Review

A Contemporary Review of the Use of Extracorporeal CytoSorb® Hemoadsorption Therapy in Patients with Infective Endocarditis

Anan Gong , Yupei Li * , Mei Yang , Shujing Wang , Baihai Su *

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A Contemporary Review of the Use of Extracorporeal CytoSorb® Hemoadsorption Therapy in Patients with Infective Endocarditis

Anan Gong [1,2,#], Yupei Li [1,2,#,*], Mei Yang [3,4], Shujing Wang [1,2] and Baihai Su [1,2,5,6,*]

[1] Department of Nephrology, Kidney Research Institute, Frontiers Science Center for Disease-related Molecular Network, West China Hospital of Sichuan University, Chengdu 610041, China
[2] West China School of Medicine, Sichuan University, Chengdu 610041, China
[3] General Practice Ward/International Medical Center Ward, General Practice Medical Center, West China Hospital, Sichuan University, Chengdu 610041, China
[4] Department of Nephrology, The First People's Hospital of Shuangliu District, Chengdu, China
[5] Med+ Biomaterial Institute of West China Hospital/West China School of Medicine, Sichuan University, Chengdu 610041, China
[6] Med-X Center for Materials, Sichuan University, Chengdu 610041, China
* Correspondence: Dr. Yupei Li (liyupei123@wchscu.cn) or Prof. Baihai Su (subaihai@scu.edu.cn)
[#] Anan Gong and Yupei Li contributed equally to this work.

Abstract: Infective endocarditis (IE) is a rare but severe disease with high mortality and healthcare burden. Cardiac surgery plays a major role in the contemporary clinical management of IE patients. During cardiac surgery, cardiopulmonary bypass significantly contributes to an increased risk for organ dysfunction and mortality by inducing an acute inflammatory response, vascular endothelial cell injury, impairment of the coagulation cascade, and ischemia–reperfusion injury. During the past decade, the use of extracorporeal hemoadsorption therapy with the CytoSorb® hemoadsorber has been proposed as an adjuvant therapy to mediate inflammatory responses in IE patients receiving cardiac surgery with cardiopulmonary bypass. However, there is currently a lack of systemic evaluation of the effect of CytoSorb® hemoadsorption on clinical outcomes such as hemodynamics, organ dysfunction, and mortality in patients with IE. Therefore, in this review, we exclusively discuss contemporary findings concerning the rationale, clinical evidence and future perspectives for CytoSorb® hemoadsorption therapy in IE patients.

Keywords: hemoadsorption; infective endocarditis; Cytosorb®; cardiopulmonary bypass; cardiac surgery; mortality

1. Introduction

Infective endocarditis (IE), an infection of the endothelium of the heart, has an annual incidence of 15 cases per 100,000 population and carries a high 30-day mortality of up to 30% [1]. In patients with IE, bacteremia triggers complex interactions between the microorganism, platelets, diseased valvular endothelium and host immunity, which contributes to vegetations and destruction of valvular or perivalvular tissue [2]. Accordingly, prolonged antibiotic therapy is mandatory to manage IE patients since valvular and perivalvular infections are difficult to control by host immunological responses and antibiotics [3]. Both the American Heart Association and European Society of Cardiology clinical guidelines have detailed the selection of an appropriate bactericidal regimen for IE treatment in depth [4,5].

Beyond antibiotic therapy, cardiac surgery is also needed to restore normal valve function and to resect all infected tissues during the acute phase of IE [2]. Approximately 50% of IE patients who develop severe complications, such as heart failure, severe valve dysfunction, prosthetic valve endocarditis,

