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REVIEW

Hemoadsorption: consensus report of the 30th Acute Disease Quality Initiative workgroup

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ABSTRACT

Adsorption-based extracorporeal therapies have been subject to technical developments and clinical application for close to five decades. More recently, new technological developments in membrane and sorbent manipulation have made it possible to deliver more biocompatible extracorporeal adsorption therapies to patients with a variety of conditions. There are several key rationales based on physicochemical principles and clinical considerations that justify the application and investigation of such therapies as evidenced by multiple *ex vivo*, experimental and clinical observations. Accordingly, unspecific adsorptive extracorporeal therapies have now been applied to the treatment of a wide array of conditions from poisoning to drug overdoses, to inflammatory states and sepsis, and acute or chronic liver and kidney failure. In response to the rapidly expanding knowledge base and increased clinical evidence, we convened an Acute Disease Quality Initiative consensus conference dedicated to such treatment. The data show that hemoadsorption has clinically acceptable short-term biocompatibility and safety, technical feasibility and experimental demonstration of specified target molecule removal. Pilot studies demonstrate potentially beneficial effects on physiology and larger studies of endotoxin-based hemoadsorption have identified possible target phenotypes for larger randomized controlled trials. Moreover, in a variety of endogenous and exogenous intoxications, removal of target molecules has been confirmed *in vivo*. However, some studies have raised concerns about harm, or failed to deliver benefits. Thus, despite many achievements, modern hemoadsorption remains a novel and experimental intervention with limited data, and a large research agenda.

Keywords: acute kidney injury, haemodialysis, inflammation, plasma exchange, sepsis

INTRODUCTION

Hemoadsorption has markedly evolved since the initial application close to five decades ago, and enhanced biocompatibility and effective adsorptive membranes have been developed and applied to the treatment of a variety of conditions. Moreover, developments in toxicology, pharmacology, biology, immunology and pathophysiology now provide a rationale for hemoadsorption in patients with poisoning and drug intoxication, sepsis, inflammatory states, and metabolic disorders or endogenous intoxications. However, the evidence is distributed across multiple fields and many aspects remain poorly described and integrated. They include available technologies and physicochemical principles, techniques and modalities, evidence behind possible indications, prescription and monitoring, performance characteristics for different biological and toxicological targets, and the definition of relevant biochemical, biological, physiological and clinical endpoints. Accordingly, the 30th Acute Disease Quality Initiative (ADQI) consensus conference aimed to identify these knowledge gaps, present our current understanding of such hemoadsorption, and provide consensus information to guide practice and research in the field.

METHODS

The conference chairs of the 30th ADQI consensus committee (R.B. and C.R.) convened a diverse panel of adult and pediatric clinicians and researchers representing relevant disciplines (critical care, nephrology, anesthesiology, emergency medicine, bioengineering, pharmacology and nursing) from Europe, North America, South America, the Middle East and Australia to critically review the literature on hemoadsorption. The conference participants chose the term hemadsorption in preference to hemoperfusion and/or hemadsorption to align its report with the latest consensus nomenclature. The conference was held over 2.5 days in Vicenza, Italy, on 9–12 June 2023 and followed the established ADQI process using a modified Delphi method to achieve consensus, as previously described [1, 2]. Briefly, the ADQI approach uses methods that involve a combination of both expert panel and evidence appraisal. This approach was chosen to achieve a best combined option. Like other ADQI conferences, this hemoadsorption-focused meeting was divided into three phases: pre-conference, conference and post-conference. In the first phase, groups were assigned to specific topics and questions; they were asked to conduct a literature search and generate a bibliography of key studies written in English and contained within PubMed, Medline and EMBASE databases. The conference was divided into break-out and plenary sessions. Thus, groups developed their themes in the break-out sessions and presented them in the plenary sessions for discussion and debate. This approach has previously led to important practice guidelines with wide acceptance and adoption into clinical practice [3, 4]. If the assessment of the literature indicated that further research was needed, such research was proposed to facilitate developments in the field. In addition, given the limited evidence in this field at this time, we chose not to provide practice recommendations. In this conference, participants were divided into four groups to discuss (i) the rationale and physicochemical principles of hemoadsorption; (ii) the techniques and modalities available for such therapy; (iii) the indications, prescription and monitoring of such therapies; and (iv) the biochemical, biological, physiological and clinical endpoints for the assessment of such therapies. Members of the groups reviewed the literature and where possible developed an evidence-based consensus and proposed a relevant research agenda and presented it at the plenary sessions. Finally, the overall material was reviewed, aggregated and approved in a session in the presence of all members.

RATIONALE OF HEMOADSORPTION

Hemoadsorption is an extracorporeal blood and plasma purification treatment aiming to increase extracorporeal removal of solutes, cells or pathogens, which, due to their physical-chemical features (e.g. dimension, protein binding or lipophilicity), are not amenable to diffusive or convective clearance.

Hemoadsorption represents the dynamic binding of blood-based adsorbates (see Supplementary Appendix, Table S1 for definition) to a solid surface that can remove protein bound molecules, middle and high molecular weight substances, pathogens and cells. Binding can be transient, prolonged or reversible depending upon the physicochemical properties of the surface and the conditions of exposure, and may be specific or non-specific. This binding is achieved by blood or plasma flow through a sorbent-containing cartridge [5–9]. In contrast to what happens with dialytic therapies, the removal of molecules by adsorption only requires the contact of blood or plasma with a highly adsorptive biocompatible material. While some hemoadsorption can occur even in the setting of conventional dialytic

