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Assessment of the Microcirculation During Extracorporeal Blood Purification in Septic Patients: A Narrative Review

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Abstract

Background: Microcirculatory dysfunction is a key feature of septic shock and contributes to organ failure despite the apparent normalization of systemic hemodynamic parameters. Extracorporeal blood purification (EBP) therapies aim to modulate the dysregulated inflammatory response through removal of endotoxins and cytokines; however, their impact on tissue-level perfusion remains unclear. Direct bedside assessment of microcirculation may provide mechanistic insight into the effects of EBP beyond macrohemodynamic stabilization. **Methods:** This structured narrative review summarizes current evidence on direct microcirculatory assessment during EBP therapy in sepsis. A literature search of PubMed, Web of Science, and Scopus was performed using combinations of the terms "microcirculation" and "blood purification" or "hemoadsorption." Studies published between 2015 and 2026 evaluating direct sublingual microcirculation using sidestream dark field (SDF) or incident dark field (IDF) videomicroscopy during EBP were included. Both experimental and clinical studies were considered. **Results:** Eight studies met the inclusion criteria. Selective endotoxin adsorption with polymyxin B hemoperfusion (PMX-HP) demonstrated improvements in perfused vessel density and small vessel density in both animal and clinical settings. Non-selective cytokine adsorption devices (CytoSorb and HA380) were associated with increases in microvascular flow index (MFI), perfused vessel density (PVD), and proportion of perfused vessels (PPV), although most data derive from small observational studies. Across studies, improvements in microcirculatory parameters were observed during or following hemoadsorption therapy; however, heterogeneity in design, timing, and concomitant treatments limits definitive interpretation. **Conclusions:** Current evidence suggests that EBP may positively influence microvascular perfusion in septic shock when assessed using direct videomicroscopy. Nevertheless, data remain limited and predominantly observational. Larger randomized controlled trials incorporating predefined microcirculatory endpoints are required to determine whether mediator removal translates into sustained restoration of tissue perfusion and improved clinical outcomes.

Keywords: sepsis; direct microcirculation assessment; videomicroscopy; tissue perfusion; extracorporeal blood purification

1. Introduction

Septic shock is a life-threatening condition characterized by a dysregulated immune response to infection, resulting in profound circulatory, cellular, and metabolic disturbances. These alterations lead to both macro- and microhemodynamic dysfunction, impaired tissue perfusion, and ultimately multi-organ failure [1–4], making microcirculatory dysfunction a key pathophysiological feature of septic shock. Moreover, persistent microvascular alterations may contribute to ongoing organ dysfunction even when global hemodynamics appear stabilized [5–8].

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Extracorporeal blood purification (EBP) therapies have been introduced as adjunctive treatments in septic shock with the aim of modulating the dysregulated inflammatory response [9–11]. Although conclusive evidence demonstrating improved clinical outcomes remains limited, these therapies continue to be widely adopted in clinical practice [12,13]. Several studies have reported reductions in vasopressor requirements and improvements in selected macrohemodynamic parameters [14–17]; however, whether such systemic changes translate into recovery of the microcirculation remains unclear [11,18].

Microcirculatory assessment during EBP has most commonly relied on indirect markers such as lactate clearance. However, lactate does not represent a direct measure of microvascular perfusion, thereby limiting its reliability as an indicator of true microcirculatory recovery. In contrast, direct visualization techniques such as sidestream dark field (SDF) and incident dark field (IDF) videomicroscopy enable quantitative evaluation of capillary flow and have demonstrated clinical utility in critically ill patients [19–22]. By removing circulating cytokines, endotoxins, and other inflammatory mediators, EBP devices are theoretically capable of influencing microvascular function. For these therapies to confer meaningful clinical benefit, their effects should extend beyond systemic stabilization to the restoration of effective tissue perfusion. Given the association between microcirculatory impairment and adverse outcomes in sepsis, evaluating microvascular responses during EBP therapy may provide important mechanistic and prognostic insights [8,11]. Monitoring changes in the microcirculation could help guide the initiation, duration, and termination of EBP therapy—particularly in settings where advanced biochemical immunomonitoring is not readily available [11,18]. However, despite this rationale, there is currently no standardized framework for incorporating microcirculation monitoring into clinical decision-making during EBP therapy [23,24].

