mencionaron que todos los pacientes "fueron tratados siguiendo las guías de tratamiento de la sepsis".</p>
<p><b>Sesgo debido a la falta de datos:</b> Sesgo que surge cuando falta un seguimiento posterior para los individuos inicialmente incluidos y seguidos (como la pérdida diferencial durante el seguimiento que se ve afectada por factores pronósticos); sesgo debido a la exclusión de individuos a los que les faltaba información sobre el estado de la intervención u otras variables como los factores de confusión.</p>	<p><b>Riesgo bajo.</b> No se excluyó a pacientes por falta de datos.</p>
<p><b>Sesgo en la medición de los resultados:</b> Sesgo introducido por errores diferenciales o no diferenciales en la medición de los datos de resultado. Tal sesgo puede surgir cuando los evaluadores de resultado conocen el estado de la intervención, si se utilizan diferentes métodos para evaluar los resultados en diferentes grupos de intervención, o si los errores de medición están relacionados con el estado o los efectos de la intervención.</p>	<p><b>Riesgo bajo.</b> No hubo diferencia en la medición de los resultados en ambos grupos.</p>
<p><b>Sesgo en la selección del resultado informado:</b> Informe selectivo de los resultados de una manera que depende de los hallazgos y evita que la estimación se incluya en un metanálisis (u otra síntesis).</p>	<p><b>Riesgo moderado.</b> Los resultados clínicos y de laboratorio más importantes se informaron en el estudio. Sin embargo, no se hicieron comparación entre grupos.</p>
<p><b>Juicio General de riesgo de sesgo</b></p>	<p><b>Riesgo grave.</b> Dos dominios fueron calificados como serios.</p>

<b>Brouwer et al., 2019</b>	
<b>Dominio</b>	<b>Consenso</b>
<p><b>Sesgo debido a la confusión:</b> La confusión inicial ocurre cuando una o más variables pronósticas (factores que predicen el resultado de interés) también predicen la intervención recibida al inicio.</p>	<p><b>Riesgo bajo.</b> Los autores realizaron un análisis utilizando la probabilidad inversa de los pesos de tratamiento (IPTW) para evitar sesgos.</p>
<p><b>Sesgo en la selección de participantes en el estudio:</b> Cuando la exclusión de algunos participantes elegibles, o el tiempo de seguimiento inicial de algunos participantes, o algunos eventos de resultado están relacionados tanto con la intervención como con el resultado, habrá una asociación entre las intervenciones y el resultado incluso si los efectos de las intervenciones son idénticos.</p>	<p><b>Riesgo bajo.</b> Los pacientes solo fueron excluidos del estudio, en caso de que el diagnóstico primario del paciente no fuera shock séptico.</p>
<p><b>Sesgo en la clasificación de las intervenciones:</b> Sesgo introducido por la clasificación errónea diferencial o no diferencial del estado de la intervención. La clasificación errónea no diferencial no está relacionada con el resultado y, por lo general, sesgará el efecto estimado de la intervención hacia el valor nulo. La clasificación errónea diferencial ocurre cuando la clasificación errónea del estado de la intervención está relacionada con el resultado o el riesgo del resultado, y es probable que conduzca a un sesgo.</p>	<p><b>Riesgo moderado.</b> Algunos pacientes que comenzaron con CytoSorb después de CRRT se incluyeron en el grupo CytoSorb</p>
<p><b>Sesgo debido a desviaciones de las intervenciones previstas:</b> Sesgo que surge cuando existen diferencias sistemáticas entre la intervención experimental y los grupos de comparación en la atención brindada, que representan una desviación de la(s) intervención(es) prevista(s). La evaluación del sesgo en este dominio dependerá del tipo de efecto de interés (ya sea el efecto de la asignación a la intervención o el efecto de comenzar y adherirse a la intervención).</p>	<p><b>Riesgo bajo.</b> Los pacientes fueron tratados según el protocolo como parte del estándar de atención, es decir, no se aplicaron intervenciones para el propósito de este estudio.</p>
<p><b>Sesgo debido a la falta de datos:</b> Sesgo que surge cuando falta un seguimiento posterior para los individuos inicialmente incluidos y seguidos (como la pérdida diferencial durante el seguimiento que se ve afectada por factores pronósticos); sesgo debido a la exclusión de individuos a los que les faltaba información sobre el estado de la intervención u otras variables como los factores de confusión.</p>	<p><b>Riesgo bajo.</b> No se excluyó a ningún paciente por falta de datos.</p>
<p><b>Sesgo en la medición de los resultados:</b> Sesgo introducido por errores diferenciales o no diferenciales en la medición de los datos de resultado. Tal sesgo puede surgir cuando los evaluadores de resultado conocen el estado de la intervención, si se utilizan diferentes métodos para evaluar los resultados en diferentes grupos de intervención, o si los errores de medición están relacionados con el estado o los efectos de la intervención.</p>	<p><b>Riesgo bajo.</b> Los criterios de valoración estaban claramente definidos "La mortalidad por todas las causas se midió desde el ingreso en la UCI hasta 28 días después del ingreso (independientemente de la mortalidad en la UCI, dentro o fuera del hospital)</p>
<p><b>Sesgo en la selección del resultado informado:</b> Informe selectivo de los resultados de una manera que depende de los hallazgos y evita que la estimación se incluya en un metanálisis (u otra síntesis).</p>	<p><b>Riesgo bajo.</b> El resultado de interés se informó sin ningún sesgo evidente.</p>
<p><b>Juicio General de riesgo de sesgo</b></p>	<p><b>Riesgo moderado.</b> Solo un dominio fue calificado como de riesgo moderado</p>

