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Expert consensus on use of extracorporeal hemoadsorption in septic shock: An Indian perspective

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Abstract

Septic shock is a severe form of sepsis characterised by deterioration in circulatory and cellular-metabolic parameters. Despite standard therapy, the outcomes are poor. Newer adjuvant therapy, such as CytoSorb® extracorporeal hemoadsorption device, has been investigated and shown promising outcome. However, there is a lack of some guidance to make clinical decisions on the use of CytoSorb® hemoadsorption as an adjuvant therapy in septic shock. This consensus provides statements on the use of CytoSorb® hemoadsorption as an adjuvant therapy in patients with septic shock. Using a modified Delphi approach combining evidence appraisal and expert opinion, the following topics related to CytoSorb® in septic shock were addressed: need for adjuvant therapy, initiation timeline, need for Interleukin -6 Levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and management flowchart. Eleven expert members from critical care, emergency medicine, and the intensive care participated and voted on nine statements and one open-ended question. After three iterative voting rounds and adapting two statements, consensus was achieved on nine statements out of nine statements. This Indian perspective consensus statement supports use of CytoSorb® hemoadsorption as an adjuvant treatment in patients with septic shock and provides guidance to achieve better outcomes.

INTRODUCTION

Sepsis is described as potentially fatal organ dysfunction induced by an unbalanced host response to infection [1]. Septic shock, on the other hand, is a subset of sepsis in which the underlying circulatory and cellular metabolic abnormalities are severe enough to significantly increase mortality [1]. Sepsis and Septic shock are leading health related issues. The global incidence of sepsis is estimated to be 48·9 million and sepsis related deaths to be 11·0 million worldwide, with higher burden in developing countries [2]. India has a higher death rate from sepsis than other South Asian countries [2]. It is estimated that sepsis death rate in India is 213 per 100,000 population [2].

The pathophysiology is multifaceted, with both pathogenic and host factors (pathogen-associated molecular patterns, (PAMPs) and damage-associated molecular patterns, (DAMPs) playing a significant part in its progression and subsequent outcome [2,3]. However, the diversity of septic shock requires to accurately characterise individuals, which makes clinical intervention challenging [3,4]. The backbone of treatment remains appropriate and timely antibiotic therapy, source control, if necessary, IV fluids and titrated vasopressors [5]. However, when these treatment efforts fail to improve the patients' condition in a subset of patients, adjuvant therapies are usually explored to enhance out-comes [5,6,7].

Despite clinical research efforts and the development of sepsis management guide-lines over the last few decades, the potential to improve the outcome of the condition tends to be limited [8]. Newer adjuvant therapy, such as the targeted elimination of pathogen-associated toxins and mediators by specific adsorption, are gaining recognition [6,7,9]. The use of an extracorporeal hemoadsorption device called CytoSorb® (Cyto-Sorbents corp, New Jersey, USA) for cytokine adsorption is one of the more recent adjuvants. It contains specially designed polymer beads with a large adsorption surface and an adsorption spectrum upto around 60 kDa. It is a high flow, low resistance cytokine adsorbent [7]. CytoSorb extracorporeal hemoadsorption therapy tends to restore the

balance of the immune response to infection by eliminating the triggers for the response and the excessive cytokines produced, with the target of achieving immunological homeostasis in patients with severe cytokinemia, including septic shock [4].

Although, there is a substantial amount of clinical data from case series and prospective/retrospective research [10,11,12] that supports the likelihood of improving treatment outcomes with CytoSorb® hemoadsorption in septic shock, the limited evidence from randomised clinical trials [7] makes it difficult to endorse or adopt in management guide-lines. Furthermore, published evidence on proper patient selection, timing and dosing of CytoSorb® therapy is still scarce. So, there is lack of a consensus guidance to make clinical decisions on the use of CytoSorb® hemoadsorption as an adjuvant in the management of septic shock. Our aim/objectives were to formulate/establish specific consensus statements on the use of CytoSorb® hemoadsorption treatment based on the best available evidence and contextualised to the Indian scenario. Firstly, this Indian consensus provides statements on the use of hemo-adsorption as an adjuvant therapy in patients with sepsis. This expert consensus statements provides general physicians, emergency care physicians, anaesthetist, and intensivists with current information regarding the use of haemo-adsorption as an adjuvant treatment in patients with refractory septic shock. Secondly, this Indian perspective consensus statement supports use of hemo-adsorption as an adjuvant treatment in patients with septic shock and provides guidance to achieve better outcomes. Thirdly, it may also contribute in the optimization of refractory septic shock treatment in India.