Given the central role of microvascular dysfunction in septic organ failure, a clearer understanding of how EBP influences tissue-level perfusion is needed. The aim of this narrative review is to critically evaluate current clinical studies assessing microcirculatory changes during extracorporeal blood purification in sepsis and septic shock. By synthesizing available evidence and identifying methodological limitations and knowledge gaps, we seek to clarify the current state of evidence and its implications for clinical practice.

2. Materials and Methods

This manuscript provides an overview of the impact of inflammatory mediators—particularly endotoxins and cytokines—on the microcirculation, and summarizes currently available EBP techniques and bedside microcirculation monitoring methods, thereby establishing the background necessary for interpreting clinical studies evaluating microcirculatory changes during EBP therapy in septic shock patients.

Search Strategy and Study Selection

This narrative review was prepared in accordance with SANRA principles for narrative reviews. A structured literature search was conducted in three electronic databases: PubMed, Web of Science, and Scopus. The search included studies published between January 2015 and March 2026. The search strategy combined controlled vocabulary (Medical Subject Headings, MeSH, in PubMed) and free-text terms related to microcirculation, sepsis, and extracorporeal blood purification. To ensure transparency and reproducibility, the full database-specific search strategies are provided in the Supplementary Materials (**Table S1**).

The search aimed to identify studies evaluating microcirculatory alterations in septic patients undergoing EBP therapy, with particular focus on direct microcirculation assessment using techniques such as SDF or IDF videomicroscopy. Broader search terms were retained to minimize the risk of missing relevant studies due to variability in terminology and indexing.

Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. The screening process was performed independently by two reviewers, with disagreements resolved through discussion and consensus.

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Studies were included if they met the following criteria: (1) publication in English; (2) availability of full text; (3) publication between 2015 and 2026; and (4) evaluation of direct microcirculation in the context of EBP therapy in septic patients. Eligible study designs included observational, interventional, experimental studies, and relevant case reports.

To ensure comprehensive study identification, the database search was supplemented by manual screening of reference lists of included articles and relevant review papers, as well as targeted searches using specific device names (e.g., CytoSorb, HA380, polymyxin B hemoperfusion) and related articles suggested by database algorithms.

The final selection of articles was based on relevance to the objectives of the review, as determined through consensus among the reviewers. This review does not aim to provide an exhaustive systematic synthesis but rather to critically summarize the available evidence and highlight key methodological considerations, principal findings, and existing knowledge gaps.

No formal risk-of-bias assessment tool was applied; however, methodological limitations of the included studies were considered during data interpretation.

3. Pathophysiological and Methodological Background

3.1. Microcirculatory Change in Septic Shock

The pathophysiology of septic shock is thought to involve complex interactions between pathogen and a dysregulated host immune system, leading to the release of excess inflammatory mediators, immunosuppression and immune paralysis [3,4]. A dysregulated inflammatory response to infection refers to the breakdown of the coordinated function of large (macro) and small (micro) blood vessels, also known as loss of coherence [5–7]. Sepsis-induced microcirculatory disturbances are characterized by reduced capillary density and increased microvascular perfusion heterogeneity resulting from dysregulated vasodilation and vasoconstriction [6–9]. These alterations play an important role in the heterogeneity of oxygen delivery to tissues and lead to the development of organ dysfunction and sepsis progression [5,8].

The resuscitation strategy recommended in international guidelines [26] for septic shock has historically focused on improving the macrocirculation (although the ultimate goal is to normalize the microcirculation and maintain end-organ perfusion), primarily by restoring mean arterial blood pressure (MAP) and cardiac output. While a pre-defined MAP above 65 mmHg is the most common approach, recent evidence suggests that MAP may not correlate with adequate blood flow through the end capillaries (microcirculation) and that microcirculatory dysfunction may exist despite a normal MAP. This means that even if the blood pressure (macrocirculation) normalizes, the microcirculatory dysfunction persists and leads to organ failure [5]. For this reason, microcirculatory assessment tools have been developed, although microcirculatory function is not currently routinely monitored at the bedside.