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recurrent systemic embolization, large mobile vegetations and persistent sepsis, require a cardiac operation [6]. During cardiac surgery, cardiopulmonary bypass (CPB) will be established to temporarily replace the heart and lung function of a patient [7]. Nevertheless, CPB is significantly associated with multiple pathological changes, including an acute inflammatory response, vascular endothelial cell injury, impairment of the coagulation cascade, and ischemia–reperfusion injury, which jointly contribute to multiple organ dysfunction syndrome and mortality in patients receiving cardiac surgeries [8]. The acute inflammatory response is characterized by the release of proinflammatory mediators, such as complements, interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α), and is thought to play vital immunopathologic roles in CPB-associated complications [7,9]. Furthermore, a prospective case–control pilot study by Diab et al. demonstrated that patients with IE had higher inflammatory mediator levels than those without IE at the end of CPB and that the plasma level of IL-6 during CPB was significantly correlated with the severity of postoperative organ dysfunction in IE patients [10]. Therefore, it is reasonable to speculate that the removal of such circulating inflammatory mediators might help to reduce organ dysfunction in IE patients receiving cardiac surgery with CPB.

Recently, the use of extracorporeal hemoadsorption therapy with the CytoSorb® hemoadsorber has been proposed as an adjuvant therapy to mediate inflammatory responses by eliminating proinflammatory cytokines during cardiac surgery [9]. Although several studies have been conducted to evaluate the efficacy of CytoSorb® hemoadsorption in patients undergoing cardiac surgery, the results have been inconsistent [9,11–16]. For instance, two randomized controlled studies failed to demonstrate a reduction in either postoperative organ dysfunction or vasopressor use through intraoperative CytoSorb® hemoadsorption in IE patients [9,13]. In contrast, other retrospective studies found that intraoperative CytoSorb® hemoadsorption significantly reduced sepsis-associated mortality and resulted in significantly faster recovery of hemodynamics and organ function [11,12]. Of note, there are several nonnegligible heterogeneities in study design, sample size, and Cytosorb® prescriptions regarding initiation timing and treatment duration. across these previous clinical studies, which unfortunately makes the interpretation of these results challenging. Considering that there is currently a lack of systemic evaluation of the effect of CytoSorb® on patients with IE, we are motivated to conduct a narrative review to exclusively discuss contemporary findings concerning the rationale, clinical evidence and future perspectives for hemoadsorption therapy in IE patients receiving cardiac surgery.

2. Rationale for hemoadsorption therapy in IE patients receiving cardiac surgery

Cardiac surgery may activate of the complement system and the immune system induced by surgical trauma, CPB, artificial surfaces and ischemia-reperfusion injury, which might further lead to systemic inflammatory response syndrome (SIRS) [17,18]. In 2017, a retrospective cohort study enrolling 28,513 patients found that the overall prevalence of postoperative SIRS within the first 24 h after cardiac surgery was as high as 58.7% [19]. Another retrospective study also showed that 142 (28.3%) of 502 patients who underwent cardiac surgery with CPB fulfilled SIRS criteria at 24 hours and that postoperative SIRS was associated with a more complicated postoperative course and higher postoperative morbidity [20]. IE patients receiving CBP are also at a high risk of developing SIRS owing to the potential intraoperative bacterial spread [14]. Therefore, it is reasonable to speculate that the control of unwanted SIRS might help to improve the outcomes of IE patients receiving cardiac surgery with CPB.

Hemoadsorption refers to the circulation of blood through a hemoadsorber containing specific sorbents, with adsorption as the only mechanism for the removal of specific solutes or substances [21]. Hemoadsorption has been commonly used to remove inflammatory cytokines and metabolic wastes in multiple hyperinflammation conditions (namely, sepsis, acute liver failure, acute pancreatitis, acute respiratory distress syndrome, severe COVID-19, etc.) or acute poisoning during the past two decades [22–26]. Currently, CytoSorb® (CytoSorbents Europe GmbH, Berlin, Germany), HA 330 (Jafron Biomedical Co., Ltd, Zhuhai, China) and Toraymyxin™ (Toray Medical Co., Ltd, Tokyo, Japan) are three mainstream hemoadsorbers that are widely used in critical care settings [27]. Among them, CytoSorb®, a CE-approved hemoadsorber, can significantly remove cytokines, bilirubin, toxic bile acids, and myoglobin in the circulating blood [28–31]. Equipped with highly porous, biocompatible sorbent polystyrene

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divinylbenzene beads, CytoSorb® cartridges have a total surface area of > 45,000 m^2 and are capable of adsorbing various hydrophobic cytokine molecules within the 5–55 kDa molecular weight range [22].

