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J C N JOURNAL OF CLINICAL NEPHROLOGY
ISSN 2576-9529

Review Article

Efficiency, Effectiveness and Clinical Results of Extracorporeal Therapies in Non-Renal Settings: How are they to be evaluated? The Case of their Application in Liver Failure

Fausto Bruno Campana and Mauro Atti*

Aferetica Srl, Via Spartaco 10 – 40138, Bologna, Italy

More Information

***Address for correspondence:** Mauro Atti, Aferetica Srl, Via Spartaco 10 – 40138, Bologna, Italy, Email: mauro.atti@aferetica.com

Submitted: February 02, 2024
Approved: February 19, 2024
Published: February 20, 2024

How to cite this article: Campana EB, Atti M. Efficiency, Effectiveness and Clinical Results of Extracorporeal Therapies in Non-Renal Settings: How are they to be evaluated? The Case of their Application in Liver Failure. J Clini Nephrol. 2024; 8: 008-016.

DOI: 10.29328/journal.jcn.1001120

Keywords: Extra blood purification therapies; Sorbents; Mass balance; Bilirubin; Liver failure

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Abstract

There are various Extra Blood Purification Therapies (EBPTs) used in the context of critical care, including but not limited to Acute Kidney Injury (AKI). These therapies aim to remove toxins, inflammatory mediators, and excess fluids from the bloodstream. While some blood purification therapies were initially developed for renal support, they have been explored for use in other medical conditions as well, including liver pathologies and sepsis. Here is a brief explanation of some therapies such as MARS (Molecular Adsorbents Recirculating System), Prometheus, CPFA (Coupled Plasma Filtration Adsorption), PAP (Plasma Adsorption), and SPAD (Single-Pass Albumin Dialysis). Some of these therapies have entered clinical use, while others have faced challenges, such as negative evidence, poor purifying efficacy, or difficulties in practical use. The field of extracorporeal liver support is dynamic, with ongoing developments aimed at improving the effectiveness and practicality of these therapies. Sorbents mark the latest frontiers in blood purification to remove various toxic molecules, with specific emphasis on the modulation of bilirubin and other substances in critically ill patients suffering from liver failure. In the above-mentioned pathologies, substances may be continuously generated within the body, and Mass Balance is the only valuable tool for distinguishing between generation and removal processes. The effectiveness of sorbents in removing bilirubin and bile acids, as demonstrated in both in vitro and in vivo studies, distinguishes them and shows their superiority over traditional liver cleansing methods, such as CPFA, PAP, SPAD, Prometheus, and MARS.

Introduction

Various adjuvant Extra Blood Purification Therapies (EBPTs) have been developed to modulate toxins and uncontrolled substances in different pathologies. Some EBPTs derive directly from dialysis techniques. High-volume hemofiltration (HVHF) is described as a modification of continuous renal replacement therapy (RRT) in hemofiltration mode. The focus is on using high fluid volumes for filtration to enhance substance removal. Hemofiltration with Highly Adsorbing Membranes involves using highly adsorbing membranes during hemofiltration to enhance the removal of substances from the blood. High Cut-Off membranes are used to expand the range of middle molecular weight molecule removal and the membrane cut-off value is increased. This modification aims to improve the efficiency of the blood purification process. Other EBPTs come directly from Plasma Exchange (PEX). The PEX technique has been evaluated in the context of liver failure. The goal is to remove or exchange plasma components to address specific pathologies. Unfortunately, PEX does not always have its advantages. In a prospective, randomized, controlled, multicenter trial, Larsen, et al. [1] randomly assigned 182 patients with ALF to receive either standard medical therapy (SMT;90 patients) or SMT plus High-volume plasma exchange (HVP) for three days (92 patients). 1,5 l of plasma was exchanged and the total volume exchanged was 15% of body weight or about 8-12 l per day per procedure. The data showed that the main effect of HVP on survival was achieved in the patients not undergoing emergency liver transplantation or were either not transplant candidates or not transplanted. Treatment with HVP improved outcomes in patients with ALF by increasing liver transplant-free survival. This was attributable to the attenuation of innate immune activation and the amelioration of multi-organ