De Backer et al. (2013) [27] confirmed that microvascular and macrovascular parameters operate independently. Their study also showed that microcirculatory alterations are more pronounced in the early phase of sepsis, and that the proportion of perfused small vessels (reflecting perfusion heterogeneity) serves as an independent predictor of outcome. Similar results were reported in an animal study by Zhang et al. which showed that microcirculation and macrocirculation behave independently in endotoxemic shock, with disturbances in microcirculation occurring before changes in macrocirculation parameters [28]. In the study by Nicolas Fage et al., fluid-responsive patients demonstrated significant increase in cardiac output following fluid infusion and MAP after administration of noradrenaline. However, the capillary refill time (CRT) response was variable — decreasing in some patients while remaining unchanged in others—highlighting a dissociation between macro- and microhemodynamic variables [29]. In contrast to the previously mentioned studies, several investigations have shown a positive correlation between macro- and microcirculatory parameters during septic shock, particularly in the early phase of treatment [30,31].

The role of inflammatory mediators in microcirculatory dysfunction

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The exaggerated host response in sepsis can lead to both structural and functional damage to the endothelium — the key regulator of microvascular homeostasis. Critical endothelial functions become impaired, contributing to the formation of microthrombi, tissue edema, interstitial fluid leakage and dysregulation of vascular tone [8,9]. As a result, the primary function of the microcirculation—delivering oxygen from red blood cells to tissue cells—becomes impaired [23,30].

In case of gram negative sepsis, the excessive release of cytokines is often triggered by lipopolysaccharide (LPS, endotoxin), an integral component of the outer membrane of bacteria [32]. Endotoxin per se can lead to a variety of microcirculatory changes by reprogramming endothelial cells in a proinflammatory sense: damage to the glycocalyx with subsequent loss of endothelial integrity, dysregulation of vascular tone due to overproduction of NO and coagulopathy [33]. While endotoxin is the main coordinator of gram-negative septic shock, it can also occur in gram-positive septic shock, where the presence of endotoxin could be explained by translocation of bacteria from an ischemic gut. Even at relatively low doses, endotoxin can significantly impair the immune system [34], while higher levels are strongly associated with the development of septic shock [35,36]. The subsequent overproduction of pro-inflammatory cytokines further exacerbates endothelial damage and leads to microcirculatory disturbances [6,8].

The enhanced immune response contributes to a toxic concentration that leads to multiorgan failure, coagulopathy and hyperlactatemia [37]. Therefore, it seems logical that inflammatory mediators such as endotoxin and cytokines play a key role in disrupting macro- and microcirculatory coherence in septic shock. Therapeutic approaches aimed at reducing inflammatory mediators below toxic thresholds may help to restore the disrupted interplay between micro- and macrohemodynamics [19].

3.2. Extracorporeal Blood Purification Techniques in Septic Shock

Various types of extracorporeal blood purification therapies aimed at removing excess inflammation to achieve physiologic homeostasis have been proposed as supportive therapy in the treatment of septic shock [10,38]. In the context of EBP therapy for septic patients, the method is primarily based on the physical principle of adsorption rather than diffusion or convection. It is therefore often referred to as hemoadsorption (previously termed hemoperfusion). Hemoadsorption (HA) therapies can be classified as either targeted (selective) or broad-spectrum (non-selective) based on their solute removal properties, and may be performed either as stand-alone treatments or in combination with continuous renal replacement therapy (CRRT). Broad-spectrum technologies act on multiple solutes simultaneously, whereas targeted technologies aim to remove specific molecules, such as endotoxin [12,39].

The most commonly used non-selective EBP devices include the Oxiris® membrane (Vantive, IL, USA), which adsorbs both cytokines and endotoxins, as well as the CytoSorb® cartridge (CytoSorbents Corporation, USA) and the HA380 cartridge (Jafron Biomedical, China), both of which provide non-selective cytokines adsorption. The only widely used selective EBP therapy currently available is polymyxin B hemoperfusion (PMX-HP; Toray Industries Inc., Tokyo, Japan), which specifically targets endotoxin removal [10,12]. In recent years, additional adsorption devices have been introduced, including the Efferon® LSP cartridge (Efferon OÜ, Estonia), designed for selective endotoxin removal [17], and the CA330 series cartridges (Jafron Biomedical, China), developed for cytokine adsorption in septic patients [18]. However, clinical data supporting their widespread use and effectiveness in routine practice remain limited.