In vitro studies indicate that CytoSorb® can rapidly reduce the levels of multiple cytokines in experimental settings of endotoxemia [32,33]. However, the effect of CytoSorb® hemoadsorption on hyperinflammation remains controversial across different clinical studies. Some observational studies suggest that CytoSorb® may lower circulating cytokine concentrations and improve organ dysfunction and hemodynamics in critically ill patients with various hyperinflammatory conditions [34–36]. Similarly, a prospective, randomized single center study by Ingo et al. showed that a significant short-term reduction in proinflammatory cytokine levels of Il-8 and TNFα at 6 h after CPB could be observed in patients receiving on-pump cardiac surgery and intraoperative CytoSorb® hemoadsorption [37]. In contrast, another pilot randomized controlled trial enrolling 30 patients undergoing elective cardiac surgery showed that CytoSorb® hemoadsorption during CPB was not associated with a reduction in both pro- and anti-inflammatory cytokines [38]. More recently, Daniela et al. performed a retrospective study with 56 participants to investigate whether the use of CytoSorb® has an effect on IL-6 levels in patients undergoing cardiac surgery [17]. The results showed that IL-6 peaked on the first postoperative day in both the Cytosorb® and control groups (Cytosorb®: 775.3 ± 838.4 vs. control: 855.5 ± 1,052.9 pg/ml) and that intraoperative CytoSorb® hemoadsorption was not associated with a significant reduction in IL-6 levels or periprocedural mortality. A subgroup analysis of a recent meta-analysis also found that Cytosorb® treatment did not lower mortality in patients who received cardiac surgery with CPB (0.91 [0.64; 1.29], RR [95%-CI]) [39]. To gather enough evidence for safe use of CytoSorb® in clinical practice, we are motivated to discuss contemporary clinical evidence for CytoSorb® hemoadsorption therapy in IE patients receiving cardiac surgeries in the next section.

3. Clinical evidence for hemoadsorption therapy in IE patients receiving cardiac surgery

As discussed above, CytoSorb® hemoadsorption holds promise for attenuating inflammation during CPB sessions. Thus, several clinical studies have determined the efficacy of CytoSorb® hemoadsorption in IE patients receiving cardiac surgery, as shown in **Table 1**. It should be noted that both baseline patient characteristics and hemoadsorption prescriptions varied significantly among these studies, which contributed to the difficulty in the interpretation of study conclusions. In this section, we mainly discuss the efficacy of CytoSorb® hemoadsorption on patient-centered outcomes, such as mortality and hemodynamics.

The effect of intraoperative hemoadsorption with CytoSorb® on hemodynamics in IE patients receiving cardiac surgery remains debatable. Early in 2017, Karl et al. first conducted a case series study to evaluate the efficacy of intraoperative CytoSorb® treatment in 39 IE patients [40]. The results showed a marked intraoperative increase in inflammatory mediators, including IL-6 and IL-8, after the surgical procedure. Compared with a historical group, intraoperative CytoSorb® treatment was associated with a marked reduction in IL-6 and IL-8 plasma levels postoperatively and hemodynamic stability before, during, and after the operation, as evidenced by a rapid decrease in the need for vasopressors. Recently, Zaki et al. included 130 patients with confirmed *S. aureus* IE to investigate the effect of intraoperative hemoadsorption on the vasoactive-inotropic score within the first 72 h postoperatively [41]. Significantly decreased vasoactive-inotropic scores were observed in the hemoadsorption group vs. the control group at all time points. In contrast, another small randomized, controlled, nonblinded clinical trial showed that the use of Cytosorb® hemoadsorption in IE patients undergoing valve surgery was related to an insignificantly reduced accumulated norepinephrine dose at postoperative time points compared to the control group (24 h: median 36 [25-75 percentiles; 12-57] µg v 114 [25-559] µg, p = 0.11; 48 h: 36 [12-99] µg v 261 [25-689] µg, p = 0.09) [13]. Furthermore, Silke et al. also failed to demonstrate a beneficial effect of Cytosorb® treatment on hemodynamics in IE patients who received hemoadsorption intraoperatively and 24 hours postoperatively [14].

