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Blood-incompatibility in haemodialysis: alleviating inflammation and effects of coagulation

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ABSTRACT

Blood-incompatibility is an inevitability of all blood-contacting device applications and therapies, including haemodialysis (HD). Blood leaving the environment of blood vessels and the protection of the endothelium is confronted with several stimuli of the extracorporeal circuit (ECC), triggering the activation of blood cells and various biochemical pathways of plasma. Prevention of blood coagulation, a major obstacle that needed to be overcome to make HD possible, remains an issue to contend with. While anticoagulation (mainly with heparin) successfully prevents clotting within the ECC to allow removal of uraemic toxins across the dialysis membrane wall, it is far from ideal, triggering heparin-induced thrombocytopenia in some instances. Soluble fibrin can form even in the presence of heparin and depending on the constitution of the patient and activation of platelets, could result in physical clots within the ECC (e.g. bubble trap chamber) and, together with other plasma and coagulation proteins, result in increased adsorption of proteins on the membrane surface. The buildup of this secondary membrane layer impairs the transport properties of the membrane to reduce the clearance of uraemic toxins. Activation of complement system-dependent immune response pathways leads to leukopenia, formation of platelet–neutrophil complexes and expression of tissue factor contributing to thrombotic processes and a procoagulant state, respectively. Complement activation also promotes recruitment and activation of leukocytes resulting in oxidative burst and release of pro-inflammatory cytokines and chemokines, thereby worsening the elevated underlying inflammation and oxidative stress condition of chronic kidney disease patients. Restricting all forms of blood-incompatibility, including potential contamination of dialysis fluid with endotoxins leading to inflammation, during HD therapies is thus still a major target towards more blood-compatible and safer dialysis to improve patient outcomes. We describe the mechanisms of various activation pathways during the interaction between blood and components of the ECC and describe approaches to mitigate the effects of these adverse interactions. The opportunities to develop improved dialysis membranes as well as implementation strategies with less potential for undesired biological reactions are discussed.

Keywords: biocompatibility, blood haemocompatibility, clinical outcomes, coagulation, complement activation, haemodialysis membranes, inflammation

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INTRODUCTION

The success of haemodialysis (HD) as a life-sustaining therapy is, in large part, attributed to technological achievements [1, 2]. Nevertheless, it is recognized to be an imperfect therapy, not just because of the brief and intermittent nature of the detoxification processes that the natural kidney performs continuously [3]. Several untoward clinical consequences have been associated with extracorporeal procedures. The 'residual syndrome' and 'dialysis-induced systemic stress' are two explanations of the additional disturbances HD creates [4, 5]. Together with the partial correction of the uraemic syndrome by dialysis, these effects perhaps explain why further improvements of patient outcomes have been so difficult to achieve. Adverse interactions between blood and components of the extracorporeal circuit (ECC)—blood-incompatibility—is yet another manifestation of the unphysiological nature of HD [6].

Blood-incompatibility in HD is the consequence of repeated contact of flowing blood with a variety of foreign surfaces, air and geometrical conduits during every therapy session, thrice weekly [7]. In the body, blood is environed by the endothelium, the largest organ in the body particularly when size is expressed as surface area exposed to circulating blood [8]. By leaving the protection of the blood vessels and the monolayer lining of endothelial cells that help blood maintain its fluidity, blood is exposed to hostile surroundings, encountering noxious chemical stimuli as well as physical trauma. Of the hundreds, if not thousands, of compounds present in this tissue, each of which must cope with the new environment; the series of heterogeneous insults during HD could result in an alteration of their natural biological reactivity that is vastly different to that within the body [6, 7, 9–11]. Exogenous stimuli from components of the ECC can modulate sensitive endothelium-dependent responses to disturb the homeostasis and signalling reactions between the vascular wall and vessel lumen contents [8, 12–14]. In addition, activation of diverse biochemical pathways generates compounds that result in cellular or tissue damage, inflammation and oxidative stress [13, 15, 16]. For the three classes of blood cells, especially platelets, periodic thrice-weekly activation results in irreversible damage that patients must endure throughout the time they are on HD therapy [17, 18]. No artificial surface, inside or outside the body, can emulate the endothelium in terms keeping blood fluid and preventing unwanted activation of biochemical pathways; alterations of endothelial cells and the vasculature play a central role in the pathogenesis of a broad spectrum of diseases [19].