Despite its promising potential, the efficacy of EBP therapies in septic shock patients remains controversial, as large randomized controlled trials have not demonstrated a clear long-term survival benefit [13,16]. Major challenges include suboptimal timing for the initiation and termination of hemoadsorption, premature saturation of hemoadsorption devices that often goes undetected in time, and inadequate patient selection due to the lack of effective immunomonitoring methods [10,12,13]. Although the removal of target solutes— such as endotoxins or cytokines— is the primary goal of initiating EBP therapy, the measurement of these molecules is often limited by the availability,

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accuracy and cost of the tests [35,37]. Therefore, treatment decisions are typically based on clinical indicators such as hemodynamic instability, organ dysfunction and microcirculatory impairment. However, there is currently no standardized approach for integrating advanced microcirculation monitoring techniques into clinical decision-making during EBP therapies, and clinicians continue to rely on visual or biochemical markers of microcirculatory dysfunction [12,40].

3.3. Microcirculatory Assessment in Septic Shock and Its Relevance During Blood Purification

Given the loss of coherence between micro- and macrohemodynamics in sepsis, management strategies in septic shock should incorporate assessment of the microcirculation rather than relying solely on systemic hemodynamic variables [6,8]. Historically, the most commonly used approaches for evaluating microcirculation in clinical practice have been visual bedside assessment and biochemical markers [1]; however, both provide only indirect information regarding microvascular function.

Visual assessment methods—including the skin mottling score (SMS) and capillary refill time (CRT)—offer simple and non-invasive estimates of peripheral perfusion and have demonstrated prognostic relevance in septic shock [43,44]. Nevertheless, these tools remain semi-quantitative and operator-dependent. The ANDROMEDA-SHOCK-2 trial [44] described a standardized approach to CRT assessment, aiming to improve measurement consistency and reduce variability. Furthermore, automated CRT systems have been developed to minimize observer bias by applying controlled pressure and using optical sensors to detect reperfusion following blanching [45,46]. Although these technologies may improve reproducibility, current evidence is limited by small sample sizes, and large-scale clinical validation is still lacking.

The biochemical approach primarily relies on serial serum lactate measurements and lactate clearance. Lactate remains one of the most widely used biomarkers of tissue hypoperfusion in septic shock [1,47]. However, lactate reflects global metabolic stress rather than direct microvascular flow and lacks specificity for microcirculatory dysfunction. Moreover, in the context of extracorporeal blood purification—particularly when hemoadsorption is combined with renal replacement modalities—lactate levels may be influenced by extracorporeal removal, potentially limiting their reliability as indicators of true microcirculatory recovery.

Given the limitations of visual and biochemical approaches [48–51], optical imaging techniques have increasingly been adopted in research practice over recent decades [23,25]. These include near-infrared spectroscopy (NIRS), photoplethysmography-based indices, and videomicroscopy. NIRS measures regional tissue oxygen saturation, reflecting the balance between oxygen delivery and consumption at the tissue level. Photoplethysmography-derived indices, such as the perfusion index or pulse amplitude index, estimate peripheral perfusion by quantifying pulsatile blood flow within the microvascular bed. While NIRS and photoplethysmography provide indirect information on tissue oxygenation or peripheral perfusion, they do not directly visualize capillary blood flow. Thus, videomicroscopy currently represents the only direct bedside method for assessing microcirculation in clinical research.

Direct microcirculatory assessment relies on high-resolution videomicroscopy techniques, such as sidestream dark field (SDF) and incident dark field (IDF) imaging [23]. These methods enable in vivo visualization of the microvascular network and allow quantitative measurement of capillary density, perfusion, and flow dynamics. Key parameters include small vessel density (SVD), total vessel density (TVD), perfused vessel density (PVD), proportion of perfused vessels (PPV), microvascular flow index (MFI), and flow heterogeneity index (HI). SVD and TVD reflect the structural density of the capillary network, whereas PVD and PPV represent the functional component of perfusion by quantifying the proportion and density of vessels with continuous blood flow. MFI provides a semi-quantitative assessment of flow quality using a score from 0 (no flow) to 3 (normal continuous flow), while the HI describes the spatial variability of perfusion between different quadrants of the imaging field. Impaired microcirculation is characterized by reduced functional capillary density, decreased perfused vessel proportion, heterogeneous or intermittent

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flow, and increased flow heterogeneity—findings that are associated with organ dysfunction and adverse outcomes in septic shock [26]. In clinical research, microcirculatory assessment using videomicroscopy has been most extensively performed at the sublingual site, where the thin epithelial layer permits optimal image acquisition and reliable visualization of capillary flow [7,52]. Changes observed in the sublingual microvascular network have been shown to correlate with perfusion abnormalities in internal organs, supporting its use as a surrogate marker of global tissue perfusion [47,53–55].