METHODS

This consensus statement was intended for a target audience of healthcare professionals/ clinicians representing /working in the intensive care units/ critical care units and emergency departments.

Consensus statement development

Members of the scientific panel conducted a comprehensive literature review on the use of CytoSorb® hemoadsorption in patients with sepsis, septic shock, or who were critically ill. The results of a PubMed and Medline database search using suitable Mesh and search keywords yielded a reference list of CytoSorb® publications. The statements for a consensus document were developed based on the summarised literature analysis and identification of knowledge gaps. A total of nine consensus question statements focused on the use of CytoSorb® therapy in septic shock were formulated. One question was kept open-ended for discussion.

Consensus Expert Group

The scientific panel convened a consensus expert group of 11 members, each with more than 20 years of expertise in emergency medicine or critical care medicine. These individual experts from India's various geographical cities (Gurugram, Mumbai, Mohali, Kolkata, Delhi, Pune, Vadodara, and Hyderabad) were invited for voting and to express their expert opinion in the consensus process.

Consensus Process

The Delphi procedure gathers a group of experts for decision making through an iterative series of questions, anonymous responses, and controlled feedback to the respondents [13]. Using a modified Delphi approach, involving combination of scientific evidence appraisal and expert opinion based on clinical experience of the consensus members, the following topics related statements to CytoSorb® in refractory septic shock were addressed to achieve consensus: need for adjuvant therapy, initiation timeline, need for Interleukin-6 Levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and (therapy) management flowchart.

The consensus expert members were asked to vote on all of the statements (agree/yes, disagree/no, or abstain) based on their clinical experience and scientific evidence appraisal obtained from systematic review. They were also asked to offer feedback on the content and/or phrasing of the statements, as well as to suggest any new statements they thought would be beneficial.

Consensus was reached for a particular statement when there was at least 80% agreement in the voting. Statements with no consensus (less than 80% agreement), statements with consensus but relevant remarks that resulted in paraphrasing, and additional statements suggested by experts were reformulated and presented for voting in subsequent modified Delphi rounds. To achieve a decision, maximum three modified Delphi voting rounds were held. The total number of consensuses achieved were calculated.

RESULTS

All 11 experts in the consensus group (100%) participated in the first, second and third round of voting and commenting for the consensus statements.

In the first round, consensus was obtained in 8 (Q1- Q8) of the 9 selected initial statements, whereas consensus was not reached in 1 statement (Q9). It was discussed and re-posted for the second round of voting and comments. Furthermore, 1 statement (Q8) with consensus had positive comments that prompted a modest revision of the phrases. This revised statement Q8 was sent out again along with Q9 for the second round of voting. The one revised statement (Q8) obtained consensus in the second round of voting. For the last statement (Q9, flowchart) agreement was reached in the third round of voting after therapy timelines were modified (Figure 1 and 2). Overall, consensus was reached in all nine out of nine statements (Table 1).

The consensus expert panel also recognised the necessity to form an association or society that can keep a registry regarding the use of CytoSorb® for all indications in the open-ended question (Q10) focusing on "future recommendations for CytoSorb® therapy". The potential of this treatment for treating a variety of clinical disorders and its impact on patient outcomes will be better understood with the aid of this registry.

Summary of Consensus statements

Q1: Is there a need for adjuvant therapy in the management of refractory septic shock patients when standard of care is insufficient?