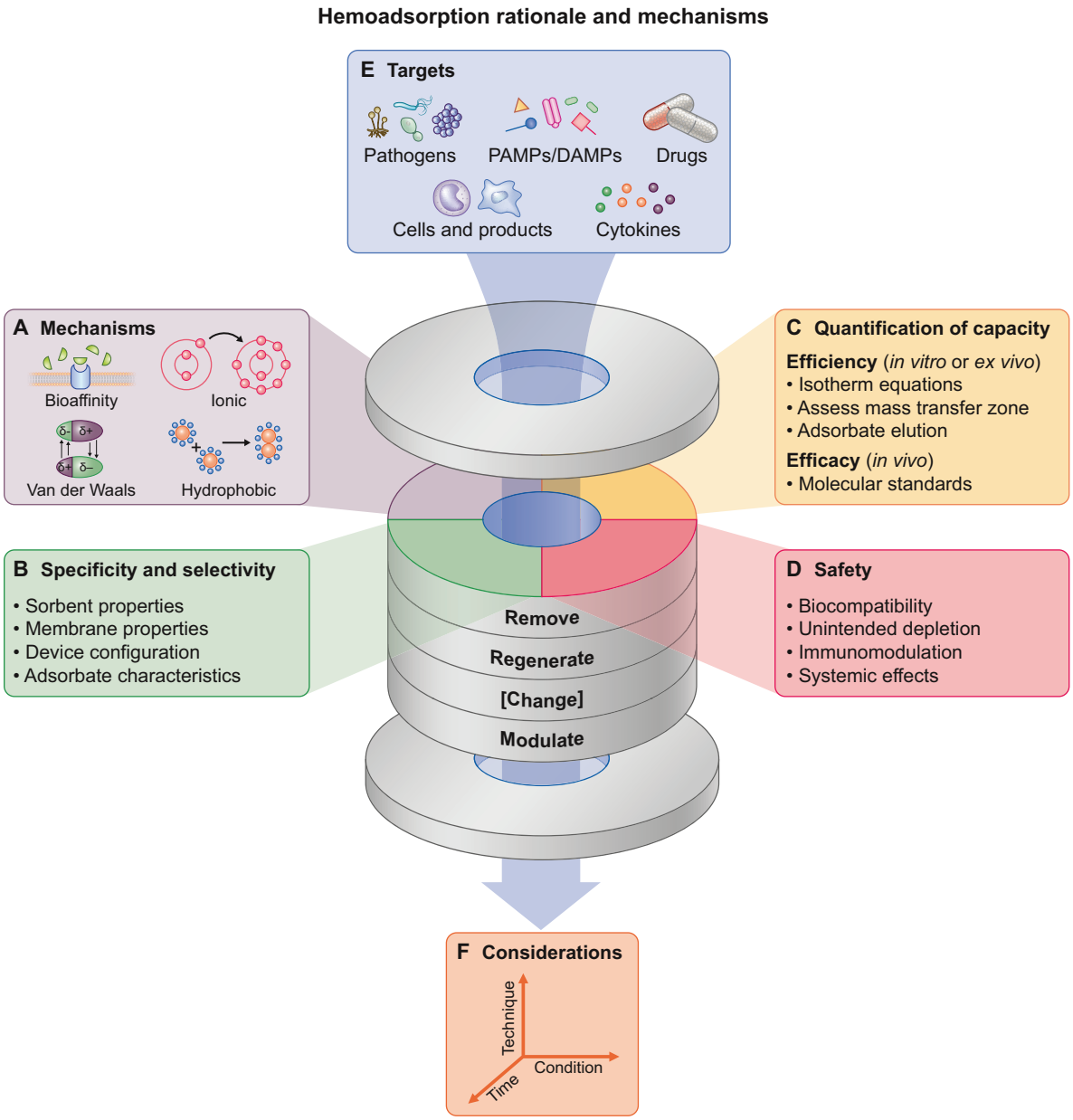

Figure 1: Conceptual diagram of rationale and mechanisms of hemoadsorption. The diagram summarizes the mechanism, specificity, quantification of capacity, concept of removal, regeneration, changes and modulation of hemoadsorption, including consideration of safety, targets, and the interaction between hemoadsorption with the condition being treated and time. Each disc refers to a unique mechanism offered by hemoadsorption to alter the concentration of substrates/solutes/circulating factors. The colors denote how one can assess, compare and contrast each type of hemoadsorption effect. White indicates mechanisms (**A**); green indicates specificity and selectivity (**B**); yellow indicates quantification (**C**); red indicates safety (**D**); blue indicates targets (**E**). The brackets refer to "concentration" as in [Cr]. So [change] = changes in the concentration. (**F**) The considerations figure (lower figure) indicates that the timing and duration of hemoadsorption affects all the above elements, that the condition of the patient modifies all of the effects of hemoadsorption and that the technique applied will also modify such effects. It also indicates that time, condition and technique have dynamic aspects which interact at a three-dimensional level. This figure also underlines different mechanisms: the term "remove" indicates the removal of a specific molecule; the term "regenerate" indicates the restoration of blood concentrations to its pretreatment level; the term "change" indicates a measurable change in blood concentration; and the term "modulate" indicates action of a specific molecule or molecules which, through its changes, then affects the downstream concentration of other molecules that are not directly affected by hemoadsorption.

therapies employing membranes with avid binding properties, the use of beads with very large surface area to mass ratios offers the ability to target more specific molecules or molecular classes and the opportunity to remove greater amounts of such solutes. Moreover, the direct contact with blood and plasma permits removal of cells and pathogens, and inflammatory molecules (Fig. 1).

PHYSICOCHEMICAL PRINCIPLES FOR HEMOADSORPTION

Chemical adsorption (chemisorption) is a relatively specific, energy-intensive process involving the formation of chemical bonds between the solute and sorbent (relatively uncommon in extracorporeal applications). Physical adsorption is a non-specific process typically mediated by hydrophobic interactions between

Table 1: Proposed set of molecular markers to assess efficiency, efficacy and safety of adsorption.[a]

Efficiency-efficacy	Safety
Cytokines: IL-6, IL-10, TNF-α	Albumin
Antibodies: IgG	Hemolysis profile
Microbes: *Escherichia coli*, viruses (CMV, EBV)	Complement activation
PAMPs: endotoxins	Coagulation parameters
DAMPs: HMGB1	Cell depletion (WBC, platelets)
Middle/large molecules: beta 2-microglobulin, myoglobin	Drugs (vancomycin. gentamicin and other antimicrobials)
Protein-bound: bilirubin	

[a]The molecules listed in this table have all been sued in different clinical conditions and have been assessed as possible markers of biological efficacy and/or have been used *in vitro* to study efficiency in terms of the specific removal of a molecule during a single pass though the sorbent.
IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha; IgG, immunoglobulin G; CMV, cytomegalovirus; EBV, Epstein and Barr virus; HMGB1, high mobility group box 1 protein; WBC, white blood cell count.

solute and sorbent. Ionic interactions, van der Waal forces and biological affinity binding may also mediate physical adsorption [9]. At any given time, one or more of these mechanisms may be active, and the features of the adsorptive surface (i.e. surface area, structure, pore size, etc.) and the sorbent configuration (bead size, packing density, etc.) determine the efficiency of adsorption. Solute binding by physical adsorption may occur at high rates due to low energy thresholds. However, such binding is relatively weak (i.e. highly reversible)—thus, the rates of desorption and/or displacement by competitive solutes may also be high [9]. Such desorption maybe a significant drawback of hemoadsorption.

Adsorption to membrane-based and other extracorporeal porous polymers (e.g. bead-based hemoperfusion columns) is based on certain basic principles: (i) a solute reaches the vicinity of the specific binding site by mass transfer, a process impacted by flow rate and solution characteristics; (ii) the "active" binding area is within the pore structure (pore size is a critical determinant of access to the sorbent); and (iii) once a solute reaches a potential binding site, the likelihood of adsorption and the rate of its occurrence are influenced by factors related to the solute, solvent and sorbent [9].

QUANTIFYING HEMOADSORPTION

Adsorptive capacity can be measured in terms of efficiency [9]. For a sorbent cartridge, efficiency can be measured *in vitro* as mass removal quantified using isotherm equations, elution of the adsorbates and mass transfer zone; and *in vitro* and *in vivo* using the removal ratio over time (see Supplementary data, Table S1).

The isotherm equation curves can be evaluated *in vitro* as a first step using standard saline solution to assess the affinity of the material for binding specific adsorbates. The removal ratio should also be tested *in vitro* using saline and blood/plasma to mimic extracorporeal therapies and to study the potential impact of other molecules/cells present in body fluids.

The efficacy of adsorption represents the effect of the therapy from a clinical perspective and can be quantified by measuring specific biomarkers (Table 1) and/or clinical parameters representing the purpose(s) of the therapy, for instance blood levels of specific biomarkers representing molecules potentially involved in tissue injury during acute diseases [10]. Typical examples of clinical parameters to test the efficacy of hemoadsorption include the Sequential Organ Failure Assessment (SOFA) score; hemodynamic stability [mean arterial pressure (MAP), vasopressor dose, etc.]; lung function (PaO_2/FiO_2 ratio) and kidney function (serum creatinine, estimated glomerular filtration rate, urine output, urinary acute kidney injury biomarkers, etc.). These clinical variables should be correlated with the removal ratio of relevant adsorbates.

FACTORS DETERMINING THE SPECIFICITY OF HEMOADSORPTION

The specificity of adsorption (e.g. the ability to bind a given target molecule) is influenced by the properties of the adsorptive membrane or sorbent cartridge configuration, the characteristics of the adsorbates and the conditions of application. In different clinical conditions and type of diseases, selectivity of adsorption may vary according to both the sorbent cartridge or the hemofilter with an adsorbing membrane, and patient features. Adsorption can be influenced by several variables including blood or plasma flow rate, timing of the procedure, starting concentrations of the adsorbate(s) and presence of other solutes in blood/plasma that may interfere with adsorptive processes.

The passage of blood/plasma through a sorbent may lead to a selective (i.e. endotoxin with polymyxin B) or broad-spectrum (i.e. cytokines) removal of mediators [5, 6].