Given these methodological differences and the limitations of surrogate markers, the present review places particular emphasis on studies employing direct optical assessment of the microcirculation when evaluating the impact of extracorporeal blood purification therapies.

4. Results

In accordance with the predefined search strategy, 46 records were identified through PubMed, 42 through Web of Science, and 84 through Scopus. After removal of duplicate records, the remaining articles underwent a two-step screening process. Titles and abstracts were first assessed for relevance, followed by full-text evaluation to determine methodological eligibility. Only studies that specifically evaluated direct microcirculatory assessment during EBP therapies using hemoadsorption devices (e.g., hemoadsorption or hemoperfusion), either as stand-alone treatments or in combination with CRRT, were considered eligible for inclusion. After applying these criteria, a total of eight studies met the inclusion requirements and were selected for detailed analysis.

The characteristics and principal findings of the eight included studies are summarized in **Table 1.** The table presents the study design, study population, type of EBP therapy, method of direct microcirculatory assessment, evaluated microcirculatory parameters, and the main reported effects on microvascular perfusion.

Table 1. Review of clinical studies in chronological order using optical imaging techniques for direct microcirculation assessment during blood purification therapies.

Study	Study design	Hemoadsorption device	Microcirculation assessment tool	Main findings
Yeh et al. (2015) [56]	Prospective clinical	Selective endotoxin adsorption with Polymyxin B-immobilized fiber column (**PMX-HP**); stand-alone mode	SDF videomicroscopy	SVD and perfused SVD higher at 48 h in PMX-HP vs control ($p = 0.001$; $p < 0.001$).
Yeh et al. (2017) [57]	Experimental animal (septic pigs)	**PMX-HP,** stand-alone mode	SDF videomicroscopy and tissue oxygen saturation	PMX-HP significantly improved perfused SVD and tissue oxygen saturation at 6 h vs untreated sepsis ($p < 0.05$); histologic injury was reduced.
Chen et al. (2020) [58]	Randomized Controlled Trial (28 adults included; 14 in interventional	**PMX-HP,** stand-alone mode	SDF videomicroscopy	PMX-HP treatment significantly improved microcirculation in patients with septic shock, as evidenced by higher TVD ($p=0.007$) and PVD ($p=0.008$)

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	group and 14 in control group)			at 48 h in the PMX-HP group compared to the control group.
Zuccari et al. (2020) [59]	Prospective Observational Study (9 adults included)	Unselective cytokines adsorption with **CytoSorb** and CRRT	SDF videomicroscopy and NIRS with vascular occlusion test	Microvascular perfusion improved over time, with a significant increase in PVD at 6 and 24 h ($p = 0.003$) and TVD at 24 h ($p = 0.0015$). No significant variations were found in NIRS-derived parameters related to tissue oxygenation or microvascular reactivity.
Bottari et al. (2021) [60]	Case report (pediatric patient with severe MIS-C)	**CytoSorb** + CRRT	IDF videomicroscopy	Serial IDF imaging showed marked microcirculatory impairment during the first 96 h (MFI <2.75, reduced TVD, PPV, PVD, increased HI). Despite early hemodynamic recovery, principal microcirculatory parameters improved only after 96 h (day 5), indicating delayed restoration of microvascular perfusion
Duran et al. (2022) [61]	Case report (adult with abdominal sepsis)	**CytoSorb** + CRRT	IDF videomicroscopy	IDF imaging showed severe baseline microcirculatory impairment with subsequent improvement in MFI and PVD during hemoadsorption therapy
Zhu et al. (2024) [62]	Randomized Controlled Trial (107 adults included; 54 patients in interventional group and 53 patients in control group)	Unselective cytokines adsorption with **HA380** hemoperfusion cartridge + CRRT	SDF videomicroscopy	HA380 hemadsorption combined with CVVHDF significantly improved microcirculatory parameters, including MFI and PPV ($p<0.01$), after 7 days of treatment compared to the control group.
Bottari et al. (2024) [63]	Single-Center Observational Study/pilot study (13 pediatric patients included)	**CytoSorb** +CRRT	IDF videomicroscopy	10 of the 13 included patients undergoing hemadsorption therapy showed improvements in microcirculatory parameters, including statistically significant increase of MFI ($p = 0.01$) and PPV ($p = 0.04$), suggesting enhanced microvascular perfusion.