dysfunction. The negative side of this study is that PEX exchanged 12 l of plasma (meaning up to 4 times the usual value of patient plasma) which is unbearable for patients, in clinical practice. Furthermore, PEX requires a plasma filter for plasma separation and high quantities of albumin solution/fresh frozen plasma, with the risks associated with this practice as it causes the removal of all plasma components. Derived directly from PEX, Cascade filtration is designed to selectively remove middle molecules while retaining smaller ones such as trace elements, vitamins, and medications. This is achieved by combining one plasma filter and a hemofilter with distinct cut-off values, allowing for targeted removal. Coupled Plasma Filtration and Adsorption (CPFA) is described as an extracorporeal therapy where plasma is separated from the blood at the start of the circuit. Plasma then runs slowly through a sorbent, facilitating the removal of certain substances. Hemoperfusion involves the patient's blood coming into contact with adsorbing materials. Molecules can adhere to these materials through various interactions, such as van der Waals, electrostatic, and hydrophobic interactions [2].

Liver failure

Among the toxins, the removal of bilirubin, bile acids, and ammonium in critically ill patients with liver failure is considered an effective strategy to improve organ dysfunction and the overall health status of these patients. Here, in particular, we discuss the parallel pathway existing between acute forms of liver dysfunction and failure and the pathophysiological features seen in sepsis. It is highlighted that both conditions involve a dysregulated inflammatory response. In fact, Acute liver failure shares significant similarities with septic shock and there is a complex interplay of systemic inflammation, immune dysfunction, and organ failure in acute liver failure. Also in Acute Liver Failure, a massive and uncontrolled activation of the systemic inflammatory response, paralleled by an equally uncontrolled anti-inflammatory response, results in progressive MODS. In ACLF, circulating cytokines are related to prognosis in different stages of cirrhosis, and a stronger anti-inflammatory response was associated with progression to death. Patients with ACLF showed systemic inflammation and systemic circulatory dysfunction, with higher levels of various inflammatory cytokines than the patients without ACLF. These data support systemic inflammation as the primary driver of ACLF in cirrhosis [3-5]. In the context of liver dysfunction, this dysregulation of the inflammatory response is considered the basis for the rationale behind using hemadsorption. Hepatic dysfunction refers to a condition where the liver experiences impairment in its main functions, which include detoxification, synthesis, and regulation. The detoxification function is particularly crucial, as it involves the metabolism of various molecules. When this function is compromised, certain molecules accumulate in the systemic circulation, leading to metabolic and biochemical alterations. To address hepatic dysfunction, Extra Corporeal Liver Support (ECLS) systems have been developed. These systems aim to support the liver's detoxification function by clearing the blood from hepatic toxic molecules. The goal is to bridge the patient either to orthotopic liver transplantation or to functional recovery. ECLS is indicated in various conditions such as acute liver failure (ALF), acute-on-chronic liver failure (ACLF), primary non-function (PNF) after liver transplantation, post-hepatectomy liver failure (PHLF), or in patients with intractable pruritus [6,7].