BIOCOMPATIBILITY AND BIOTOLERABILITY

Biocompatibility refers to the capacity of a material or solution to exist in contact with the human body without causing an inappropriate host response [11]. The biocompatibility characteristics of adsorptive therapies are like those required for dialysis. Biocompatibility remains an important clinical challenge in both chronic and acute settings due to the spectrum of cellular, humoral and other responses that may be triggered by the interaction of blood with sorbents (i.e. ISO 10993). Avoiding direct contact between blood and the adsorptive surface through plasma separation may improve system biocompatibility. However, technological advances in hemoadsorption materials have improved biocompatibility, allowing the use of sorbents in stand-alone (where the sorbent is the only device in the extracorporeal circuit) configuration [12–14]. A more suitable term to describe these interactions may be short-term biotolerability, defined as the ability of a material to reside in the body for long periods of time only with the generation of a low grade and acceptable inflammatory reaction [4, 5].

COLLATERAL BIOLOGICAL AND BIOCHEMICAL EFFECTS OF HEMOADSORPTION

Measurement of safety parameters includes determination of effects of undesired depletion of endogenous and exogenous substances (i.e. albumin) and cells (i.e. platelets), and unintentional modulation of cell responses and/or biochemical pathways like activation of the coagulation cascade and the complement system and the upregulation of granulocytes, monocytes, lymphocytes and platelet adhesion molecules [13, 14]. A set of molecular markers representing classes of solutes susceptible to adsorption can be used to characterize the safety of hemoadsorption (Table 1). For example, the systemic effects of hemoadsorption, which can be used to asses safety, include hemodynamic, immunological and metabolic adverse events attributable to the

therapy (i.e. anaphylaxis, vasodilation, micronutrient depletion, heparin-induced thrombocytopenic thrombosis, bradykinin release syndrome), depletion of cells and cell products (e.g. leukopenia, anemia, thrombocytopenia, loss of plasma proteins and immunoglobulins), subtherapeutic drug levels (e.g. vancomycin) and micronutrient deficiencies (e.g. vitamin B).

Given the above considerations, several aspects of hemoadsorption require investigation. They include: (i) identification of targets, optimal conditions, cartridge or membrane configuration; (ii) determination of the efficiency and efficacy of adsorptive therapies in the setting of simultaneous convection and diffusion; (iii) identification of situations in the context of complex diseases with multiple targets (i.e. bacteria and cytokine storm) where the use of synergistic combination of modalities can lead to improved outcomes; (iv) investigation of methodologies that can regenerate adsorptive capacity to enable reutilization; (v) establishment of a standardized nomenclature and methodology for measuring adsorptive capacity and sorbent saturation in the clinical setting; (vi) identification of technologies and methodologies to use sensors to measure biological and biochemical parameters reflecting efficacy and safety; and (vii) creation of a hemoadsorption registry.

MODALITIES AND TECHNIQUES

The term modality refers to the adsorptive methods by which blood or plasma are exposed to a sorbent or a membrane [4, 5]. For example, the modality involved in removal of endotoxin through a specific endotoxin adsorbing filter differs from that where viruses are removed through a heparin-bonded filter (Table 2).

The term technique refers to the mechanism by which the treatment acts via an extracorporeal circuit. Regardless of the technique, vascular access is required. It is typically established using a double lumen catheter placed in a central vein, although an arteriovenous fistula can be used. Adsorption will require an extracorporeal circuit with a dedicated cartridge (Fig. 2a), an intermittent hemodialysis or continuous renal replacement therapy (CRRT) circuit with a hemofilter and a hemoadsorption cartridge (Fig. 2b), an extracorporeal membrane oxygenator (ECMO) or a cardiopulmonary bypass (CPB) circuit (Fig. 2c). A possible technique is to separate plasma via a plasma filter and then deliver it to a cartridge via a parallel circuit and reinfuse it back into the blood circuit (Fig. 2d) [17, 18]. Anticoagulation of the extracorporeal circuit should be optimized considering patient characteristics, the modality employed and the duration of treatment.

SPECIFIC TECHNIQUES

Hemoadsorption may be combined with an intermittent hemodialysis or CRRT circuit where the cartridge can be placed before or after the filter [19, 20]. Blood flow may vary according to the prescribed hemodialysis treatment. In patients undergoing ECMO, a hemoadsorption cartridge may be inserted within the ECMO circuit [21–26]. However, such use is off-label in the European Union and is not allowed in some countries (e.g. Germany). In cardiac surgery patients, the cartridge can be connected to the CPB circuit [27–34]. Suggested blood-flow ranges are provided by the manufacturers, although technical challenges may be encountered given that the flow through the cartridge and hydrostatic pressure gradients must be adjusted to achieve adequate flows while avoiding perturbations and malfunctioning of the main circuit. The simplest application, however, is that of direct hemoadsorption where blood is circulated through a cartridge by a peristaltic pump and is in direct contact with the sorbent particles [35, 36]. All these approaches have been described in the literature but there is still a need to define key areas such as estimation of cartridge saturation, optimal blood flow, type of anticoagulation, clotting risk, duration of each individual session, frequency of sessions (e.g. daily, alternate days), efficacy of combining techniques, and application on whole blood or plasma.

SAFE AND EFFICIENT DELIVERY OF HEMOADSORPTION

The treatment of critically ill patients with hemoadsorption requires a specific set of skills and knowledge base for the intensive care unit (ICU) nurses and medical staff [37]. Once a decision to treat is made, nurses can effectively manage the technique by following a series of steps in sequence including patient and machine circuit preparation, connection of the extracorporeal circuit to the patient's vascular access, initiation of the prescribed anticoagulation, consideration of potential drug dose changes or rescheduling and monitoring for safety, similar to the use of CRRT. An advancement in skills and knowledge, using a background of acute experience with CRRT or dialysis, but with additional requirements of the other nursing tasks employed for hemoadsorption, is needed [25].

REMOVAL OF MOLECULES BY HEMOADSORPTION

Hemoadsorption can remove endogenous and exogenous toxic adsorbates (Table 2). Various materials can be used to achieve removal by adsorption. Such materials, their commercial name and manufacturer and the target solute for removal are summarized in Supplementary data, Table S2. Finally, adsorption can result in the collateral removal of endogenous (i.e. nutrients) and/or exogenous (i.e. antibiotics) non-toxic adsorbates, potentially leading to depletion of key solutes, mediators and therapeutic solutes necessary for the homeostasis and recovery of the host.

Medium-middle (>15–25 kDa), large-middle (>25–58 kDa) or large (>58 kDa) [10] water-soluble molecules are poorly cleared by filters, even those with higher permeability to solutes, such as medium or high cutoff membranes [10, 38]. Additionally, protein-bound molecules cannot be removed by traditional therapies. These solutes may be removed by plasmapheresis. However, plasmapheresis has the inconvenience of removing beneficial blood components such as immunoglobulins and coagulation factors [39–41]. Hemo- or plasma-adsorption provide a more selective alternative to plasmapheresis. The use of adsorption in treatment of intoxications has been well documented over the past 50 years [42–49] and includes removal of toxic chemicals following either deliberate or accidental ingestion such as organophosphate pesticides [50–52], but also the removal of medications such as antiepileptic drugs [53] or removal of anticoagulants before unplanned surgery. These techniques have not been subjected to randomized controlled trials (RCTs). Adsorption-based therapies have also been employed in some autoimmune diseases with the aim of antibody removal [54–57].

Hemoadsorption-based modalities have also been utilized in patients with liver disease—mostly plasma-adsorption but also hemoadsorption using bilirubin and bile acids as surrogate markers of therapeutic efficacy [58–66].

The area that has achieved most attention is the use of hemoadsorption in sepsis. This includes targeted removal of endotoxin, which can be achieved with specific cartridges or filters

Table 2: Sorbents and endogenous or exogenous molecules tested for sorbent-based removal[a].