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Below is a list of variables used to assess microcirculation with brief explanations, mentioned in the referenced studies.

Total Vessel Density (TVD, mm/mm²): The TVD is calculated as the total length of vessels divided by the total surface area of the region of interest. It reflects the structural vessel density within the observed microvascular network, independent of flow status.

Small Vessel Density (SVD, mm/mm²): SVD represents the total length of small vessels (typically ≤20 μm in diameter) divided by the total surface area of the region of interest. It specifically quantifies capillary-level vessel density and is particularly relevant in septic shock, where small-vessel alterations are most pronounced.

Perfused Vessel Density (PVD, mm/mm²): an indicator of functional vessel density and is determined as the total length of perfused vessels divided by the total surface area. It reflects the density of vessels with continuous blood flow and is often used as a surrogate for functional capillary density.

Proportion of Perfused Vessels (PPV, %): reflects the overall quality of microvascular perfusion and is calculated as the number of perfused vessels divided by the total number of vessels, expressed as a percentage. It represents the proportion of vessels that are effectively perfused within the observed field.

Microvascular Flow Index (MFI): a semi-quantitative measure of flow quality in microcirculation. The imaging field is divided into four quadrants, each scored from 0 to 3 based on observed flow characteristics (0 = no flow, 1 = intermittent flow, 2 = slow flow, 3 = continuous flow). The final MFI is calculated as the average of these scores, providing an overall assessment of microvascular perfusion.

Abbreviations: CRRT (continuous renal replacement therapy); CVVHDF (continuous veno-venous hemodiafiltration); (IDF) (Incident Dark Field videomicroscopy), MIS-C (multisystem inflammatory syndrome); MFI (microvascular flow index); NIRS (Near-Infrared Spectroscopy), PMX-HP (Polymyxin B-immobilized fiber column), PVD (perfused vessel density), PPV (proportion of perfused vessels), SDF (Sidestream Dark Field videomicroscopy), SVD (small vessel density), TVD (total vessel density)

As mentioned above, videomicroscopy provide a direct assessment of the changes in microcirculation in critically ill patients, including patients undergoing EBP. Several recent studies have demonstrated the utility of SDF or IDF videomicroscopy in evaluating microcirculatory changes during hemoadsorption therapy.

In a recent randomized controlled trial, Chen et al. (2020) [58] demonstrated the improvement of microcirculation in patients with septic shock treated with selective endotoxin hemoadsorbent PMX-HP. The main finding of this study was that total vessel density (TVD) and perfused vessel density (PVD) were higher in the PMX-HP group than in the control group, indicating improved microcirculation as a result of treatment. These findings are consistent with earlier investigations by Yeh et al. In an experimental septic pig model, Yeh et al. (2017) [57] showed that PMX-HP significantly improved perfused small vessel density and tissue oxygen saturation within 6 h compared with untreated sepsis, and was associated with reduced histologic organ injury. Similarly, in a prospective clinical study of patients with severe sepsis and septic shock, Yeh et al. (2015) [56] reported significantly higher small vessel density and perfused small vessel density at 48 h in patients treated with PMX-HP compared with controls.

In a prospective observational study, Zuccari et al. (2020) [59] assessed microcirculatory parameters using SDF videomicroscopy and NIRS in septic patients undergoing non-selective cytokine hemoadsorption with the CytoSorb cartridge during continuous renal replacement therapy. Changes in microcirculation were assessed at baseline, 6 h, and 24 h after the start of the procedure. The study showed a significant improvement in microvascular perfusion, particularly in PVD at 6 and 24 h and in TVD at 24 h. In contrast, NIRS-derived parameters showed no significant changes, highlighting the superior sensitivity of videomicroscopy in detecting early improvements in microcirculation.