Expert panel Agreement: A total of 90.91% experts agreed on the need for adjuvant therapy in the management of refractory septic shock patients. (Consensus Achieved)

Reason /Scientific evidence: Standard of care in septic shock with the cornerstones of source control and fluid and catecholamine therapy is of unquestionable importance, however, not directly addressing the dysregulated immune response as a central problem. Especially in refractory patients, with no adequate response to standard therapy measures, adjuvant approaches might be needed and be able to fill this therapeutic gap. Consequently CytoSorb® hemoadsorption treatment attempts to restore the balance of the immune response to infection by eliminating some triggers for the response and the excessive cytokines produced, with the target of achieving immunological homeostasis [4,14]. It has the capacity to disrupt the immune response at various stages by eliminating various inflammatory mediators like PAMPs, DAMPs and cytokines from blood, thereby directly addressing the problem of the dysregulated host response.

Q2: In case of refractory septic shock cycle, CytoSorb® hemadsorption should ideally be initiated within a maximum of 24 h after diagnosis and start of standard therapy.

Expert panel Agreement: All experts (100%) agreed that in refractory septic shock, CytoSorb® should ideally be initiated within a maximum of 24 h. (Consensus Achieved)

Reason /Scientific evidence: Kogelmann *et al* (2021) presented a dynamic scoring system to support patient selection for CytoSorb® therapy in early refractory septic shock. Among other things analysis of nearly 200 patients treated with CytoSorb® in septic shock revealed that those treated within the first 24 h had a higher chance of surviving than those treated after 24 h, and for every hour of CytoSorb® hemoadsorption treatment delay, the risks of death at Day 56 increased by 1.5% ($P<0.034$) [15]. These positive findings are in line with various other publications, like data from Singh YP *et al* (2019) [16] and Paul R *et al* (2021) [17], in which CytoSorb® therapy was shown to be a safe and well tolerated rescue therapy which should be used

preferably within the first 24 h after onset of septic shock. Approaches in which CytoSorb® therapy was initiated in selected refractory patients within the first 24 h of onset of septic shock or start of standard therapy respectively showed positive effects with regard to improved hemodynamic stabilization and signals for improved survival [12].

Q3: IL-6 Level is not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients.

Expert panel Agreement: A total of 90.91% experts agreed that IL-6 Level is not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved)

Reason /Scientific evidence: Although IL-6 Levels are a promising target due to its involvement in the pathogenesis of septic shock, the profile of IL-6 kinetics in critically ill patients may be heterogeneous and influenced by a number of factors. Furthermore, IL-6 Levels alone may not be especially predictive of the patient's future reaction [4]. Addition-ally, from a practical perspective IL-6 Levels might not be available in a timely manner in every center. Various clinical studies have shown good results with CytoSorb® therapy when patient selection was not based on IL-6 Levels, but rather the clinical picture of (refractory) septic shock with elevated (and increasing) levels of vasopressor needs and other criteria [7,12,18]. In the light of all this it was decided that measuring IL-6 Levels before initiating CytoSorb® treatment for refractory septic shock was NOT mandatory.

Q4: There are patients who may require more than one CytoSorb® adsorber to achieve sufficient hemodynamic stabilization.

Expert panel Agreement: A total of 90.91% experts agreed that there are patients who may require more than one CytoSorb® adsorber to achieve sufficient hemodynamic stabilization (Consensus Achieved).

Reason /Scientific evidence: In a systematic review and meta-analysis, Hawchar *et al* (2021) examined the role of hemoadsorption using CytoSorb® in attaining quick haemo-dynamic stabilisation in patients with refractory vasoplegic shock [10]. The

available data demonstrated that early CytoSorb® therapy resulted in a considerable reduction in vasopressor (norepinephrine) need following treatment [median from 0.55 µg/kg/min to 0.09 microg/kg/min, p 0.05], which indicates the important contribution of early hemoadsorption in achieving rapid hemodynamic stabilization in patients with refractory vasoplegic shock [10]. Rugg *et al* (2020) could improve hemodynamic stabilization with only one adsorber having been used in the majority of the patients [12]. Friesecke *et al* (2017) on the other hand utilized a mean of 3 ± 1.5 CytoSorb® adsorbers per patient when they con-ducted a prospective clinical study in twenty patients with refractory septic shock [19]. Also, in this research, CytoSorb® therapy had favorable outcomes. and resulted in a considerable reduction in vasopressor (noradrenaline) needs as well as an increase in lactate clearance. Shock reversal was achieved in 65% (*n* = 13) of the patients [19]. So, in conclusion the number of adsorbers needed might vary from patient to patient and there are patients who may require more than one CytoSorb® adsorber to achieve sufficient hemodynamic stabilization.