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate $= (C_{baseline} - C_{end\ of\ session})/C_{baseline}$		Notes of clinical application
				Efficacy	Efficiency	
Molecules						
Antibodies	Phenylalanine immobilized polyvinylalcohol gel		PP	IgG, IgA, IgM [1]		Clinical data are mostly available for neurological and rheumatic diseases (particularly rheumatoid arthritis and systemic lupus erythematosus), myasthenia gravis, Guillain–Barré syndrome, multiple sclerosis [2, 3]
	Tryptophan immobilized polyvinylalcohol gel		PP	AChR, IgG, IgM, cryoglobulins		
	Synthetic peptide Gam146 immobilized immunosorbent		PP	IgG, IgA, IgM [4]		
Beta 2-microglobulin		PMMA	IHD, CRRT (as CVVH, or CVVHD, or CVVHDF)	33.9 (±2.8) [5]		Clinical data available from 20 patients treated with 4-h IHD (Qb 300 mL/min, Qd 500 mL/min)
Bile acids	Porous polymer beads–polystyrene divinylbenzene		HA, PP	82 [6, 7]		Clinical data are mostly available from case reports on liver failure in pediatric patients
Bilirubin	Porous polymer beads–polystyrene divinylbenzene		HA, PP	44.6 (14.5) to 72 [5, 6, 7]	90 [8]	Clinical data are mostly available from case reports on liver failure in pediatric patients
Cytokines, pro-inflammatory (IL-3, IP-10, IL-17α, MIP-1α, MIP-1β, HMGB-1, IL-8, IFN-γ, Eotaxin, IL-6, MIF, MCP-1, TNF-α, IL-1β)	Porous polymer beads–polystyrene divinylbenzene		HA		IL-3 [99.4 (±0.0)], IP-10 [99.1 (±0.2)], IL-17α [97.6 (±0.3)], MIP-1α [97.3 (±0.4)], MIP-1β [92.4 (±0.0)], HMGB-1 [91.8 (±0.9)], IL-8 [100 (±0.0)], IFN-γ [95.7 (±0.6)], Eotaxin [99.0 (±0.0)], IL-6 [99.6 (±0.1)], MIF [83.0 (±20.2)], MCP-1 [100 (±0.0)], TNF-α [98.4 (±0.2)], IL-1β [97.2 (±0.0)] [9]	Clinical data are mostly available for hyperinflammatory syndromes (e.g. sepsis, acute pancreatitis, etc.)

Table 2: Continued.

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate = $(C_{baseline} - C_{end\ of\ session})/C_{baseline}$ Efficacy	Efficiency	Notes of clinical application
	PMX covalently bound to polypropylene-polystyrene fiber		HA		IL-3 [70.2 (±11.1)], IP-10 [68.6 (±11.9)], IL-17α [74.0 (±6.2)], MIP-1α [91.0 (±0.4)], MIP-1β [70.3 (±9.0)], HMGB-1 [61.5 (±1.9)], IL-8 [34.5 (±13.1)], IFN-γ [37.4 (±8.3)], Eotaxin [42.2 (±7.9)], IL-6 [41.8 (±14.6)], MIF [45.1 (±13.8)], MCP-1 [11.3 (±4.4)], TNF-α [17.9 (±9.2)], IL-1β [15.0 (±13.3)] [9]	Clinical data are mostly available for hyperinflammatory syndromes (e.g. sepsis, acute pancreatitis, etc.)
		AN69-PEI-heparin	CVVH, CVVHD, CVVHDF	IL-6 (81.8), IL-6 (76.8), TNF (63.1), IL-8 (64.5) [10]	IL-3 [99.3 (±0.0)], IP-10 [99.3 (±0.3)], IL-17α [98.7 (±0.4)], MIP-1α [97.3 (±0.4)], MIP-1β [91.5 (±1.2)], HMGB-1 [89.5 (±0.4)], IL-8 [100 (±0.0)], IFN-γ [99.5 (±0.3)], Eotaxin [99.1 (±0.1)], IL-6 [93.5 (±1.4)], MIF [78.0 (±24.4)], MCP-1 [100 (±0.0)], TNF-α [90.1 (±2.2)], IL-1β [86.8 (±1.0)] [9]	Clinical data are mostly available for hyperinflammatory syndromes (e.g. sepsis, acute pancreatitis, etc.). Data from [10]. Included 44 patients with sepsis or septic shock. Duration of treatment with AN69-PEI-heparin filter was ~48 h. In all cases AN69-oXiris more effective at removal than AN69-ST
		PMMA	CRRT (as CVVH, or CVVHD, or CVVHDF)		IL-3 [92], IP-10 [90], IL-17α [59], MIP-1α [87], MIP-1β [80], IL-8 [21], IFN-γ [46], Eotaxin [91], IL-6 [70], MIF [24], MCP-1 [82], TNF-α [40], IL-1β [7, 11]	Clinical data are mostly available for hyperinflammatory syndromes (e.g. sepsis, acute pancreatitis, etc.)

Table 2: Continued.

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate = $(C_{baseline} - C_{end\ of\ session})/C_{baseline}$		Notes of clinical application
				Efficacy	Efficiency	
		AN69-ST	CRRT (as CVVH, or CVVHD, or CVVHDF)	IL-6 (60.1), TNF (47.5), IL-8 (48.4) [10]		Data from reference [10]. Included 44 patients with sepsis or septic shock. Duration of treatment with AN69-PEI-heparin filter was ~48 h. In all cases AN69-oXiris more effective at removal than AN69-ST
Cytokines, anti-inflammatory (IL-4, IL-2, IL-10, IL-13, IL-1Ra, IL-12p70)	Porous polymer beads–polystyrene divinylbenzene		HA		IL-4 [99.9 (±0.0)], IL-2 [99.3 (±0.3)], IL-10 [99.8 (±0.0)], IL-13 [94.2 (±0.0)], IL-1Ra [92.1 (±0.0)], IL-12p70 [76.5 (±2.5)] [9]	Clinical data are mostly available from studies in which the treatment was used to counterbalance dysregulated anti-inflammatory responses and anergic phenotype (e.g. during sepsis)
	PMX covalently bound to polypropylene-polystyrene fiber		HA		IL-4 [55.9 (±16.0)], IL-2 [61.6 (±13.6)], IL-10 [40.6 (±14.9)], IL-13 [73.7 (±20.6)], IL-1Ra [35.4 (±16.2)], IL-12p70 [6.9 (±8.0)] [9]	
		AN69-PEI-heparin	CVVH, CVVHD, CVVHDF	IL-10 (58.0) [10]	IL-4 [99.9 (±0.0)], IL-2 [99.4 (±0.2)], IL-10 [99.0 (±0.4)], IL-13 [93.5 (±0.0)], IL-1Ra [90.2 (±2.8)], IL-12p70 [22.1 (±4.5)] [9]	Clinical data are mostly available from studes in which the treatment was used to counterbalance dysregulated anti-inflammatory responses and anergic phenotype (e.g. during sepsis). Data from reference [10]. Included 44 patients with sepsis or septic shock. Duration of treatment with AN69-PEI-heparin filter was ~48 h. In all cases AN69-oXiris more effective at removal than AN69-ST

Table 2: Contnued.