Extra blood purification therapies

Different EBPTs have been proposed for liver failure, specifically involving bilirubin modulation (Figure 1). Some of them have entered clinical use, while some have been largely abandoned. This could be due to various reasons, including a lack of evidence supporting their effectiveness. Poor purifying efficacy and difficulty in use are mentioned as specific challenges that have led to the abandonment of certain therapies. These challenges could relate to the limitations in effectively removing toxins, including bilirubin, from the bloodstream. MARS consists of a double circuit: the blood circuit and the albumin circuit, which are separated from each other by an impermeable albumin membrane whose pores are about 50 kDa. Prometheus combines plasma separation and absorption. It consists of a double circuit: the blood circuit and the plasma circuit are separated by a membrane whose pores of about 250 kDa are permeable to albumin. SPAD is based on hemodialysis and hemofiltration principles and is the simplest system, as it can be implemented with a standard CRRT device. The patient's blood passes through a standard high-flow membrane impermeable to albumin, and dialyses counter-currently with a solution containing 2-5% albumin that is discarded after a single passage Coupled Plasma Filtration Adsorption (CPFA) is a technique that separates the plasma from the blood by means of a plasma filter. The plasma is then passed through a synthetic resin cartridge and returned to the blood. A second blood filter can be then used to remove excess fluid and small molecular weight toxins where necessary, as in the case of acute renal failure. PAP (very similar to CPFA) consists of plasma separation from the blood by a plasma filter (material effective surface area 0,45m^2, pore size 0.5/0.7 µm, sieving coefficient of albumin) and then passage through a sorbent cartridge at a flow rate of 40 mL/min. All these techniques have produced contradictory results, and technical complexity, and have limited treatment duration, limited hepatic toxin removal, and difficulty in albumin-bound toxin removal [8-11].

Hemadsorption

Among the EBPTs, hemadsorption by sorbents marks the latest frontier [12]. Hemadsorption involves placing sorbents contained in cartridges in direct contact with the blood via an extracorporeal circuit. This process is designed to remove