Currently, there are four major clinical trials evaluating the effect of CytoSorb® on the survival and organ dysfunction of IE patients. In 2022, Jurij et al. included 202 high-risk patients with active left-sided IE to compare the incidence of postoperative sepsis, sepsis-associated death and in-hospital mortality

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between CytoSorb® and the standard of care [12]. After propensity score matching, hemoadsorption significantly reduced the incidence of postoperative sepsis and sepsis-related mortality compared to the standard of care (22.2% vs. 39.4%, p = 0.014 and 8.1% vs. 22.2%, p = 0.01, respectively). In-hospital mortality tended to be insignificantly lower in the hemoadsorption group (14.1% vs. 26.3%, p = 0.052). Multivariate regression analysis also confirmed that CytoSorb® treatment was associated with lower sepsis-associated (OR 0.09, 95% CI 0.013–0.62, p = 0.014) as well as in-hospital mortality (OR 0.069, 95% CI 0.006–0.795, p = 0.032), which was in line with the results of another dual-center retrospective study by Zaki et al [41]. However, in another study, David found no significant difference in in-hospital mortality, major adverse cardiac and cerebrovascular events or postoperative renal failure between patients receiving hemoadsorption and those receiving standard of care [15]. More importantly, hemoadsorption was associated with an increased need for vasoactive agents, including norepinephrine (88.4 vs. 52.8%; p = 0.001) and milrinone (42.2 vs. 17.2%; p = 0.046). Cytosorb® treatment also led to a higher incidence of reoperation for bleeding, along with increased postoperative demand for blood products (red blood cell concentrates and platelets) [15]. The ROMOVE study, the largest multicenter, randomized, nonblinded, controlled trial thus far in this field, enrolled 288 IE patients undergoing cardiac surgery to further study the effect of hemoadsorption vs. standard of care on postoperative organ dysfunction as determined by the change in sequential organ failure assessment score [9]. The study also included 30-day mortality, duration of mechanical ventilation, and need for vasopressor and renal replacement therapy as secondary outcomes. The results showed that hemoadsorption therapy failed to reduce organ dysfunction compared with the standard of care, although the levels of IL-1β and IL-18 in the hemoadsorption group were significantly lower than those in the control group. Meanwhile, 30-day mortality did not differ between the hemoadsorption and the control group (21% vs. 22%; p=0.782). Hemoadsorption also did not reduce the duration of postoperative renal replacement therapy, mechanical ventilation, or vasopressor therapy or the lengths of ICU and hospital stay. Therefore, although the concept of cytokine elimination in IE patients undergoing cardiac surgery is tempting, there is no solid evidence to favor routine clinical application of intraoperative hemoadsorption in such patients. These conflicting results also remind us that we have the obligation to perform CytoSorb® hemoadsorption in properly selected CPB patients, taking into account the treatment timing, duration and dose.

The HA-330 cartridge is another type of hemoadsorber with a similar solute removal spectrum analogous to Cytosorb®, which has been studied in multiple cohorts in the context of inflammatory conditions such as sepsis, acute lung injury, hepatitis, CPB, and pancreatitis [42]. Unlike Cytosorb®, the HA-330 cartridge has been approved for use in various critical care settings in mainland China. Recently, Ke et al. retrospectively evaluated the efficacy of HA-330 cartridges in 287 adult patients undergoing cardiac valve replacement surgery with CPB [43]. During hemoperfusion sessions, the HA-330 cartridge was connected to the CPB circuit with a blood flow rate ranging from 200 to 300 mL/min. The results showed that patients in the HA-330 group had relatively lower IL-6 and IL-8 levels on day one post-CPB than those in the control group, suggesting that HA-330 might also mitigate inflammatory responses associated with CPB. Therefore, it is of great clinical significance to further determine the efficacy of such hemoadsorber in IE patients receiving cardiac surgery in the future since the clinical use of Cytosorb® outside Europe is still limited. Since the majority of these trials only included European participants, external validation of the conclusions of the abovementioned clinical trials to guide the use of Cytosorb® hemoadsorption worldwide is also needed in the future, taking into account differences in genetic information and clinical practice patterns across different populations and countries.