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate = $(C_{baseline} - C_{end\ of\ session})/C_{baseline}$		Notes of clinical application
				Efficacy	Efficiency	
		PMMA	CVVH, CVVHD, CVVHDF		IL-4 [96], IL-2 [93], IL-10 [61], IL-13 [97], IL-1Ra [10], IL-12p70 [22] [11]	Clinical data are mostly available from studies in which the treatment was used to counterbalance dysregulated anti-inflammatory responses and anergic phenotype (e.g. during sepsis)
		AN69-ST	CVVH, CVVHD, CVVHDF	IL-10 (45.9) [10]		Data from reference [10]. Included 44 patients with sepsis or septic shock. Duration of treatment with AN69-PEI-heparin filter was ~48 h. In all cases AN69-oXiris more effective at removal than AN69-ST
Complement (C3, C4, C5)	Tryptophan immobilized polyvinylalcohol gel		PP	C3 (48%), C4 (72%)		Autoimmune diseases
	Porous polymer beads–polystyrene divinylbenzene		HA		C3a [98.2 (±0.2)], C5a [95.7 (±1.2)] [9]	Preliminary clinical results are available from [12]
	PMX covalently bound to polypropylene-polystyrene fiber		HP		C3a [67.9 (±7.5)], C5a [38.8 (±7.9)] [9]	
		AN69-PEI-heparin	CRRT (as CVVH, or CVVHD, or CVVHDF)		C3a [96.4 (±1.2)], C5a [90.7 (±0.6)] [12]	
Endotoxin		AN69-PEI-heparin	CRRT (as CVVH, or CVVHD, or CVVHDF)	71.4 [13]	From 30.5 to 66.6 [2]	Clinical data are available from RCT comparing LPS removal in 16 pts
	PMX covalently bound to polypropylene-polystyrene fiber		HA		From 51.6 to 75.9 [12]	Clinical data are available from [14, 15, 16]
Factor Xa inhibitors	Porous polymer beads–polystyrene divinylbenzene		HA, PP		Rivaroxaban [from 95 (t0) to 16 (t120′)] [17, 18], edoxaban (from 99 to 100, 19), apixaban (from 81 to 100, 18]	Removal rate available from *in vitro* study. Clinical data mostly available from case report on emergency surgery [20]

Table 2: Continued.

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate = $(C_{baseline} - C_{end\ of\ session})/C_{baseline}$		Notes of clinical application
				Efficacy	Efficiency	
Fibrinogen	Tryptophan immobilized polyvinylalcohol gel		PP	782		Mostly used during hyperfibrinogenemia
Free light chains		PMMA	CRRT (as CVVH, or CVVHD, or CVVHDF)	kFLC [55.3 (±3.4)], lambda FLC [37.8 (±17.3)] [4]		Used for multiple myeloma. 20 patients treated with 4-h IHD (Qb 300 mL/min, Qd 500 mL/min)
	Cellulose beads immobilized hexadecyl as ligand		PP		kFLC 49.0%, lambda FLC 44.0% [21]	*In vitro* comparison among high cut-off membranes, plasmafilter and cartridges
Growth factors (FGF-23, FGF-21, G-CSF)	Porous polymer beads–polystyrene divinylbenzene		HA		FGF-23 [99.4 (±0.8)], FGF-21 [99.9 (±0.0)], G-CSF [99.4 (±0.0)] [9]	
	PMX covalently bound to polypropylene-polystyrene fiber		HA		FGF-23 [88.4 (±5.5)], FGF-21 [70.9 (±10.1)], G-CSF [16.9 (±8.0)] [9]	
		AN69-PEI-heparin	CRRT (as CVVH, or CVVHD, or CVVHDF)		FGF-23 [98.7 (±1.1)], FGF-21 [96.0 (±0.9)], G-CSF [36.0 (±2.9)] [9]	
		PMMA	CRRT (as CVVH, or CVVHD, or CVVHDF)		FGF [7], G-CSF [60], GM-CSF (86), VEGF (22), HGF [11, 30]	
Iodinated contrast media	Porous polymer beads–polystyrene divinylbenzene		HA, PP		96 [22]	
Myoglobin	Porous polymer beads–polystyrene divinylbenzene		HA, PP	50 [25, 23]		*In vivo* comparison of HCO, MCO and cartridge in 15 patients with rhabdomyolysis
Platelet $P2Y_{12}$ inhibitors	Porous polymer beads–polystyrene divinylbenzene		HA, PP		Ticagrelor (from 62 to 100) [18, 24]	Clinical data mostly available from case report on emergency cardiac surgery [20, 25–27]
Serine protease (PAI-1)	Porous polymer beads–polystyrene divinylbenzene		HA		*PAI-1* [95.5 (±0.4)] [9]	
	PMX covalently bound to polypropylene-polystyrene fiber		HA		*PAI-1* [30.9 (±9.6)] [9]	

Table 2: Continued.

Adsorbate	Sorbents	Membranes	Modality	Removal rate (%), Removal rate = $(C_{baseline} - C_{end\ of\ session})/C_{baseline}$		Notes of clinical application
				Efficacy	Efficiency	
		AN69-PEI-heparin	CRRT (as CVVH, or CVVHD, or CVVHDF)		*PAI-1* [87.9 (±1.8)] [9]	
Thrombin inhibitor	Porous polymer beads–polystyrene divinylbenzene		HA		Dabigatran (from 94 to 100) [28]	
Cells and microorganisms						
Immune cells						
Bacteria	Heparin covalently bound to polyethylene		HA		Inadequate data	Clinically used during bacteremia
Fungi	Heparin covalently bound to polyethylene		HA		Inadequate data	Clinically used during fungemia
Viruses	Heparin covalently bound to polyethylene		HA		Inadequate data	Clinically used during viremia

[a] All numbers in red and within square brackets refer to PubMed identifiers—the list of relevant Table 1 related references is presented in Supplementary Appendix List S8.
Removal rate has been calculated as $RR = \{CB_{(T0)} - CB_{(Tend)}\}/CB_{(T0)}$, where $CB_{(T0)}$ is the concentration at baseline (t0) and $CB_{(Tend)}$ is the concentration at the end of the session. Removal rate is expressed in this table as median (interquartile range) or mean (±standard deviation), according to distribution of data in the referenced article. Finally, this parameter is reported precisely as specified among the study's results, or it is estimated by study's figures or calculated by solute concentrations reported among the study results.
CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor (glycoprotein); GM-CSF, granulocyte macrophage colony-stimulating factor; GF, hepatocyte growth factor; HMGB-1, high-mobility group box 1 protein; HA, hemoadsorption; IL, interleukin; IFN, interferon; IP, interferon-induced protein; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; MIP, macrophage inflammatory protein; PAI, plasminogen activator inhibitor; PP, plasma perfusion; TNF, tumor necrosis factor; Ra, receptor agonist; RR, removal rate; VEGF, vascular endothelial growth factor.