Rugg et al., 2020	
Dominio	Consenso
<p><b>Sesgo debido a la confusión:</b> La confusión inicial ocurre cuando una o más variables pronósticas (factores que predicen el resultado de interés) también predicen la intervención recibida al inicio.</p>	<p><b>Riesgo moderado.</b> El inicio de la terapia con CytoSorb varió de 0,5 a 719 h después del ingreso en la UCI, probablemente a muchos pacientes se les indicó comenzar con cytosorb debido a una evolución tórpida, sin embargo, los autores realizaron una "combinación genética" para minimizar el riesgo de sesgo</p>
<p><b>Sesgo en la selección de participantes en el estudio:</b> Cuando la exclusión de algunos participantes elegibles, o el tiempo de seguimiento inicial de algunos participantes, o algunos eventos de resultado están relacionados tanto con la intervención como con el resultado, habrá una asociación entre las intervenciones y el resultado incluso si los efectos de las intervenciones son idénticos.</p>	<p><b>Riesgo grave.</b> El "matching" se realizó manualmente principalmente, debido a la falta de datos sobre los diagnósticos de admisión y los requisitos de TRR y la definición general de la línea de base difería entre los grupos..</p>
<p><b>Sesgo en la clasificación de las intervenciones:</b> Sesgo introducido por la clasificación errónea diferencial o no diferencial del estado de la intervención. La clasificación errónea no diferencial no está relacionada con el resultado y, por lo general, sesgará el efecto estimado de la intervención hacia el valor nulo. La clasificación errónea diferencial ocurre cuando la clasificación errónea del estado de la intervención está relacionada con el resultado o el riesgo del resultado, y es probable que conduzca a un sesgo.</p>	<p><b>Riesgo moderado.</b> Estaba bien definida la intervención, sin embargo, algunos pacientes fueron incluidos en el grupo de cytosorb después de estar solo con TRR.</p>
<p><b>Sesgo debido a desviaciones de las intervenciones previstas:</b> Sesgo que surge cuando existen diferencias sistemáticas entre la intervención experimental y los grupos de comparación en la atención brindada, que representan una desviación de la(s) intervención(es) prevista(s). La evaluación del sesgo en este dominio dependerá del tipo de efecto de interés (ya sea el efecto de la asignación a la intervención o el efecto de comenzar y adherirse a la intervención).</p>	<p><b>Riesgo bajo.</b> Los pacientes fueron tratados por protocolo como parte del estándar de atención, sin embargo, en el grupo de control se incluyeron pacientes tratados desde 2011 (el protocolo de atención estándar)</p>
<p><b>Sesgo debido a la falta de datos:</b> Sesgo que surge cuando falta un seguimiento posterior para los individuos inicialmente incluidos y seguidos (como la pérdida diferencial durante el seguimiento que se ve afectada por factores pronósticos); sesgo debido a la exclusión de individuos a los que les faltaba información sobre el estado de la intervención u otras variables como los factores de confusión.</p>	<p><b>Riesgo grave.</b> Debido a la falta de datos, fue necesario incluir pacientes en un período de tiempo muy grande.</p>
<p><b>Sesgo en la medición de los resultados:</b> Sesgo introducido por errores diferenciales o no diferenciales en la medición de los datos de resultado. Tal sesgo puede surgir cuando los evaluadores de resultado conocen el estado de la intervención, si se utilizan diferentes métodos para evaluar los resultados en diferentes grupos de intervención, o si los errores de medición están relacionados con el estado o los efectos de la intervención.</p>	<p><b>Riesgo bajo.</b> El desenlace primario se definió claramente</p>
<p><b>Sesgo en la selección del resultado informado:</b> Informe selectivo de los resultados de una manera que depende de los hallazgos y evita que la estimación se incluya en un metanálisis (u otra síntesis).</p>	<p><b>Riesgo bajo.</b> No hubo información selectiva de los resultados.</p>
<p><b>Juicio General de riesgo de sesgo</b></p>	<p><b>Riesgo grave.</b> Dos dominios fueron clasificados como riesgo grave</p>