Q5: If you want to continue with CytoSorb® therapy, the adsorber should be changed after 6-24 h depending on the clinical course and the machine type availability.

Expert panel Agreement: All experts (100%) agreed that if CytoSorb® therapy is continued, the adsorber should be changed after 6-24 h depending on the clinical course and the machine type availability. (Consensus Achieved)

Reason /Scientific evidence: According to the current IFU [20], one adsorber can stay for upto 24 h on a patient. Recent experiences however suggest that some patients seem to benefit from earlier changes of the adsorber i.e., after 12 h or even earlier. Back in April 2020 the US Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) had been granted for CytoSorb® extracorporeal blood purification treatment to reduce hyperinflammation in seriously ill COVID-19 patients [21]. An FDA-specific dose of 12:12:24:24 h had to be used in these patients. Song *et al* retrospectively analysed the data from a US CytoSorb® Therapy in COVID-19 (CTC) Registry. The analysis showed that CytoSorb® treatment was linked with improved survival rates in critically ill COVID-19 patients who received extracorporeal membrane oxygenation (ECHO) [21].

Earlier changes might ensure an ongoing high removal capacity of the adsorber avoiding early saturation in situation with a high cytokine load for the device [22]. Therefore, a change of adsorber might be appropriate anytime between 6-24 h. It was discussed that it does not need to be changed earlier than 6 h as the device would work properly but a change should not occur later than 24 h to comply with the cur-rent IFU, also as no significant removal capacity beyond this point should be expected from the adsorber. As usual, the exact timing of adsorber changes (if applicable) would vary from patient to patient.

Q6: CytoSorb® therapy is generally a safe therapy.

Expert panel Agreement: A total of 90.91% experts agreed that CytoSorb® is generally a safe therapy. (Consensus Achieved)

It was also acknowledged that as with all other therapeutic measures even CytoSorb® has its own side effects, but it is generally safe therapy.

Reason /Scientific evidence: To date CytoSorb® therapy has been used in a wide variety of critically ill patients [23]. Features like size-selectivity and concentration dependency as well as the high biocompatibility support a favourable safety profile of the device, which was further supported by various publications [23].

Diab *et al* (2022) conducted a multicenter randomized controlled trial of CytoSorb therapy in patients undergoing surgery for infective endo carditis (REMOVE trial) [24]. A total of 288 patients were randomly allocated to either intraoperative CytoSorb® hemoadsorption (n = 142) or control (n = 146). Apart from the effect on postoperative organ dysfunction, the trial also investigated the safety profile in the two groups, which included peri-operative complications and adverse events [24]. The trial found that the frequency and pattern of postoperative complications and adverse events (distributive shock, acute renal dysfunction, respiratory insufficiency, re-exploration for bleeding, central nervous system related, and cardiac events) were comparable in both groups, confirming the safety of this device [24].

The results of the Eleventh analysis of registry data from an International CytoSorb® Registry conducted by Hawchar *et al* (2022) further supported the favourable safety

profile of CytoSorb® therapy [25]. Data from 1434 critically ill patients (sepsis/septic shock (65.3%), cardiac surgery perioperatively (11.9%), cardiac surgery postoperatively (4.7%), and other (18.1%) indications) from 46 centres revealed that CytoSorb® treatment related complications (cardiac, respiratory, blood, central nervous, and kidney related) were re-ported in only 2.16% (n = 31) patients, whereas the majority of patients (97.8%, n = 1403) had no reported CytoSorb® treatment-related complications [25]. They concluded that in line with all other papers published so far, regardless of the type of the study or case report, the 11th analysis of the Registry data further suggests that CytoSorb® therapy is safe [25]. So, despite acknowledging that, like any other therapeutic interventions, CytoSorb® can also have adverse effects, *e.g.*, with regard to unwanted drug removal or complications associated with the extracorporeal circuit, the therapy was regarded as generally safe.