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Table 1. Summary of major clinical trials evaluating the effect of Cytosorb® hemoadsorption in patients receiving cardiac surgery with CPB.

Author, publication year	Study location	Study design	Study period	Sample size	Mean or median EuroScore II	Hemoadsorption prescription	Main findings
Silke Asch, 2021 [14]	Göttingen, Germany	RCT	November 2018 to March 2020	20	Cytosorb: 8.5 Control: 3.6	Cytosorb® hemoadsorption was initiated intraoperatively and continued for 24 hours postoperatively.	Cytosorb® hemoadsorption did neither result in a reduction of inflammatory parameters nor an improvement of hemodynamics in IE patients.
Mahmoud Diab, 2022 [9]	Multicenter, Germany	RCT	January 17, 2018 to January 31, 2020	282	Cytosorb: 19.1±17.3 Control: 20.2±17.8	Hemadsorption during CPB	Although Cytosorb® hemoadsorption reduced plasma cytokines, there was no difference in clinically relevant outcome measures and no reduction in postoperative organ dysfunction.
Ingo Garau，2019 [37]	Hamburg, Germany	RCT	September 2013 to June 2015	40	Cytosorb: 6.1 Control: 6.3	Hemadsorption during CPB with a blood flow of 300 mL/min	In elective on-pump cardiac surgery patients, Cytosorb® hemoadsorption was associated with a short-term reduction in pro-inflammatory cytokine levels of IL-8 and TNFα.
Elettra C Poli, 2019 [38]	Lausanne, Switzerland	RCT	May 2016 to January 2018	30	Cytosorb: 3.0 Control: 5.1	Hemadsorption during CPB	CytoSorb® hemoadsorption during CPB was not associated with a decrease in pro- or anti-inflammatory cytokines nor with an improvement in relevant clinical outcomes.
Anna Holmen, 2022 [13]	Gothenburg, Sweden	RCT	April 2019 to September 2020	19	NA	Hemadsorption during CPB	Cytosorb® hemoadsorption contributed to an insignificantly decreased vasopressor use after surgery in IE patients.
Zaki Haidari, 2023 [41]	Essen and Nuremberg, Germany	Retrospective study	January 2015 to March 2022	130	Cytosorb: 11.9 Control: 12.0	Hemadsorption during CPB with a blood flow ranging from 100 to 700 mL/min	Intraoperative Cytosorb® hemoadsorption significantly contributed to reduced sepsis-associated mortality, 30- and 90-day mortality, and improved hemodynamics in high-risk IE patients.