<b>Schittek et al., 2020</b>	
<b>Dominio</b>	<b>Consenso</b>
<p><b>Sesgo debido a la confusión:</b> La confusión inicial ocurre cuando una o más variables pronósticas (factores que predicen el resultado de interés) también predicen la intervención recibida al inicio.</p>	<p><b>Riesgo grave.</b> Algunos pacientes recibieron más de una sesión de Hemoadsorción y hubo una gravedad significativamente mayor de la enfermedad como se muestra en APACHE II y dependencia de catecolaminas en pacientes tratados con Hemoadsorción</p>
<p><b>Sesgo en la selección de participantes en el estudio:</b> Cuando la exclusión de algunos participantes elegibles, o el tiempo de seguimiento inicial de algunos participantes, o algunos eventos de resultado están relacionados tanto con la intervención como con el resultado, habrá una asociación entre las intervenciones y el resultado incluso si los efectos de las intervenciones son idénticos.</p>	<p><b>Riesgo moderado.</b> Estaba claramente definido ya que cada grupo pertenecía a diferentes períodos de tiempo, sin embargo, los criterios de inclusión diferían en ambos grupos.</p>
<p><b>Sesgo en la clasificación de las intervenciones:</b> Sesgo introducido por la clasificación errónea diferencial o no diferencial del estado de la intervención. La clasificación errónea no diferencial no está relacionada con el resultado y, por lo general, sesgará el efecto estimado de la intervención hacia el valor nulo. La clasificación errónea diferencial ocurre cuando la clasificación errónea del estado de la intervención está relacionada con el resultado o el riesgo del resultado, y es probable que conduzca a un sesgo.</p>	<p><b>Riesgo bajo.</b> Quedó bien definida la intervención.</p>
<p><b>Sesgo debido a desviaciones de las intervenciones previstas:</b> Sesgo que surge cuando existen diferencias sistemáticas entre la intervención experimental y los grupos de comparación en la atención brindada, que representan una desviación de la(s) intervención(es) prevista(s). La evaluación del sesgo en este dominio dependerá del tipo de efecto de interés (ya sea el efecto de la asignación a la intervención o el efecto de comenzar y adherirse a la intervención).</p>	<p><b>Riesgo bajo.</b> Los autores dijeron que todos los pacientes fueron tratados de acuerdo con el protocolo local de tratamiento de la sepsis.</p>
<p><b>Sesgo debido a la falta de datos:</b> Sesgo que surge cuando falta un seguimiento posterior para los individuos inicialmente incluidos y seguidos (como la pérdida diferencial durante el seguimiento que se ve afectada por factores pronósticos); sesgo debido a la exclusión de individuos a los que les faltaba información sobre el estado de la intervención u otras variables como los factores de confusión.</p>	<p><b>Riesgo bajo.</b> Los datos faltantes se referían únicamente a los resultados de las pruebas de laboratorio y, por lo tanto, no influyeron en la interpretación de los resultados primarios o secundarios.</p>
<p><b>Sesgo en la medición de los resultados:</b> Sesgo introducido por errores diferenciales o no diferenciales en la medición de los datos de resultado. Tal sesgo puede surgir cuando los evaluadores de resultado conocen el estado de la intervención, si se utilizan diferentes métodos para evaluar los resultados en diferentes grupos de intervención, o si los errores de medición están relacionados con el estado o los efectos de la intervención.</p>	<p><b>Riesgo bajo.</b> El punto final primario se definió claramente</p>
<p><b>Sesgo en la selección del resultado informado:</b> Informe selectivo de los resultados de una manera que depende de los hallazgos y evita que la estimación se incluya en un metanálisis (u otra síntesis).</p>	<p><b>Riesgo bajo.</b> No hay evidencia de notificación selectiva.</p>
<p><b>Juicio General de riesgo de sesgo</b></p>	<p><b>Riesgo grave.</b> Un dominio fue calificado como un riesgo grave</p>