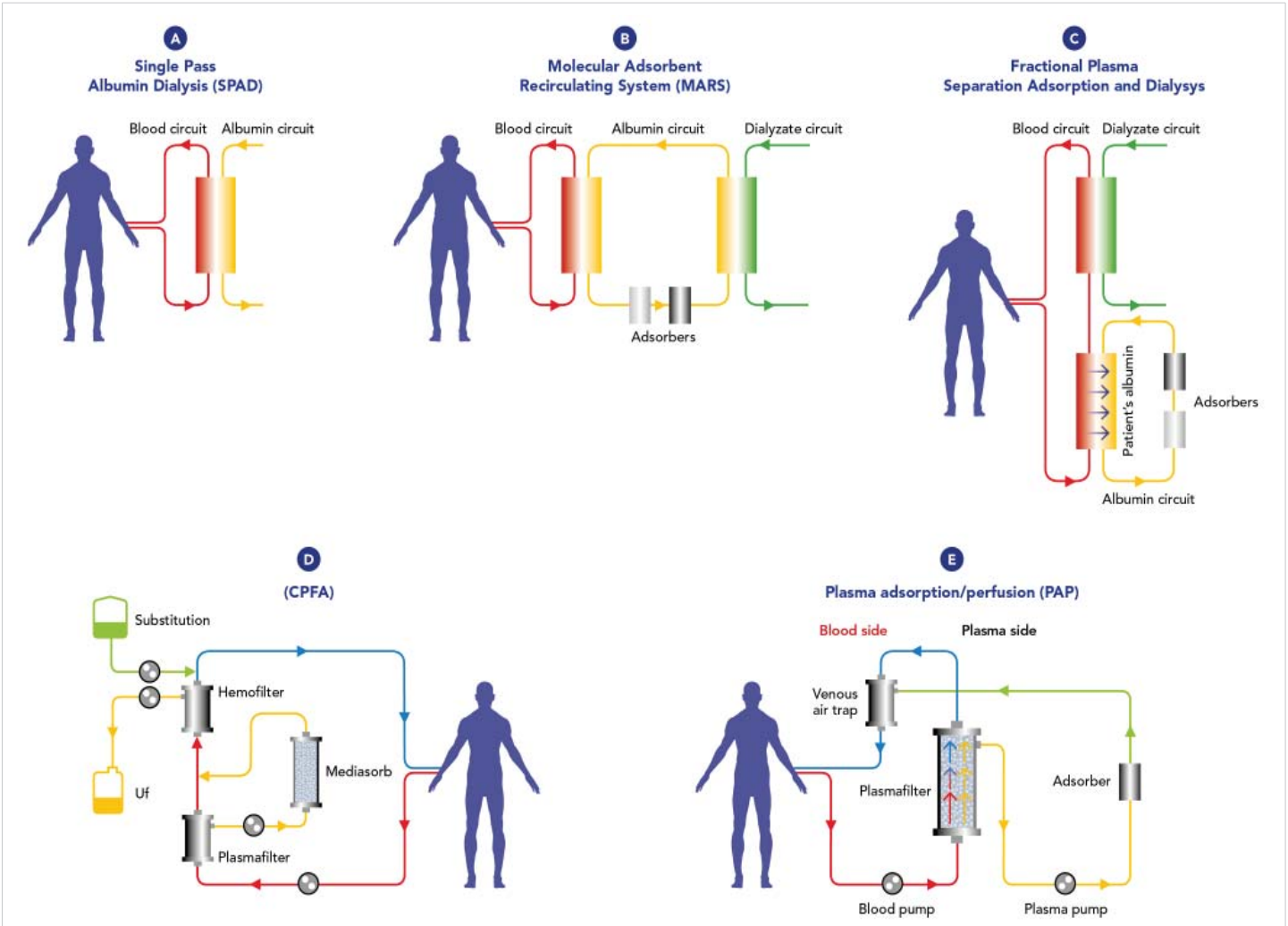

Figure 1: Extra blood purification therapies for liver failure. A(SPAD); B(MARS);C(Prometheus);D(CPFA);E(PAP).

toxins (e.g. bilirubin, myoglobin, drugs) and inflammatory mediators from the blood. To show that, Gruda, et al. [13] have added purified proteins to whole blood at clinically relevant concentrations and recirculated through a device filled with hemoadsorbent polymer beads or control (no bead) device in vitro: hemadsorption through porous polymer bead devices have reduced the levels of a broad spectrum of cytokines (MIP1-α, IL-6, and IFN-γ, TNF-α DAMPS (C5a, HMGB-1, procalcitonin, and S100-A8), PAMPS (α-toxin, SpeB, and TSST-1) and mycotoxins (aflatoxin, T-2 toxin). Initially designed for the modulation of cytokines, it has proven to be effective in bilirubin and bile acid removal as well. In fact, in an *in Vitro* study, Gemelli, et al. [14] demonstrated with the same sorbent the capability to efficiently remove bilirubin over 24 hours, with minimal albumin loss and no detectable bilirubin release from the charged resin. In a patient with liver dysfunction, Buttner, et al. [15] performed the measurement of pre- and post-adsorber values, showing that also the removal of ammonia is directly attributable to the adsorber, although this is a debated concept [16]. The rationale behind using adsorption therapy is to restore the immune balance, encompassing both pro-inflammatory and anti-inflammatory responses, as a cytokine storm is characterized by an excessive release of pro- and anti-inflammatory cytokines, which can lead to severe systemic inflammation. Extracorporeal hemadsorption is commonly employed by intensive care specialists to prevent or counteract the effects of a cytokine storm, primarily in conditions such as septic shock and other forms of vasoplegic shock [17].

Here we summarize various studies (Table 1) evaluating the effectiveness, efficiency, and clinical results of extracorporeal therapies, focusing on sorbents in non-renal settings, particularly on liver failure, highlighting that Mass Balance (MB) is the only valid parameter for assessing the purification effectiveness of extracorporeal systems, as it is not affected by endogenous generation (Figure 2). Gemelli, et al. [14] have demonstrated sorbent's capability to efficiently remove bilirubin over 24 hours, with minimal albumin loss and no detectable bilirubin release from the charged resin. The Authors conducted four in vitro experiments with different albumin-bilirubin solutions, showing massive and irreversible adsorption of bilirubin