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Jurij Matija Kalisnik, 2022 [12]	Nuremberg, Germany	Retrospective study	January 2015 to April 2021	202	Cytosorb: 9.89 Control: 8.95	Hemadsorption during CPB	After propensity score match, intraoperative Cytosorb® hemoadsorption significantly reduced sepsis and sepsis-associated mortality after cardiac surgery in high-risk patients with active left-sided native and prosthetic valve IE.
David Santer, 2021 [15]	Basel, Switzerland	Retrospective study	2009 to 2019	241	Cytosorb: 7.8 Control: 8.6	Hemadsorption during CPB with a blood flow of 500 mL/min	Intraoperative Cytosorb® hemoadsorption did not reduce in-hospital mortality, incidence of delirium, myocardial ischemia, stroke, and postoperative renal failure, but was significantly associated with increased in-hospital stay, and incidence of reoperation for bleeding in IE patients.
Lars-Uwe Kühne, 2019 [44]	Hamburg, Germany	Case series	July 2017 to April 2018	20	Group 1：26.8 Group 2：33.8	Group 1: intraoperative hemoadsorption with a blood flow rate between 300 and 600 mL/min Group 2: intraoperative plus postoperative hemoadsorption with a blood flow rate between 300 and 600 mL/min	IE patients recieving intraoperative plus postoperative Cytosorb® hemoadsorption showed a similar ICU and 90-day survival compared to those recieving intraoperative Cytosorb® hemoadsorption only. However, postoperative continuation of hemoadsorption treatment was associated with a higher rate of postoperative complications and a longer intensive care unit stay despite a significant diffirence in baseline disease severity between two groups.
Karl Träger, 2017 [40]	Ulm, Germany	Case series with a historical group	September 2013 to August 2016	67	Cytosorb: 11 Historical control: 9 for ICU survivors	Hemadsorption during CPB with a blood flow ranging from 200 to 400 mL/min	Intraoperative Cytosorb® hemoadsorption contributed to a reduced plasma IL-6 and IL-8 levels and improved hemodynamics in IE patients.

* Abbreviations: IE, infective endocarditis; CPB cardiopulmonary bypass; ICU intensive care unit; IL interleukin.

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4. Safety concerns and health economics

Generally, CytoSorb® hemoadsorption was safe and well tolerated with no de-vice-related adverse events during or after CPB sessions [12,38,40]. Major safety concerns associated with the use of CytoSorb® in clinical practice include the nonspecific adsorption of antibiotics, anticoagulants, and coagulation factors [38,45–47]. Specifically, several small-size observational studies collectively found that CytoSorb® treatment significantly reduced vancomycin levels in critically ill patients [46,48]. Regarding the important role of antibiotics in the management of IE, dose adjustment of antibiotics should be considered in IE patients receiving CPB with CytoSorb® hemoadsorption, especially in those with prolonged postoperative Cytosorb® hemoadsorption.

Intraoperative hemoadsorption in IE patients might have economic benefits related to reduced length of ICU stay, resulting in improved healthcare resource use 49]. Using data from the German healthcare system, Cristina et al. developed an Excel-based budget impact model to simulate the patient course over the ICU stay in IE patients. In the base-case scenario, CytoSorb® hemoadsorption resulted in a saving of EUR 2298 per patient. In the case of full device-specific reimbursement, the savings could increase to EUR 3804 per patient. Furthermore, the results of deterministic and probabilistic sensitivity analyses confirmed the robustness of savings, with a probability of savings of 87% and 99% in the base case and full reimbursement scenario, respectively. However, this study also has some limitations. First, the cost associated with antibiotic therapy adjustment during CytoSorb® hemoadsorption and length of in-hospital stay, which might also have an impact on the final calculated savings, were not taken into consideration. Second, recent studies have not confirmed the reduction in length of ICU stay used to inform this model. Therefore, these findings must be confirmed by further prospective analyses reporting benefits in terms of reduced ICU stay.

5. Conclusions

Infective endocarditis is a rare but severe disease with high mortality and healthcare burden. Cardiac surgery plays a vital role in the clinical management of IE patients; however, it also contributes to an unexpected activation of inflammatory responses. Hemoadsorption with the CytoSorb® hemofilter theoretically holds promise as an adjuvant treatment by attenuating inflammation during CPB sessions. Unfortunately, the effect of CytoSorb® hemoadsorption on patient-centered outcomes such as hemodynamics, organ dysfunction, length of ICU stay and in-hospital mortality remains controversial in IE patients who receive cardiac surgery with CPB, which prevents the routine clinical use of CytoSorb® hemoadsorption in this unique patient population. Therefore, more evidence from large, well-designed randomized controlled trials is urgently needed to clarify our CytoSorb® prescription, including the timing of initiation, treatment duration, frequency of filter change, and dose adjustment of antibiotics, and to identify the most appropriate patient group who will benefit from CytoSorb® hemoadsorption in the future.

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