**ANEXOS:****• CARTA DE ACEPTACIÓN**

18-Mar-2023

Dear Dr. Saldaña:

It is a pleasure to accept your manuscript entitled "Cytokine Hemoadsorption with Cytosorb in Sepsis. A systematic Review and Meta-Analysis." in its current form for publication in the Revista Brasileira de Terapia Intensiva. The comments of the reviewer(s)/associate editor who reviewed your manuscript are included at the foot of this letter.

Your manuscript will now undergo technical and scientific revision. During this process, usually some minor issues are raised. They must be solved before the manuscript is considered ready for publication. Our editorial team will contact you soon. We thank you for your promptness in solving all issues.

Thank you for your fine contribution. On behalf of the Editors of the Revista Brasileira de Terapia Intensiva, we look forward to your continued contributions to the Journal.

Sincerely,  
Dr. Felipe Dal-Pizzol  
Editor-in-Chief, Revista Brasileira de Terapia Intensiva  
[fdpizzol@gmail.com](mailto:fdpizzol@gmail.com)

Associate Editor Comments to Author:

Associate Editor  
Comments to the Author:  
(There are no comments.)

Entire Scoresheet:  
Reviewer: 1

Recommendation: Accept

Comments:  
Dear Authors, I have read the new version of your manuscript and have no further suggestions regarding methodological issues. However, I still believe that it is possible to improve the writing of the article. I suggest that authors carefully review the writing of the text before approving the final version. Consulting an English language specialist can help with this step.

Additional Questions:  
Does the manuscript contain new and significant information to justify publication?: Yes

Does the Abstract (Summary) clearly and accurately describe the content of the article?: Yes

Is the problem significant and concisely stated?: Yes

Are the methods described comprehensively?: Yes

Are the interpretations and conclusions justified by the results?: Yes

Is adequate reference made to other work in the field?: Yes

Is the language acceptable?: Yes

Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 5

Length of article is: Adequate

Number of tables is: Adequate

Number of figures is: Adequate

Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable).: None

Rating:

Interest: 2. Good

Quality: 3. Average

Originality: 3. Average

Overall: 3. Average

Reviewer: 2

Recommendation: Accept

Comments:

Once again, thank you for the opportunity to review this article. I think that the paper has improved a lot, and I congratulate you.

I have no further suggestions for improvement.