Q7: Sepsis-induced AKI requiring renal replacement therapy (RRT) is no prerequisite to initiate CytoSorb® therapy in refractory septic shock patients.

Expert panel Agreement: All experts (100%) agreed that sepsis-induced AKI requiring RRT is not a prerequisite to initiate CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved)

Reason /Scientific evidence: CytoSorb® therapy is a hemoadsorption therapy targeting small and middle-sized hydrophobic substances. This is in contrast to the classical hydrophilic targets of RRT. Circuits from renal replacement systems can be used technically for integration of the CytoSorb® adsorber, however, in principle the decision for or against CytoSorb® should be made independent of the indication and start of continuous renal replacement therapy (CRRT) or other extracorporeal therapies as one cannot replace the other [26].

Hawchar *et al* (2019) conducted a prospective, randomised pilot study of CytoSorb® as a stand-alone therapy in patients with septic shock in Hungary [7]. Twenty (n = 20) patients with septic shock of medical origin, on mechanical ventilation, norepinephrine > 10 µg/min, procalcitonin > 3 ng/mL, but no requirement for RRT were included in this proof-of-concept trial and were randomised into CytoSorb® (n = 10) and Control (n

= 10) groups [7]. Over the assessed time-points, vasopressor (norepinephrine) requirements and procalcitonin levels decreased significantly in the CytoSorb® group compared to the control group ($P<0.05$) [7].

If early need for RRT due to sepsis-induced AKI crises, integration of CytoSorb® into the circuit can still be easy, however waiting for an RRT indication shouldn't delay the start of CytoSorb® when appropriate to address hyperinflammation and ongoing haemo-dynamic instability in early refractory septic shock. Therefore, sepsis-induced AKI requiring RRT was NOT seen as a prerequisite to initiate CytoSorb® therapy in these patients.

Q8: Evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like hemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality.

Expert panel Agreement: A total of 90.91% experts agreed that the evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like hemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality. (Consensus Achieved)

Reason /Scientific evidence: Sepsis is a syndrome and not a disease and septic shock is a disorder with a diverse phenotype. First of all, CytoSorb® therapy is not primary therapy to treat sepsis, but only an adjunctive option to address the dysregulated immune response as an underlying problem in septic shock patients. So CytoSorb® is solely used to eliminate cytokines (and other mediators) and decrease the complications of a dysregulated host response [8]. Thus, objective assessment of CytoSorb® in septic shock is challenging. Furthermore, the reason for mortality in septic shock patients may be multifunctional and not directly attributable to the host response, which can lead to overestimation of syndrome-attributable risks [27].

Various endpoints such as hemodynamic stabilisation, improvement in organ function or inflammatory biomarkers, and survival have been recorded in studies with Cyto-Sorb® in sepsis / septic shock [7,8,10,19]. Understanding the complexity of the syndrome, assessment of the efficacy of CytoSorb® treatment in studies should be based on the

complexities of critical illness syndromes with endpoints such as hemodynamic stability, inflammatory biomarkers, and/or improvement in organ function rather than mortality.

Q9: Do you think this flowchart can be helpful to a doctor very new to the therapy to ensure a certain level of best practice?

Expert panel disagreement: initially but all experts (100%) agreed on the revised flowchart for doctors new to therapy. (Consensus Achieved)

Reasons: Based on the following discussion, the original flowchart was revised and the revised flowchart was agreed upon (see Figure 1).

Suggested modifications in original flowchart:

1) Changing the time period to change the adsorber from the 12 h specified in the chart to 6-24 h based on clinical criteria.

2) The flowchart should preferably be modified to contain three distinct pathways for patients who were significantly improving, slightly improving, and not at all improving.

3) For the benefit of physicians with less experience in this area, it may also be necessary to mention the potential criteria for starting therapy with inclusion of the **CytoScore** [15] definition along with therapy flow chart.