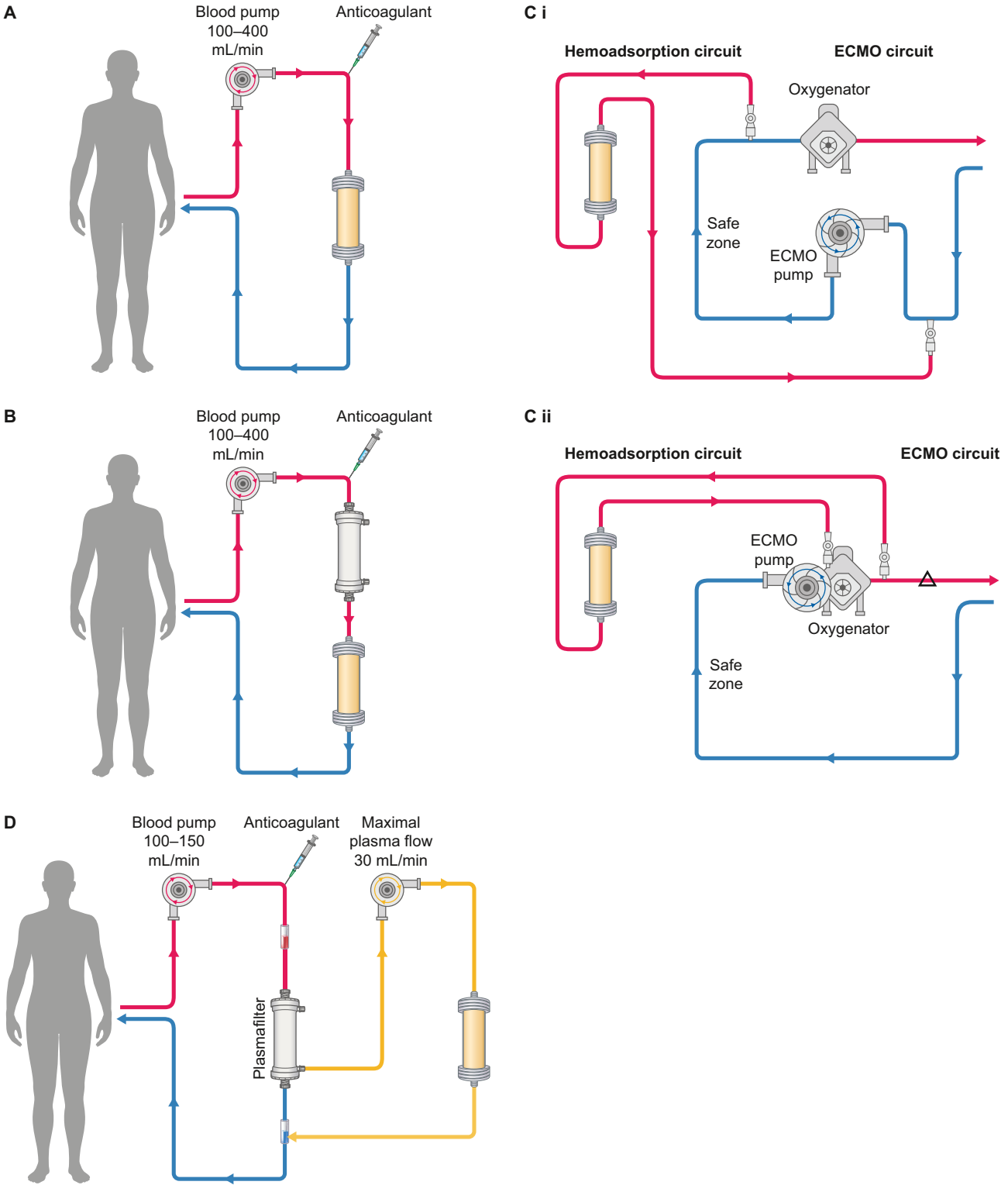

Figure 2: This series of figures illustrates different techniques of hemodsorption. They include direct hemoperfusion (**A**); direct hemoperfusion followed by hemodialysis or hemofiltration (**B**); hemoadsorption inserted with an ECMO circuit [(**C**) usual ECMO configuration and (c) ECMO Cardiohelp configuration] (note that the safe zone refers to the part of the circuit where it is safe to attach a connection to a side circuit for hemoadsorption therapy) and plasma filtration (note that the grey device is identified as plasma filter) followed by plasma adsorption and regeneration (**D**). Anticoagulation delivery should precede the contact of blood with any device placed in the circuit. It is preferable to have the hemofilter before the hemoadsorption cartridge because the current plug and play model of CRRT machines makes the addition of hemoadsorption cartridge easier after the hemofilter.

[67–69] or modulation of the dysregulated host response, with the nonspecific removal of mediators in the middle-molecular weight range [70, 71]. More recently, techniques have been described using cartridges containing heparin-bonded sorbent beads which directly remove pathogens including viruses, bacteria and fungi [72]. However, little is known about the optimal treatment duration or the effect of patient factors on performance.

UNINTENDED REMOVAL OF KNOWN COLLATERAL SUBSTRATES AND RESEARCH AGENDA

Hemoadsorption can be nonspecific and may remove useful endogenous or exogenous substrates. For example, the removal of medications has to be considered [73], accounted for and acted upon. Where treatment is for a limited period, antimicrobial dosing should be scheduled appropriately. Where continuous antibiotic infusions are being used, dose adjustment may be needed. Hemoadsorption removes other drugs such as the antiepileptic agent carbamazepine or direct oral anticoagulants. Hence, drug dosing should be adjusted. When drug monitoring is not available, empiric adaptation of drug dosing may be necessary [74–78].

Several areas of research exist that focus on technical assessment. They include: (i) comparison of performance of different adsorptive modalities, techniques and functionalized sorbents (where the sorbent has been modified to achieve binding to a specific molecule); (ii) comparison of operative conditions with effects on adsorptive performance such anticoagulation strategy, blood flow and circuit pressures; (iii) identification of adsorbates which may influence outcome; (iv) evaluation of the optimal healthcare professional allocation strategies and health economic evaluations; and (v) comparison of patient conditions (hematocrit, hemodynamics, inflammation, coagulation status) and effects on adsorptive performance.

INDICATIONS, PRESCRIPTION AND MONITORING

Hemoadsorption has been primarily used in states of exogenous or endogenous intoxication. Experience regarding the technique and safety of hemoadsorption has accumulated (Supplementary data, Tables S3–S6) Current data indicate biochemical effects (e.g. reduction in circulating cytokines [79] and endotoxin [80]; reduction of unwanted therapeutic drug levels of apixaban in the acute setting [74]), biological effects (e.g. improved monocyte HLA-DR expression [81]), microbiological effects (removal of viruses [82]) and clinical effects (e.g. improved hemodynamics [83]) with the use of extracorporeal adsorption. Most studies, however, are of low quality, retrospective and of single-center design, and some have failed to show such effects [84–114]. Given various sub-phenotypes in several disease scenarios (e.g. sepsis [115]) it is plausible that some sub-phenotypes may show differential treatment responses to hemoadsorption. Tailored, adaptive studies that include only patients meeting specific and objective criteria (i.e. biomarker, clinical phenotypes), such as in ongoing trials (ClinicalTrials.gov, NCT03901807; NCT04742764; NCT04963920), may offer plausible indications for treatment and/or endpoints for hemoadsorption.

There is no evidence to guide the start of hemoadsorption. However, such start should be logically based on the pathophysiology of the underlying condition where biological and/or clinical criteria suggest that the clinical course may be favorably modified by the therapy. In addition, it seems logical that hemoadsorption should not be initiated too late once the deleterious sequelae caused by toxins or mediators have been established. Therapy can be discontinued if resolution of the clinical indication or treatment futility has occurred. Before prescribing these therapies, however, important considerations include local availability (machines, cartridges, disposables, etc.) and human resources (nursing staff) to initiate, monitor and guarantee the appropriateness and safety of the prescribed treatment. Finally, it is mandatory to establish adequate vascular access, apply monitoring, and provide adequate laboratory support and therapeutic drug monitoring whenever possible.

The hemoadsorption prescription should include age, weight, body mass index, sex and illness severity, which significantly impact the prescription strategy. Key parameters that require prescription include blood-flow rate, therapy timing, anticoagulation choices and plans for the maintenance of vascular access. Blood-flow rates depend on many factors. However, optimal blood-flow rates in different clinical scenarios remain undefined. Another key parameter is time to scheduled cartridge changes. While some cartridge manufacturers provide time-to-saturation limits, further research is needed to determine the optimized time to schedule cartridge change with various sorbents and in different clinical scenarios. Other timing parameters include scheduled off-therapy periods (time needed between consecutive therapy sessions) and duration of total therapy. However, no high-quality data exist to guide such decisions. Such lack of quality data on so many elements of hemoadsorption prescription highlights that recommendations or guidelines for clinical practice are currently not possible. It also highlights that the research agenda dominates the prescription and clinical practice agenda and that, at this stage, all clinical practice should be viewed as research and reported as such.

MONITORING OF HEMOADSORPTION

In view of the relative lack of controlled clinical trial data on clinical effectiveness and safety of hemoadsorption, there should be detailed real-time monitoring, recording and analysis of the efficacy (therapeutic effects), safety (including off-target effects and technical issues) and clinical effectiveness (patient-centered outcomes) of these therapies in practice.