Additional Questions:

Does the manuscript contain new and significant information to justify publication?: Yes

Does the Abstract (Summary) clearly and accurately describe the content of the article?: Yes

Is the problem significant and concisely stated?: Yes

Are the methods described comprehensively?: Yes

Are the interpretations and conclusions justified by the results?: Yes

Is adequate reference made to other work in the field?: Yes

Is the language acceptable?: Yes

Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 6

Length of article is: Adequate

Number of tables is: Adequate

Number of figures is: Adequate

Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable).: None

Rating:

Interest: 2. Good

Quality: 3. Average

Originality: 2. Good

Overall: 2. Good

## • DOCUMENTO DE APROBACIÓN DEL COMITÉ DE ÉTICA

COMITÉ INSTITUCIONAL DE ÉTICA EN  
INVESTIGACIÓN



### CONSTANCIA N° 261-CIEI-CIENTÍFICA-2021

El presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) da constancia que el proyecto de investigación, cuyos datos se registran a continuación, ha sido **aprobado** por el CIEI-CIENTÍFICA.

Código de registro: **377-2021-POS50**

Título: **Uso de la Remoción extracorpórea de Citoquinas con Cytosorb en Shock séptico: Una Revisión Sistemática**

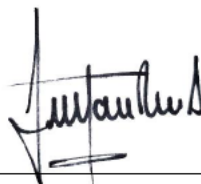
Investigador(a): **Jiovany Saldaña Gastulo**

La aprobación del proyecto de investigación implica que el documento presentado a evaluación cumple con los lineamientos de Universidad en materia de investigación y ética, los cuales se sustentan en la normativa internacional vigente. Adicionalmente, en el contexto de la pandemia de enfermedad por COVID-19, le recomendamos cumplir con las normas publicadas por el estado peruano (accesos, medidas de bioseguridad, etc.) y tener los permisos de las instituciones en las que realizará el estudio antes de ejecutarlo.

En tal sentido, esta aprobación carecerá de valor si es que el proyecto de investigación arriba indicado es modificado de cualquier forma. Toda enmienda, añadido, eliminación o eventualidad (eventos adversos, etc.) posterior a la fecha de aprobación debe ser reportado al CIEI-CIENTÍFICA.

La vigencia de la aprobación de este documento es de dieciocho (18) meses (**hasta el 7 de enero del 2023**), periodo en el que puede desarrollarse el proyecto. Cualquier trámite para su renovación deberá ser enviado antes del término de la vigencia de este documento, debiendo suspenderse todo desarrollo hasta que la renovación sea aprobada. La presente aprobación será ratificada en la sesión del CIEI más próxima.

Villa El Salvador, 8 de julio de 2021




Mg. Fulton Paul Rivera Albinagorta  
Presidente  
Comité Institucional de Ética en Investigación

- **EXTENSIÓN DE APROBACIÓN DEL COMITÉ DE ÉTICA**

**COMITÉ INSTITUCIONAL DE ÉTICA EN  
INVESTIGACIÓN**



**Constancia**

Luego de la revisión de la solicitud, el presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) hace constar que el CIE-CIENTÍFICA ha aprobado de forma expedita la **renovación** del proyecto de investigación que se detalla continuación:

Código de registro: **377-2021-POS50**

Título: **“Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metaanálisis”**

Investigador(es): **Jiovany Jhan Carlos Saldaña Gastulo**

Constancia de aprobación: **CONSTANCIA N° 261-CIEI-CIENTÍFICA-2021**

Por consiguiente, se otorga:

**Renovación de vigencia del periodo de aprobación ética.** Vista la solicitud, se **renueva** la vigencia de la aprobación ética por un periodo de seis meses; es decir, hasta el **16 de noviembre del 2023**. El proyecto solo podrá ejecutarse entre los periodos detallados en este documento y el **investigador** tendrá que realizar la solicitud de una nueva ampliación 30 días antes de finalizar esta renovación de la aprobación.

Dejando constancia que hay un periodo de ventana (entre el 7 de enero del 2023 hasta el 17 de mayo de 2023) que toda actividad de investigación estuvo suspendida, sin el amparo del comité.

Todas las demás características de la investigación descritas en el proyecto original permanecen; por lo que cualquier otra modificación deberá informarse a este Comité, para su evaluación.