Study	Design	Patients Number	Inclusion Criteria	End Point	Results	Endpoint Achieved	Intervention
Larsen FS et Al[1]	An open randomised controlled trial	182	Patients with acute liver failure	Liver transplantation-free survival during hospital stay	Overall hospital survival was 58.7% for patients treated with HVP versus 47.8% for the control group; HVP prior to transplantation did not improve survival	PARTIALLY	PEX
Ocskay K[6]	International Registry	109	Critically ill patients with liver dysfunction	Bilirubin levels	Compared with patients who received SMT alone profound change from T1 to T2 was observed in the serum bilirubin levels	YES	CytoSorb
Riva I et Al[7]	A retrospective comparative analysis	39	Patients presenting with liver failure	TB, DB, and BA levels evaluated through the MB and adsorption per hour, in comparison between CytoSorb, CPFA, MARS, Prometheus, and PAP	TB, DB, BAs MB was signifcantly higher (up to 5 times) trhan other ECLS tecniques	YES	CytoSorb
Banares R et Al[9]	Prospective randomized controlled multicenter	189	ACLF	Liver transplantation-free survival within 28 days	The 28-day survival was similar in intervention and control group	NO	MARS
Kribben A et Al[9]	Prospective, randomized, controlled, parallel-group, multicenter trial	145	ACLF	Survival probabilities at days 28 and 90	Extracorporeal liver support with FPSA does not increase the probability of survival	NO	Prometheus
Faenza S et Al[10]	Clinical experience	56	ACLF	Purification efficiency	Both systems MARS and Prometheus accomplished a good purification efficiency	YES	MARS/ Prometheus
Gemelli et Al[14]	In vitro experiments	-	-	Assess irreversible bilirubin adsorption	All experiments showed the resin's ability to break the albumin-bilirubin complex, with minimal albumin loss. No sign of bilirubin release from the charged resin was detected	YES	CytoSorb
Dominik A et Al[18]	In vitro experiments	-	-	Comparison of liver support techniques	Ammonia, albumin bound toxins, total bilirubin and subfractions, Bile acids, interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) removal was increased using CytoSorb	YES	CytoSorb
Greimel A et Al[24]	Monocentric, prospective	20	Intensive care patients with cholestatic liver dysfunction	Bilirubin and different Bas adsorption	CytoSorb can adsorb bilirubin and toxic as well as protective Bas	PARTIALLY	CytoSorb
Grafe C et Al[25]	Monocentric retrospective, observational	82	Critically Ill Patients with Hyperbilirubinemia	30d mortality	No significant reduction in 30-day mortality	YES	CytoSorb

Table 1: Comparative Analysis of Extracorporeal Sorbent Therapies in Liver Failure.

by the resin. Efficacy in detaching unconjugated bilirubin from albumin and continuous adsorption over 24 hours were highlighted. In addition to what we have said, bear in mind that also in dialysis techniques mass balance is crucial in understanding and comparing various methods. Mass balance allows us to evaluate the effectiveness of a purifying therapy by distinguishing the components of equilibrium between the input and output of solutes in the body during the dialysis process. Normalization of the distribution's volume, the apparent space in the body available to contain a solute, suggests how to adjust the mass balance to obtain the right Kt/V, the parameter universally used in dialysis treatments. This normalization helps in comparing different dialysis methods more effectively by accounting for variations in the distribution of substances within the body. Therefore, applying mass balance and normalization techniques ensures accurate comparisons and a better understanding of the underlying processes. Among the sorbents, CytoSorb® is a notable technology and has been described as the most investigated and clinically established procedure among the presented technologies. It is specifically approved for the remodulation of pro and anti-inflammatory cytokines, as well as bilirubin and myoglobin, in addition to the removal of certain medications like ticagrelor and rivaroxaban. This suggests that CytoSorb® is recognized for its efficacy in addressing a range of inflammatory and toxic substances in the blood during extracorporeal blood purification therapies [18-41]. Furthermore, it is the only certified sorbent that can remove bilirubin (as well as cytokines) directly from the whole blood [42], without any need for plasma separation as indicated in Jafron CE [43]. This is confirmed by Riva, et al. [7] in a published in vivo study. The Authors indicate the superior adsorption of the sorbent in terms of Mass Balance (MB) compared to other extracorporeal techniques (CPFA, MARS, Prometheus, PAP). The study showed significantly higher adsorption of Total Bilirubin (TB), Direct Bilirubin (DB), and Bile Acids (BAs) with sorbent, with an average 5-fold higher MB for CytoSorb sorbent compared to other methods (Figure 3). These in vivo results are consistent with the results of in vitro studies conducted by Stange's group [18]. Furthermore, the study by Ocksay, et al. [6] in a 1434-patient registry, specifically in a subgroup of 109 liver failure patients, confirms that hemadsorption significantly removes bilirubin from the blood. This finding is notable as previous studies