Therapeutic efficacy may be monitored by clinical responses (e.g. pruritus in liver failure; vasopressor requirements in shock; gas exchange and lung mechanics in respiratory failure); and serial monitoring of target molecules for absorption (e.g. endotoxin activity assay in endotoxemia; clotting parameters when removing anticoagulants) (Supplementary data, Table S7). If possible, such companion diagnostics should be used to titrate therapy, but these tools have not been developed for every indication. Moreover, hemoadsorption may affect the concentration of diagnostic markers (e.g. C-reactive protein, procalcitonin, troponin) even though this has not been formally studied. Technical details of prescribed and delivered therapy should be routinely monitored including sorbent type and surface area, blood flow (prescribed and delivered), system pressures, treatment duration (hours and number of cartridge changes), and evidence of system clotting for a treatment and in total. Safety should also be monitored by vigilance to detect any treatment-emergent (e.g. hemorrhage, seizure, or arrhythmia) or potentially treatment-associated adverse events (e.g. hypotension, increased vasopressor use, hypothermia, worsening sepsis caused by off-target removal of antibiotics and/or anti-inflammatory

mediators). In future, greater availability of companion diagnostics may further enhance safe prescribing. In addition, clinical use of these treatments should be carefully recorded and subject to scrutiny by local audit and analysis of international registries.

MINIMUM DATASET FOR LOCAL AUDIT OR MULTICENTER REGISTRIES

RCTs remain the gold standard for clinical research. However, due to their high cost, large sample size requirements and other research design obstacles, RCTs are challenging to execute. Prior to the ultimately mandatory conduct of such trials, a data collection pathway, documentation of clinical data by local audit and/or multicenter registries may be useful to define epidemiology and outcomes and to inform trial design prior to the conduct of RCTs. Compared with RCTs, clinical registries allow for the potential of easier inclusion of larger datasets under real world clinical circumstances but do not allow inferences about causality and are affected by selection bias. Despite such limitations, observational data can help establish quality assurance and improvement, and supplement existing safety reporting pathways for adsorption therapies. To minimize the risk of biased and confounding data, research protocols for prospective/retrospective data collection, standardization of patient datasets, including longitudinal and time-point based, and outcome data should be incorporated in the design of clinical registries, including data on patients with target conditions not treated with hemoadsorption.

The minimum observational dataset should include demographics (i.e. weight, age, comorbidity index scores), clinical presentation (i.e. other extracorporeal organ support, severity of illness), therapeutic intent (i.e. immunomodulation), indications for the therapy and therapeutic target [i.e. reducing toxic levels of drug(s), removal of molecules with a pathophysiological role], prescribed and delivered therapy parameters such as the modality of extracorporeal adsorption and operational characteristics [i.e. adsorber selection, timing of therapy, blood/plasma flow (mL/min)], measured clinical/biological responses (if available) (i.e. mechanical respirator-free days, vasopressor dose decrease/discontinuation, modulation of target molecules), anticipated and/or unanticipated adverse events (i.e. prolonged bleeding, drug removal, cartridge clotting) and clinical course, which should be determined not only by short-terms effects (i.e. 28-day ICU clinical improvement and/or mortality) but also longer term-effects (i.e. 90- and/or 180-day mortality, presence of chronic disease/states related to indication for adsorber therapy prescription).

Large, prospective RCTs of hemoadsorption addressing patient-centered endpoints are unlikely to eventuate soon, leaving clinical adoption without a strong evidence base. Given this evidence gap, research efforts should focus on gathering data that will inform the design of future prospective studies and maximize information gathered from current clinical use of these therapies in the setting of clinical trials. Identifying phenotypes and endotypes of patients that predictably characterize these who may most benefit from adsorption modalities is a priority. Novel biomarkers defining endotypes where clinical benefits from therapy can be forecast should also be sought. Similar techniques can be applied to the use of diagnostics to guide the titration and discontinuation of adsorption treatment. High-quality prospectively defined registries documenting clinical use may be helpful. Such processes have the potential to evolve into platforms for before-and-after trials, or even RCTs. In this regard, defining key endpoints is important.

PRINCIPLES FOR SELECTING ENDPOINTS IN HEMOADSORPTION

The selection of endpoints should be based on the phase of development, the clinical indication, the specifics of the adsorption therapy and the intended patient population. Moreover, outcomes can be technical, biological, physiological, biochemical, hematological, organ-function related, logistic, organ support and duration of care related, and finally clinical. This demands consideration of disease and context-specific factors when selecting both surrogate (biomarker) and clinical endpoints (patient-centered outcomes) for clinical trials and for clinical practice.

For instance, in patients with cholestatic hepatitis or neonates with kernicterus, bilirubin is a disease-specific biomarker and direct surrogate endpoint to monitor the response and gauge the therapeutic effect (Fig. 3a). Similarly, blood concentrations of a medication, along with physiologic effects of toxicity, are suitable biomarkers and direct and indirect surrogate endpoints for the application of a specific extracorporeal adsorption therapy. Furthermore, the endpoint may be unique to a particular patient population or disease condition; for instance, in children, nephron maturation or neurocognitive development is particularly important whereas in patients with rhabdomyolysis a reduction in myoglobin coupled with improvement in renal function could be employed. The assessment of the relative benefits and potential harms (i.e. off-target effects) of hemoadsorption remains an important consideration for selecting endpoints (i.e. surrogate endpoints of efficacy vs toxicity; clinical endpoints of effectiveness vs adverse events). In addition, an assessment of the balance of benefit to risks must consider the potential "fixed" adverse effects associated with exposure to any extracorporeal adsorption therapy (e.g. catheter insertion and maintenance; blood exposure to extracorporeal circuit; anticoagulation). It must also consider whether desorption overcomes adsorption over time if a sorbent cartridge is used for extended periods (6–8 h) and when such desorption may occur, as this is of concern and may be a drawback of extended cartridge use. Naturally, selected endpoints interrogated in pre-clinical and pilot studies will inform healthcare professionals and patients during adoption and use in clinical practice (Fig. 3b).

BIOMARKERS AS SURROGATE ENDPOINTS FOR HEMOADSORPTION

Biomarkers can inform about efficacy, efficiency and safety. Biomarkers employed as surrogate endpoints should not be confounded by other therapies (e.g. renal replacement therapy). Pilot and pivotal investigations may need to assess multiple biomarkers specific to therapeutic intent of the specific extracorporeal adsorption therapy (Fig. 3).

Many biomarkers have been used as surrogate endpoints in preclinical, pilot and pivotal trials of adsorption therapies [26, 116–118]. These studies have included cytokines, endotoxin activity, procalcitonin, C-reactive protein; myoglobin, cell-free DNA; 0athogen-associated molecular pattern molecules (PAMPs); damage-associated molecular pattern molecules (DAMPs); monocyte function and exogenous biomarkers (e.g. drug, toxin, pathogens) and clinical features (e.g. changes in hemodynamic profile, organ failure scores, laboratory data) (Table 2). Selected biomarkers are suitable surrogate endpoints when aligned with