Lima, 17 de mayo de 2023




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Mg. Cinthya Ruth Chipana Herquinio  
Presidente  
Comité Institucional de Ética en Investigación

• RESOLUCIÓN DIRECTORAL DE APROBACIÓN DEL PROYECTO



RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 485 - DACMH-DAFCS-U. CIENTIFICA-2021

Lima, 19 de julio del 2021

**VISTO:**

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de tesis titulado: **“USO DE LA REMOCIÓN EXTRACORPÓREA DE CITOQUÍNAS CON CYTOSORB EN SHOCK SÉPTICO: UNA REVISIÓN SISTEMÁTICA”**.

**CONSIDERANDO:**

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el **Grado de Maestro**.

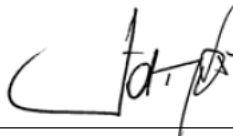
Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

**SE RESUELVE:**

**ART. 1° Aprobar**, en vías de regularización e inscribir el proyecto de tesis titulado: **“USO DE LA REMOCIÓN EXTRACORPÓREA DE CITOQUÍNAS CON CYTOSORB EN SHOCK SÉPTICO: UNA REVISIÓN SISTEMÁTICA”**, presentado por el alumno **JIOVANY SALDAÑA GASTULO** con N° de registro: **377-2021-POSSO**.

**ART. 2° Nombrar** a la Docente Leda Yamileé Hurtado Roca, como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.



**Mg. JORDI GRAU MONGE**  
**Director Académico**  
**Carrera de Medicina Humana**



c.c. Archivo

- ENMIENDA DE PROYECTO DE INVESTIGACIÓN

COMITÉ INSTITUCIONAL DE ÉTICA EN  
INVESTIGACIÓN



Constancia

Luego de la revisión de la solicitud, el presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) hace constar que el CIE-CIENTÍFICA ha aprobado de forma expedita la **enmienda** del proyecto de investigación que se detalla continuación:

Código de registro: **377-2021-POS50**

Título: **Hemoadsorción de citoquinas con Cytosorb en sepsis. Una revisión sistemática y metaanálisis**

Investigador(es): **Jiovany Jhan Carlos Saldaña Gastulo**

Documentos vinculados: **CONSTANCIA N° 261-CIEI-CIENTÍFICA-2021**

La **enmienda** corresponde a los siguiente:

Proyecto de investigación, en su versión recibida el día 28 de abril del 2023 en donde se detalla de las modificaciones del proyecto de investigación, que se encuentran descritas en el **Anexo 1: Formato de resumen de enmienda de protocolo de investigación**.

Todas las demás características de la investigación descritas en el proyecto original permanecen; por lo que cualquier otra modificación deberá informarse a este Comité, para su evaluación.

Lima, 17 de mayo de 2023




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Mg. Cinthya Ruth Chipana Herquinio  
Presidente

Comité Institucional de Ética en Investigación



• RESOLUCIÓN DIRECTORAL DE APROBACIÓN DEL PROYECTO CORREGIDO



**RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 352 - DACMH-DAFCS-U. CIENTIFICA-2023**

Villa el Salvador, 01 de junio del 2023

**VISTO:**

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de investigación titulado: **“HEMOADSORCIÓN DE CITOQUINAS CON CYTOSORB EN SEPSIS. UNA REVISIÓN SISTEMÁTICA Y METANÁLISIS”**.

**CONSIDERANDO:**

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el **Grado de Maestro**.

Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

**SE RESUELVE:**

**ART. 1° Aprobar**, en vías de regularización e inscribir el proyecto de tesis titulado **“HEMOADSORCIÓN DE CITOQUINAS CON CYTOSORB EN SEPSIS. UNA REVISIÓN SISTEMÁTICA Y METANÁLISIS”**, presentado por el alumno: Jiovany Jhan Carlos Saldaña Gastulo con N° de registro: **377-2021-POS50**.

**ART. 2° Nombrar** al Docente Leda Yamileé Hurtado Roca como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.




**Mg. JORDI GRAU MONGE**  
**Director Académico (e)**  
**Carrera de Medicina Humana**