Analysing the clinical effects on the patient of the interaction of blood with artificial surfaces of the ECC circuit in HD is complex and compounded by several factors [20]. Most assessments, whether in the laboratory or *in vivo* during therapy, usually relate their findings to the dialyser being used, or more precisely, the material of the membrane within the dialyser [21–23]. While the membrane is unquestionably the centrepiece of the entire therapy, plasma protein pathways and cell activation are triggered by several other components of the ECC (Figure 1) [24, 25]. In HD, the moment blood leaves the body it encounters multiple stimuli that contribute to various extents to the overall blood-incompatibility equation [26]. For example, the effects of the blood–air interface are often ignored despite their potentially serious biochemical and physical impact [27]. Immediately following venipuncture, at certain points of the ECC and throughout the treatment session, microbubbles of air—air emboli—enter blood, impacting coagulation, platelets as well as plasma proteins, which may undergo denaturation through the effects of frothing [28]. Clearly, strategies that minimize the effects of these multiple reactions that occur during blood–material interaction are needed to improve HD therapy and its poor outcomes.

HAEMOCOMPATIBILITY IN HAEMODIALYSIS: DEFINITIONS, BACKGROUND AND CLINICAL RELEVANCE

Haemocompatibility—or blood compatibility—differs from tissue compatibility, both being subdivisions of the global term, biocompatibility [29]. In the artificial organs and biomaterials sciences, haemocompatibility is distinguished from tissue compatibility in that the former involves contact of artificial surfaces, devices or implants with (flowing) blood, whereas the latter relates to contact with tissues (e.g. bone, cartilage, skin) other than blood. Arguably, blood can be considered a tissue as well as a fluid, but as circulating red cells, platelets and various types of leukocytes are simultaneously activated with plasma components, it is physically distinguishable from entirely cell-based body tissues or organs [9]. As one would expect, devices intended for a particular medical application involving either blood or tissue use function-specific artificial materials.

Blood-contacting applications involve biomaterials that are used either in direct contact with blood within the body (e.g. catheters, stents, implants such as heart valves) or outside in ECCs (dialysis, oxygenation or blood bags and syringes). Anticoagulation aspects are paramount in both, with the type, mode and level of anticoagulation being dependent on the specific application the device is being used for [30–32]. Significantly, the type and intensity of the biological response elicited during the interaction of blood with artificial biomaterials depends on blood rheology, and hence the geometry of the device: interactions of biomaterials with blood in static or flowing conditions are intensely variable. For all ECC therapies applications involving blood, the overall biological response is governed by several factors including rheological considerations of not just the device (dialyser design) but of the entire circuit and application [33]. Haemo-incompatibility issues in ECC therapies are unique in that insults encountered by blood from multiple external stimuli occur briefly while outside the body only to return to its familiar environment before the cycle is repeated.

Biocompatibility—the biomaterials (non-dialysis) perspective

While the changes blood undergoes upon contacting surfaces such as glass were observed in the 1950s leading to the discovery of Hagemann factor (later factor XII of the coagulation cascade), the first use of the term 'biocompatibility' is believed to have appeared in 1970 [34, 35]. With a rapid rise in research and use of artificial materials for different medical applications, the science of biomaterials as it came to be known developed, and defining biocompatibility was considered necessary for a better understanding and assessment of the biomaterial–body tissue interface [29].

At a consensus conference on biomaterials in 1986 in Chester, UK, the participants debated and agreed to define biocompatibility as 'the ability of a material to perform with an appropriate host response in a specific application' [36]. Although the definition is concise, accurate and widely cited, it was left wanting for many as it could be interpreted in different ways and left certain issues unanswered. Adjudging