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Evidence supporting the microcirculatory effects of CytoSorb has also been reported in individual clinical cases. Duran et al. (2022) [61], in an adult patient with abdominal sepsis, used IDF videomicroscopy and demonstrated severe baseline microcirculatory impairment with progressive improvement in MFI and PVD during hemoadsorption therapy. Similarly, Bottari et al. (2021) [60] described a pediatric case of severe multisystem inflammatory syndrome in which serial IDF imaging revealed marked microcirculatory alterations during the first 96 h, followed by delayed improvement of key parameters despite early macrocirculatory stabilization. This observation suggested a lack of hemodynamic coherence in the early phase and highlighted the importance of direct microcirculatory monitoring during extracorporeal blood purification. The improvement in microcirculation during CytoSorb treatment was further demonstrated in a larger pediatric cohort by Bottari et al. (2024) [63]. In this single-center pilot study of critically ill children with septic shock receiving adjunctive hemoadsorption therapy, sublingual microcirculation was assessed using IDF videomicroscopy. The study showed statistically significant improvements in microcirculatory parameters, particularly an increase in microvascular flow index and proportion of perfused vessels, indicating enhanced microvascular perfusion during treatment.

Comparable improvements in MFI and PPV were described in a randomized controlled trial by Zhu et al. (2024) [62], which evaluated adult patients with sepsis treated with the non-selective cytokine adsorber HA380. However, within the scope of the studies analyzed in this review, HA380 was investigated in only a single trial. In that study, microcirculatory parameters significantly improved after 7 days of treatment, with both MFI and PPV being significantly higher in the intervention group compared to controls.

5. Discussion

Microcirculatory dysfunction represents a central pathophysiological hallmark of septic shock and is closely linked to endothelial injury, inflammatory mediator excess, coagulation disturbances, and impaired oxygen extraction [6–9,33]. As outlined previously [5,27], the loss of hemodynamic coherence between macro- and microcirculation explains why normalization of systemic parameters such as MAP or cardiac output does not necessarily ensure restoration of tissue perfusion. Persistent alterations in functional capillary density, perfusion heterogeneity, and flow quality may continue to drive organ dysfunction despite apparent macrohemodynamic stabilization [23,27].

Extracorporeal blood purification therapies have been introduced with the aim of attenuating the dysregulated inflammatory response by removing endotoxins and/or circulating cytokines [10–12]. While several trials and meta-analyses suggest improvements in macrohemodynamic stability—such as reduced vasopressor requirements and enhanced lactate clearance [15,16,64], the translation of these systemic effects into microvascular recovery remains uncertain. Lactate reduction, although frequently interpreted as a surrogate of improved tissue perfusion [48], may be influenced by extracorporeal clearance mechanisms, particularly when hemoadsorption is combined with renal replacement therapy [10,11]. Therefore, reliance on lactate alone may overestimate the true recovery of microcirculatory function.

The present review specifically focused on studies that directly assessed microcirculation during EBP therapy using videomicroscopy techniques. All included studies evaluated sublingual microcirculation using sidestream dark field (SDF) or incident dark field (IDF) imaging, currently the only bedside techniques allowing direct visualization of capillary flow [23,24]. Across selective endotoxin adsorption (PMX-HP) and non-selective cytokine adsorption devices (CytoSorb and HA380), improvements in functional microcirculatory parameters—particularly PVD, PPV, and MFI—were consistently reported [56–63].

In studies evaluating selective endotoxin removal with PMX-HP, microcirculatory improvement was demonstrated both experimentally and clinically. Animal data showed early enhancement of perfused small vessel density and tissue oxygenation [57], while clinical studies reported increased small vessel density and perfused vessel density [56,58]. These findings support the hypothesis that

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endotoxin-driven endothelial dysfunction plays a pivotal role in microvascular impairment [33–35] and that its targeted removal may restore functional capillary perfusion.

Similarly, non-selective cytokine adsorption strategies were associated with microcirculatory improvement in observational studies, case reports, and interventional trials. In septic patients treated with CytoSorb, significant increases in perfused vessel density and total vessel density were observed [59]. Pediatric data further demonstrated improvements in MFI and PPV during hemoadsorption therapy [63], while individual case reports highlighted delayed restoration of microcirculatory parameters despite early macrohemodynamic stabilization [60,61]. This observation underscores the phenomenon of hemodynamic incoherence and supports the value of direct microcirculatory monitoring during EBP therapy. The HA380 cartridge was evaluated in only one randomized controlled trial within the scope of this review [62]. In that study, significant improvements in MFI and PPV were observed after seven days of therapy compared with the control group. However, the limited number of studies precludes firm conclusions regarding the comparative efficacy of different adsorption strategies.