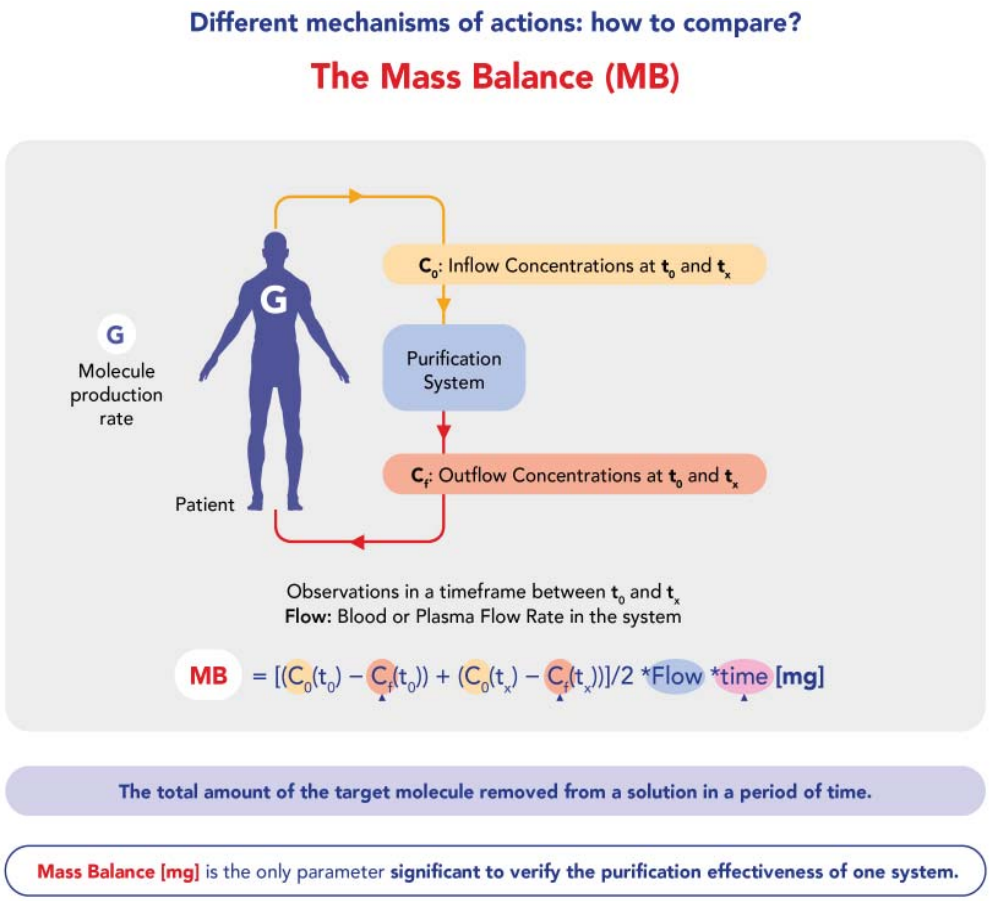

Figure 2: Mass Balance rationale and formula.