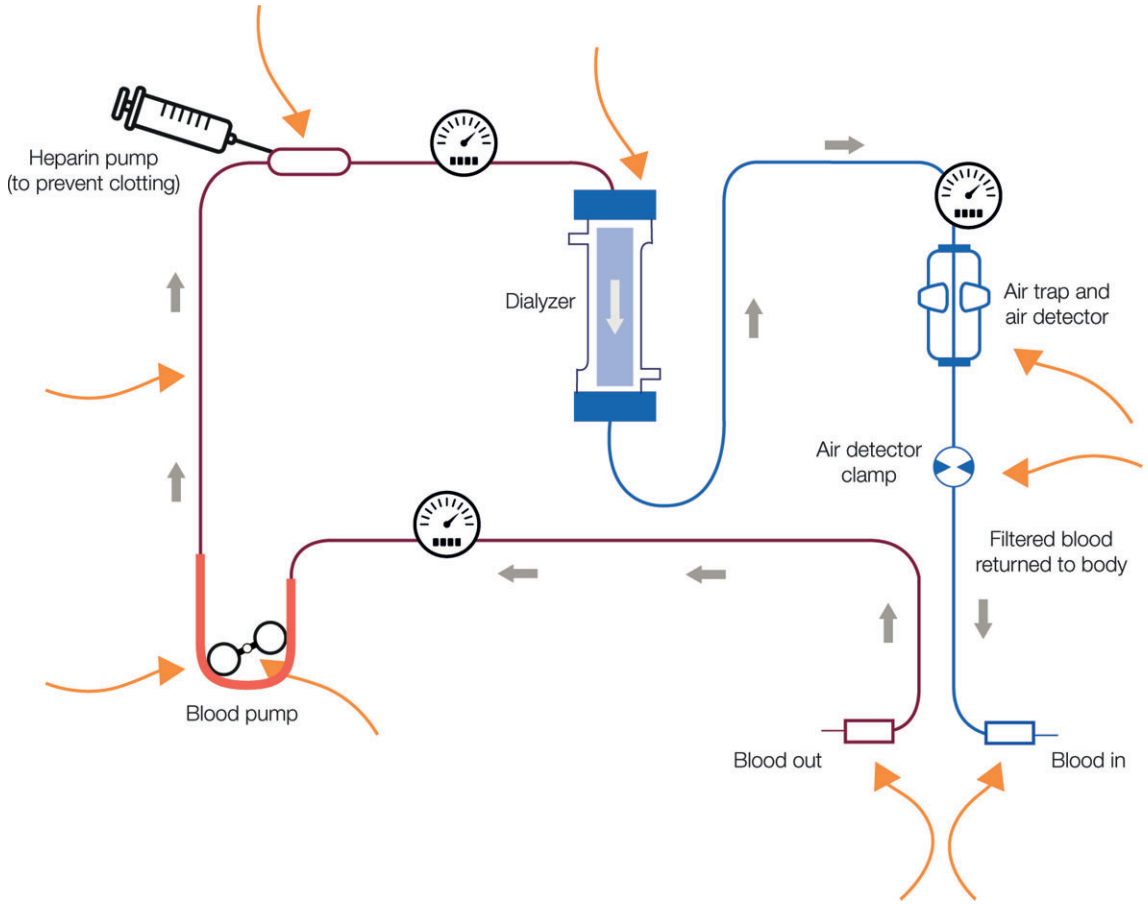

FIGURE 1: Multiple stimuli (orange arrows) arising from the entire ECC contribute to the haemo-incompatibility equation in haemodialysis therapies. Although the dialyser membrane is the focal point of most discussions around the haemocompatibility debate, activation of blood protein and cellular pathways occurs by venipuncture (needles), different types of polymers used for the ECC and is influenced by factors such as anticoagulation and blood flow rates. Blood trauma (caused by pumps or frothing) and blood–air interfaces contribute to the overall system haemo-incompatibility.

'an appropriate host response' was confounding given that most applications elicit multiple biological responses both over the short and long term. There was, also, the expectation that such a definition would provide insights to enhance or assess (*in vitro*/*in vivo*) biocompatibility [35]. Crucially, the early definitions referred solely to 'a material' rather than the device, which may be composed of multiple materials or the entire system (the ECC) [26]. In stressing the imperative of a 'systems approach to biocompatibility' the more pragmatic 'negative definition' of biocompatibility offered by Klinkmann *et al.* was more specific: absence of (or no): (i) thrombogenic, toxic, allergenic, inflammatory reactions; (ii) destruction of formed elements; (iii) changes in plasma proteins and enzymes; (iv) immunological reactions; (v) carcinogenic effects; (vi) deterioration of adjacent tissue [26, 37]. Whichever definition is considered, an important aspect to consider is that haemo-incompatibility must not impair the intended functioning of the device; in the HD case, the clearance, and sieving properties of the dialyser (membrane) should not be compromised. A subsequent definition by the European Society for Biomaterials in 2008 incorporated many of the perceived limitations of the first definition of biocompatibility but, by then, there was to be an altogether different definition and approach to biocompatibility—led by the nephrology fraternity [35, 38, 39].

Biocompatibility—the haemodialysis perspective

The circumstances of the splinter biocompatibility debate (resulting in alternative definitions) arose, uniquely, from a combination of clinical patient observations and corporate interests. In the early years of routine dialysis patients were treated almost exclusively with membranes made from cellulose. Cuprophan, first as flat-sheet and later as hollow-fibre membranes, became synonymous with the success story of dialysis as a therapy giving new lease of life to patients with end-stage renal disease. To this day, even though dialysis with cellulose-based membranes is a small fraction of that in its prime (until the early 1980s ~75% of all dialysis treatments were conducted with cellulosic membranes), publications regularly appear alluding to features of Cuprophan; the observation that Cuprophan (and similar cellulose-based membranes) caused transient leukopenia in parallel with activation of the complement cascade is still referred to mostly in a historical context to address biocompatibility [39].