An important methodological distinction across the included studies relates to the mode of extracorporeal therapy. While endotoxin adsorption studies (e.g., polymyxin B hemoperfusion) were predominantly performed as stand-alone interventions, most studies investigating cytokine adsorption devices (e.g., CytoSorb, HA380) applied hemoadsorption in combination with continuous renal replacement therapy. This heterogeneity limits direct comparability and complicates attribution of microcirculatory effects to adsorption alone. Furthermore, in most studies, the specific CRRT modality (e.g., CVVH versus CVVHDF) was not clearly specified. Given that cytokines are predominantly middle-molecular-weight solutes and are more effectively removed by convective clearance, as in CVVH, variability in CRRT modality may significantly influence the overall efficacy of extracorporeal blood purification and confound interpretation of the observed effects.

Despite the overall consistency of reported improvements in microcirculatory parameters, several limitations must be considered. Most studies were small, single-center, or observational in design, and hemoadsorption was frequently administered alongside multimodal sepsis therapy, including fluid resuscitation and antimicrobial treatment. Consequently, improvements in microcirculation cannot be attributed solely to mediator removal. Furthermore, the absence of standardized protocols for timing, duration, and monitoring of EBP therapy limits comparability across studies and reduces external validity.

From a clinical perspective, the integration of microcirculatory monitoring into routine EBP management remains limited. Although SDF and IDF videomicroscopy provide high-resolution, physiologically relevant information, their implementation is constrained by cost, equipment availability, and the need for trained personnel. Moreover, validated therapeutic algorithms incorporating microcirculatory endpoints into decision-making during EBP are currently lacking.

Future research should incorporate predefined microcirculatory endpoints into adequately powered randomized controlled trials. Standardization of acquisition techniques and automated image analysis may facilitate broader clinical application. If validated, direct microcirculatory monitoring may support patient selection, optimization of treatment duration, timely replacement of saturated adsorption cartridges, and individualized therapy strategies [12].

In summary, available evidence suggests that extracorporeal blood purification may positively influence microvascular perfusion in septic shock [65]. However, the current body of literature remains limited and methodologically heterogeneous. Although physiologically plausible based on the established role of inflammatory mediators in endothelial dysfunction, robust evidence confirming a causal relationship between mediator removal and sustained microcirculatory recovery is still lacking. Addressing this gap will be essential for achieving true hemodynamic coherence and advancing personalized management strategies in septic shock.

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6. Conclusions

Microcirculatory dysfunction is a key determinant of organ failure in septic shock and may persist despite apparent macrohemodynamic stabilization. This narrative review shows that the limited available studies using direct sublingual videomicroscopy (SDF or IDF) during extracorporeal blood purification consistently report improvements in functional microcirculatory parameters.

However, current evidence is based mainly on small and heterogeneous studies, and a causal relationship between mediator removal and sustained microvascular recovery remains unproven. Direct microcirculatory monitoring may offer a valuable adjunct to guide EBP therapy, but standardized protocols and larger randomized controlled trials are needed before routine clinical implementation can be recommended.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Abbreviations

The following abbreviations are used in this manuscript:

CRT—Capillary Refill Time
CRRT—Continuous renal replacement therapy
CVVHDF—Continuous Veno-Venous Hemodiafiltration
EBP—Extracorporeal Blood Purification
HA—Hemoadsorption
HI—Heterogeneity Index
IDF—Incident Dark Field videomicroscopy
LPS—Lipopolysaccharide
MAP—Mean Arterial Pressure
MFI—Microvascular Flow Index
MIS-C—Multisystem Inflammatory Syndrome in Children
NIRS—Near-Infrared Spectroscopy
PAI—Pulse Amplitude Index
PI—Perfusion Index
PMX-HP—Polymyxin B-Immobilized Fiber Column Hemoperfusion
PPV—Proportion of Perfused Vessels
PVD—Perfused Vessel Density
SDF—Sidestream Dark Field videomicroscopy
SMS—Skin Mottling Score
SVD—Small Vessel Density

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TVD—Total Vessel Density

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