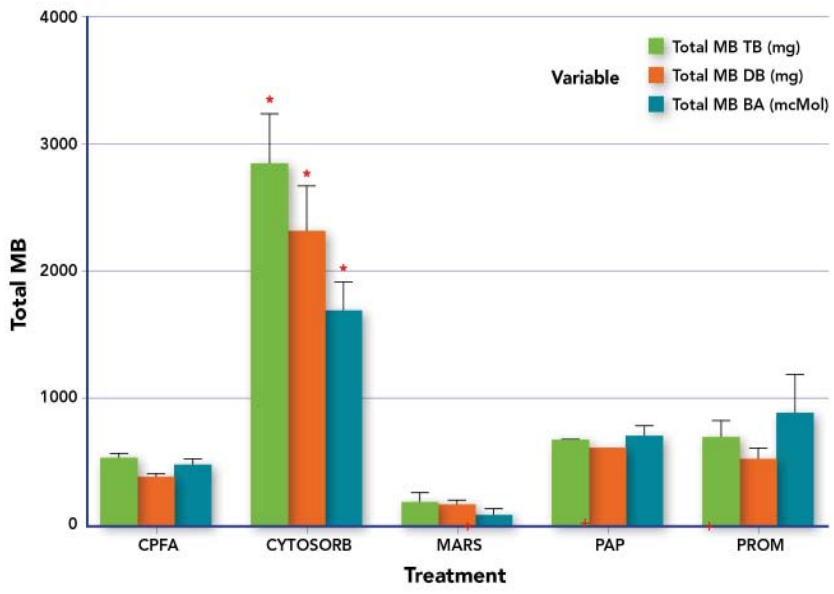

Figure 3: TB, DB and BA Total MB regarding all the techniques comparison for the overall treatments (Kruskalis-wallis).
*Total MB – TB, DB, BA: p<0.05 CYTOSORB vs.CPFA, MARS and PROM;
+Limited number of samples PAP (n = 2), MARS (n = 3), PROM (n = 5).

with small sample sizes or retrospective data had shown similar effects. Many cases reports and case series results have been collected by Turan, et al. [44], who conducted a systematic review and meta-analysis that aimed to assess the evidence on clinical outcomes following hemadsorption therapy. The systematic review and meta-analysis provide a comprehensive overview of existing studies. The search covered six electronic databases and identified 30 eligible publications from 2011 to 2023, involving a total of 335 patients with liver dysfunction related to acute critical illness. The analysis of individual cases indicated a significant reduction in levels of aspartate transaminase and vasopressor needs, as well as a trend towards lower levels of total bilirubin, alanine transaminase, C-reactive protein, and creatinine. Pooled data also showed a significant reduction in total bilirubin, confirming the direct relationship between liver toxin decrease and function improvement. Overall, the findings suggest that the use of hemadsorption for critically ill patients with acute liver dysfunction or failure appears to be safe and shows a trend toward improved liver function after therapy. Therefore, thanks to efficacy, safety profile, and easy handling, sorbents represent a clear advantage over the older techniques cited above.

On the other hand, when bilirubin and BA removal are not measured by Mass Balance, but with systemic Rate Removal or percentage decrease, the results could be misleading. For example, the study by Greimel, et al. [45], titled "Extracorporeal adsorption of protective and toxic bile acids and bilirubin in patients with cholestatic liver dysfunction: a prospective study" is limited as the Authors did not measure Mass Balance (MB), which is the sole parameter for assessing the purification effectiveness of extracorporeal systems. MB accounts for the total amount of a molecule removed from a solution, offering an accurate reflection of the system's performance. The formula for calculating MB involves pre- and post-removal concentrations at various time intervals (C0 and Cf) and the plasma flow rate (Qplasma).

$$MB\ [mg] = [(C0\ (t0) - Cf\ (t0)) + (C0\ (tx) - Cf\ (tx))] / 2 \times Qplasma \times tx)$$