The leukopenia-complement phenomenon observed and reported first by researchers in a few centres but then confirmed worldwide raised concerns about its potential impact on patient well-being [39]. With evidence indicating that leukopenia was associated with acute pulmonary dysfunction and sequestration of white cells in the lungs, speculation of the

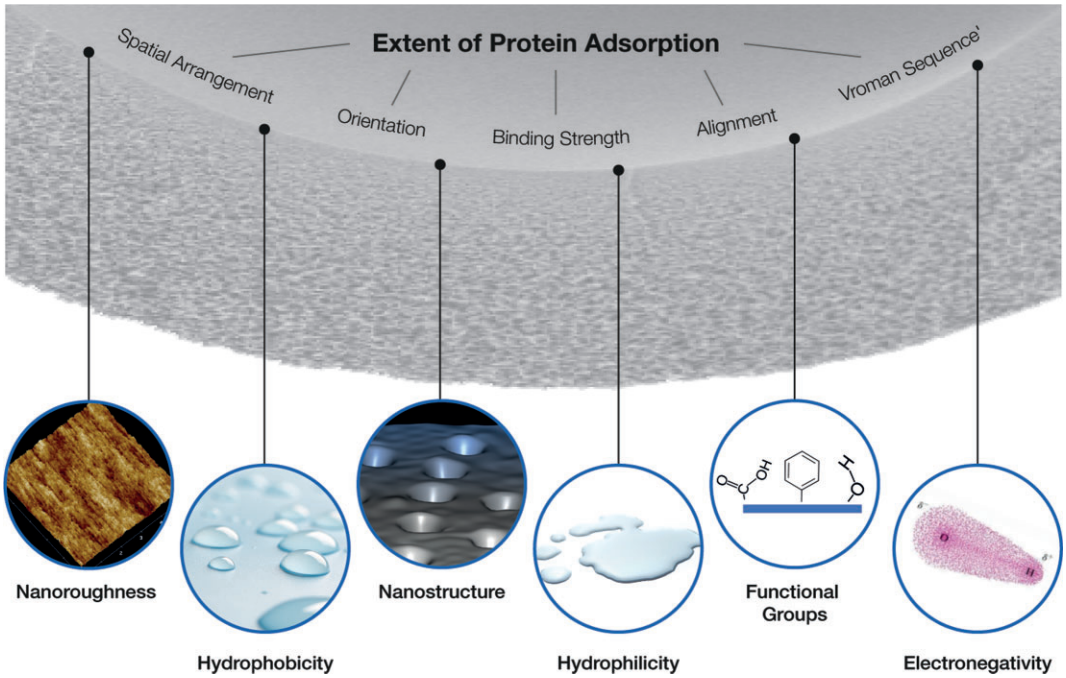

FIGURE 2: Rapid adsorption of plasma proteins is the initial step of blood–material interactions. Depending on various physiochemical properties of the inner blood-contacting membrane surface, a series of biological pathways are triggered. Only the main pathways most relevant to HD (coagulation, complement and immune) are shown. There is significant interaction of pathways during blood–material interactions, involving adhesion and activation of platelets and several types of white cells.

ill-effects intensified with concerns that the immunes system was being compromised [40]. For the manufacturers of Cuprophan (Enka Ag, later Akzo Nobel, in Wuppertal, Germany) this represented business repercussions, especially with the Fresenius Polysulfone membrane that caused considerably less complement or leukocyte loss began making its mark. With diverging explanations being offered regarding the potential clinical impact of cellulose membrane-induced leukopenia–complement, clarity was required on the clinical relevance of the observations [41, 42].

An industry-led initiative, the Consensus Conference on Biocompatibility (CCB), was held in Koenigswinter (Germany) in 1993 to address the growing concern and uncertainties regarding consequences, terminology and evaluation of biocompatibility with focus on extracorporeal blood purification therapies [43]. Pioneers of dialysis together with the world's leading nephrologists and specialists renowned for their contribution in relevant specialized fields such as immunology, blood coagulation and thrombosis, materials scientists and statisticians assembled to deliberate on the relevance of blood-incompatibility. Prior to the meeting four working groups met regularly over an 18-month period to prepare the forum for discussion at the CCB: I: Definitions and Terminology; II: Scientific Basis; III: Selection and Standardization; and IV: Clinical Relevance. The proceedings of the CCB were published the following year in *Nephrology Dialysis Transplantation* [43].