Q10: Future recommendations for CytoSorb® therapy (Open ended discussion and not for voting)

Recommendation:

To establish an association/ society that can maintain a registry on the utilization of CytoSorb® in the management of different indications. This will help to get valuable real-world evidence data about the potential of this therapy in multiple clinical conditions and its effect on patient outcomes.

DISCUSSION

Septic shock occurs from a dysfunctional host response to infection, resulting in a state described as a "cytokine storm" that progresses to shock and carries the high risk of

development of a multi organ dysfunction syndrome [1,28]. The standard therapy is timely resuscitation, antibiotics, and targeted vasopressors [5]. Despite standard therapy, a certain subset of individuals have poor outcomes and require adjuvant therapy [5]. To improve outcomes, various innovative adjuvant therapies have been explored. Blood purification treatments, such as high-volume continuous haemofiltration or cytokine and/or endotoxin elimination, have been proposed as one such strategy to promote immune homeostasis [4].

Sorbent technologies have recently garnered a lot of consideration. CytoSorb® based hemoadsorption is one such therapy. The CytoSorb® device is composed of biocompatible, extremely porous polymer beads [7,20,24]. The adsorber has a surface area of around 45,000 m^2 compared to a standard hemofilter with a surface area of 1-1.5 m^2 and a molecular cut-off of approximately 60 kDa for eliminating cytokines as well as other hydro-phobic substances. As a result, CytoSorb® does not adsorb endotoxin with a molecular weight of 100 kDa [4,7,20,29]. CytoSorb® has been developed and approved for treatment in patients with severe cytokinemia, but can also be adsorb to eliminate bilirubin, myo-globin, free haemoglobin and the antithrombotics ticagrelor and rivaroxaban during cardiopulmonary bypass [24]. Studies have revealed favorable results in patients with sepsis and septic shock, with, however, only limited evidence from randomized control trials [7,10,11,12,17,28].

In this consensus paper, an attempt was made to address the utilization and adoption of CytoSorb based hemoadsorption therapy in patients with septic shock with critical appraisal of the evidence from the current available literature. This consensus statement gives more information/ clarity on the key areas of knowledge gaps of CytoSorb® therapy: need for adjuvant therapy, initiation timeline, need for Interleukin -6 Levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and (therapy) management flowchart. Table 2 summarizes the consensus statement. The current consensus statements are based on existing literature data, primarily from case series, prospective / retrospective studies, and limited randomised

trials. These statements also augment subject experts' opinions/views based on their clinical expertise and resource settings.

These consensus statements are intended to offer guidance to clinicians working in the field of critical care/ emergency care, healthcare manager, healthcare organizations and patients regarding the use of CytoSorb® in septic shock.

We expect that this expert agreement will facilitate the personalized, safe, and pragmatic use of CytoSorb® hemoadsorption in septic shock patients in the critical care set-ting. Knowledge always lags behind evidence, and this expert consensus has shortcomings that we intend to resolve in future.

The consensus statements has both strengths and limitations.

Major strengths:

(1) Being the first sort of consensus statement that provides information and guidance on the use of CytoSorb® therapy in critically ill/ septic shock patients in India.

(2) Involving a significant group of experts from various geographical cities across India with long standing experience in the field of critical care.

(3) Providing various articles on CytoSorb therapy (based on a systematic review) and the critically appraising evidence by sharing it with all participating experts.

(4) Using a modified Delphi technique with open-ended (text-based) feedback from respondents and subsequent adaptation.

(5) Providing of a Flowchart for the Indian market which will help doctors to optimise for the use of CytoSorb® therapy in septic shock patients.

Limitations:

1) Although the majority of the publications critically evaluated after the systematic review were research studies, case series, and systematic reviews, there is substantially less evidence from randomised control trials.

CONCLUSION

This Indian perspective consensus statement supports and provides guidance on the use of CytoSorb® hemoadsorption as an adjuvant treatment in patients with septic

shock to achieve optimal outcomes. We hope that this consensus statement will help in facilitating proper treatment initiation and maintenance of CytoSorb® hemoadsorption therapy in the management of refractory septic shock and it may also contribute in the optimization of refractory septic shock treatment in India.

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