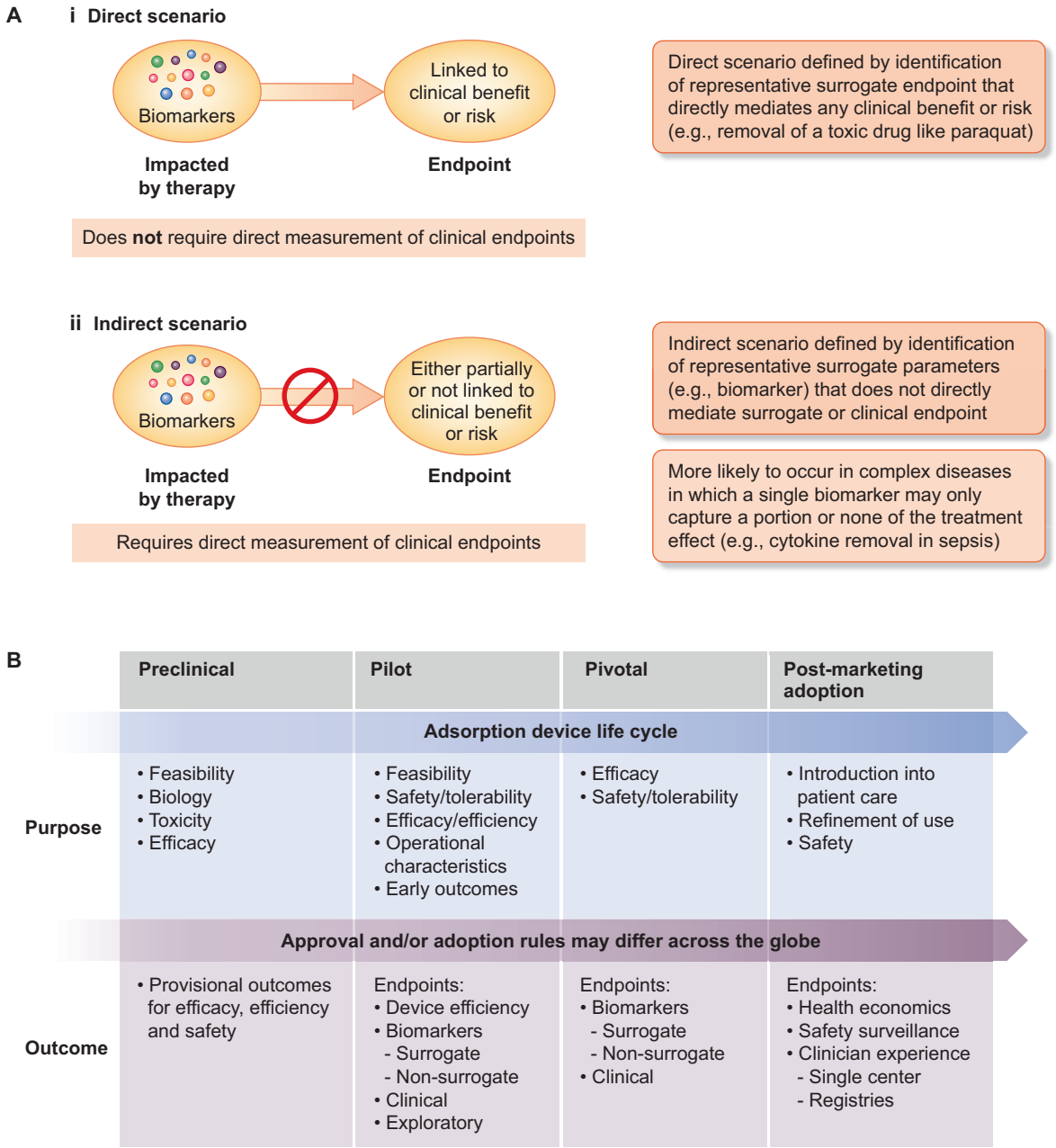

Figure 3: (**A**) Schematic representation of the choice of endpoints for trials of hemoadsorption. When a direct effect on a specific biomarker is considered as endpoint and that biomarker is directly linked with a clinical outcome, such biomarker is a legitimate endpoint. When no such biomarker exists (as is the case in most situations), then a biomarker effect is not sufficient and clinical endpoints need to be applied. (**B**) Schematic representation of different phases of sorbent assessment, purpose of assessment type and relevant outcome endpoints for such different phases and purposes.

therapeutic intent of the extracorporeal adsorption therapy [e.g. blood concentrations of dabigatran or ticagrelor; serum viral load (Ebola virus disease; SARS-CoV-2)]. Absolute and relative changes in physiologic parameters (e.g. MAP; PaO_2/FiO_2 ratio) and organ failure scores (e.g. SOFA score; multiorgan dysfunction syndrome score) have also been used as intermediate surrogate endpoints in pilot and pivotal trials. These physiologic parameters, however, have been variably defined in clinical trials and may have weak or uncertain correlation with clinical endpoints. Only a few trials have coupled a validated biomarker that correlates with and is predictive of a clinical endpoint as a therapeutic target during hemoadsorption [119, 120, 121] (e.g. EAA and polymyxin B therapy). In this instance, EAA serves as both a tool for predictive enrichment, a surrogate endpoint and a potential measure of biologic response.

CLINICAL ENDPOINTS FOR TRIALS

Clinical endpoints are the most credible characteristics used to assess the balance of the relative benefits and risks of hemoad-

sorption. Trials have generally focused on short-term survival [121], which has often been reported as a secondary endpoint in pilot and pivotal trials [122]. Importantly, many studies of adsorption therapy have failed to show a survival advantage, potentially due to trial design and the inclusion of heterogeneous populations [121]. Others have shown an association with harm [96]. These observations highlight that there is a major gap between theoretical constructs and therapeutic rationale and actual evidence of efficacy. Among survivors, functional endpoints, including short- and long-term measures of physical function and disability, are also important. Patient-reported endpoints can further include mental health, cognitive function, health-related quality of life, growth, neuro-cognitive development (particularly in children) and social wellbeing.

Ideally, endpoints selected for pilot and pivotal studies inform post-market studies and registries that describe long-term patient-centered and patient-reported outcomes. Frameworks exist to describe the barriers of therapy adoption and clinical implementation. They are informed by ethical, legal and social implications [122], variation in jurisdictional regulatory requirements [123], funding, workforce attitudes, knowledge and skill [124], and clinician and patient acceptance. The International Medical Device Regulators Forum (IMDRF) represents regulatory authorities from around the world working together to harmonize these regulatory requirements. Inequities in access to care also exist between low- and middle-income countries compared with high-income countries [125]. Promoting health equity and ensuring access to hemoadsorption will be a challenge for the global critical care nephrology community as uncertainty remains about their ability to reliably decrease inflammatory markers [126].

There has been little assessment of the cost-effectiveness of hemoadsorption [127]. This would further have to integrate the cost considerations for acquiring the adsorption cartridges, provide initial training and ongoing accreditation for healthcare professionals, and ensure standard and safe prescription and delivery. While there is a dearth of high-quality evidence demonstrating the clinical benefit and cost-effectiveness of extracorporeal adsorption therapies, there may be context with highly specialized extracorporeal therapies (e.g. therapy in response to specific drug toxicity) that means this may not be feasible. A standard core outcome set captured within a rigorous registry would enable evaluation of real-world evidence including patient-reported outcomes and cost-effectiveness.

CONCLUSIONS

There is a rationale for but only limited evidence about modern hemoadsorption. Hemoadsorption has clinically acceptable short-term biocompatibility and safety, technical feasibility, and some experimental evidence of removal of some but not all molecular targets. In addition, while the balance of benefit and harm for non-specific hemoadsorption remains controversial, studies of endotoxin-based hemoadsorption have identified possible target phenotypes for larger RCTs. Finally, it is not possible to issue guidelines for the use of hemoadsorption at this stage due to the lack of robust data and only a research agenda can be agreed upon by consensus. Thus, despite significant technical and biocompatibility-related achievements, modern hemoadsorption remains a novel and experimental intervention, with limited clinical data and a large research agenda.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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Relevant to this manuscript, the following COIs apply related to advisory board participation, consultation, honoraria, or stock options:

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Thoma Rimmele: Jafron, Estor, Toray, Exthera
Claudio Ronco: Jafron, bBraun, Nipro, Asahi Medica, Biomerieux, Sphingotec
Antoine Scheider: Cytosorbent; Jafron
Gianluca Villa: Baxter
Alexander Zarbock: Baxter, Biomerieux, Astellas, RenalGuards, Novartis, Alexion, Paion, Sphingotec
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