Last but not least, the study by Grafe, et al. [46] on the correlation between bilirubin elimination with CytoSorb® and mortality in critically ill patients with hyperbilirubinemia raises important considerations about the challenges of using mortality as a primary endpoint, the multifactorial nature of liver failure, and the need for standardized protocols and measurements in studies involving blood purification techniques. Concerns about using mortality as the primary endpoint in critically ill patients are well-founded. The variability in sepsis phenotypes and the complexity of critical conditions can make it challenging to attribute outcomes solely to one specific intervention. In fact, if using mortality as an outcome measure in studies involving critically ill patients is limiting, this is also particularly true for those with Acute Chronic Liver Failure (ACLF) and Acute Liver Failure (ALF), where the only chance of survival is liver transplantation. Mid- and long-term mortality may not be the most relevant or informative outcome to be studied in these patients. In cases where a life-saving intervention, such as liver transplantation, can significantly impact survival, focusing solely on mortality might not capture the nuances of treatment effectiveness or the overall patient experience.

Prospects

Researchers could consider other outcome measures that reflect not only survival but also quality of life, functional status, and other relevant factors for patients with ACLF or ALF. These could include parameters like post-transplant complications, graft function, and long-term morbidity. It is crucial that researchers select outcome measures that align with the clinical context and goals of the study, ensuring that the findings are meaningful and applicable to the specific patient population under investigation. Focusing on practical endpoints, as we suggest, such as improvements in clinical tests, liver function, and overall patient recovery, may provide a more comprehensive understanding of the intervention's efficacy. Acknowledging the multifactorial nature of the liver failure is crucial as well. Addressing such complexity often requires a holistic approach that considers the underlying causes, management of symptoms, and supportive care. Highlighting the need for studies to focus on practical endpoints beyond mortality is a valid perspective. The lack of a standardized protocol for the sorbent administration and the absence of measurements for bilirubin quantity removed both raise concerns about the reproducibility and effectiveness of the intervention. Variability in treatment approaches could impact outcomes and, without specific measurements, it becomes challenging to assess the true impact of sorbent on bilirubin levels. Furthermore, the potential disregard of local bilirubin generation when relying on systemic measurements alone is important. Local effects may not be fully captured through systemic assessments, and understanding the dynamics of bilirubin removal at the site of action is crucial for a comprehensive evaluation of the sorbent's impact. Our concerns highlight the need for future studies to employ standardized protocols, consider practical endpoints beyond mortality, and integrate comprehensive measurements to assess the effectiveness of blood purification techniques, such as sorbent in critically ill patients with hyperbilirubinemia. This collaborative and critical review process contributes to the ongoing improvement in research methodologies and the development of more effective interventions in critical care settings.

Conclusion

The use of extracorporeal hemadsorption in liver dysfunction is grounded in the similarities between the dysregulated inflammatory response observed in acute

liver dysfunction and that seen in sepsis. By addressing the inflammatory component, hemadsorption aims to mitigate the effects of the dysregulated immune response, providing a potential therapeutic approach in the context of liver dysfunction. Therefore, the challenge is to determine the most effective method for extracorporeal liver support, highlighting the exploration of new techniques, particularly hemadsorption, as a potential avenue for effective toxin removal, such as bilirubin, from the bloodstream in the context of liver dysfunction. The assessment of the removal efficacy of Extra Blood Purification Therapies (sorbents in particular) is contingent upon performing Mass Balance, as other measurements are influenced by endogenous generation. Considering the fact that efficiency is the measure of accomplishing a task with minimal wasted resources, including time, money, and effort, while effectiveness gauges the degree to which an action or process successfully produces the desired outcome, and bearing in mind the results achieved hitherto, the easy handling, the timing, the safety and pharmacoeconomic factors, then we can conclude that sorbents have clearly shown benefits in improving patient outcomes by mitigating the harmful effects of excessive inflammation and by removing toxins and drugs.

Conflict of interest: Fausto Bruno Campana and Mauro Atti are both employed by Aferetica Srl.

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