The CCB was one of several initiatives at the time attempting to define biocompatibility for standardization and its evaluation for biomaterials and artificial organs: IUPAC (International Union of Pure and Applied Chemistry) Working Party; International Standards Organization (ISO) 10993–1 (Part 1: Guidance on selection of tests) [44]; ISO 10993–9:2019, ISO Technical Committee 194 Working Group 9 (Biocompatibility Assessment) [45, 46]. The multiple recommendations—at times highly divergent—were an indication of the complexity of biological–artificial system interfaces and underscored the need to view biocompatibility from a specific application or device perspective. Recognition and better understanding of haemo-incompatibility issues specifically for HD led to improved devices and technologies in related blood purification therapies [47]. It also paved the way for the subsequent European Best Practice Guidelines for Haemodialysis (Section III: Blood-incompatibility) that dealt with five different aspects pertaining to biocompatibility of HD systems [48]. The guidelines focused mainly on the complement–leukocyte axis that initiated the debate about the clinical relevance of blood-incompatibility even though other pathways, plasmatic and cellular, are crucial considerations in the haemo-incompatibility phenomenon.

BLOOD–MATERIAL INTERACTIONS: THE SPECIFIC CASE OF DIALYSIS MEMBRANES

Adsorption of proteins to membrane surface

Almost instantaneously, plasma proteins begin to adsorb to the surface of biomaterials upon their exposure to blood [49]. All subsequent reactions, including the extent to which various biochemical pathways and cells during blood–material interactions are activated, are determined by this initial event. As depicted in Figure 2, protein adsorption is a complex phenomenon governed by the physiochemical characteristics of the blood-contacting surface involving hydrophobic and electrostatic interactions, hydrogen bonding and Van der Waals forces [50–52]. A certain number of platelets adhere to the surface simultaneously with protein adsorption; because of the rapidity of the process, it is often difficult to ascertain whether platelets adhere directly to the naked surface, or in unison with the first proteins that are

adsorbed. The phenomenon of adsorption of proteins, a prelude to activation of coagulation, complement and cellular pathways, it is a dynamic process that progresses throughout the duration of HD therapy. It is usually perceived from two opposing perspectives: one, it is considered as beneficial towards the pacification of artificial surfaces to hinder or minimize further adverse blood–material interactions [53] and two, a coating of proteins may be an impediment to the free transport during HD of uraemic retention solutes (uraemic toxins) across the membrane wall [50]. Analysis of the composition of the adsorbed layer, together with the study of the kinetics and thermodynamics of protein adsorption, are thus important considerations towards the development of improved HD membranes [54]. Several studies have analysed the differences between dialysis membranes in terms of their specific protein adsorption profiles [55–57].

Depending mainly on the surface chemistry (free chemical groups), surface charge and tension but also on the properties (e.g. viscosity) of the blood they are exposed to, a general membrane-specific adsorption pattern is discernible for each membrane type. However, a consistent 'fingerprinting' of membranes in terms of their protein adsorption profiles has not been possible as the analytical tools, methodology used (duration, static or flowing conditions, desorption technique, etc.) and patient variability compounds such profiling. The use of monoclonal antibodies to assess the composition of the adsorbed protein layer revealed that any of the thousands of proteins present in blood was potentially a constituent of the adsorbed layer. Every protein-specific antibody selected to detect the presence of a protein on surfaces revealed its presence in trace amounts, and one assumes every protein present in plasma could be adsorbed to membranes to some extent, depending on the surface properties of the membrane. Immunoelectrophoretic analysis of protein-adsorption to dialysis membranes have thus to be interpreted with caution as investigators pre-select the antibodies for the proteins they wish to study or assume to be present in the adsorbed layer.

Adsorption of proteins onto membrane surfaces is a complex, changing and competitive process, with constant adsorption and desorption of proteins [50, 58]. The essence of this 'Vroman effect' is that while the identities of adsorbed proteins changes over time, the total amount of adsorbed proteins remains essentially stable. Almost immediately after the establishment of circulatory flow, protein adsorption to the biomaterial surfaces occurs in a manner dependent on thermodynamic driving forces as well as the intrinsic properties of the material itself and the concentration, relative affinity and diffusion coefficients of blood proteins [59]. In the Vroman sequence large and more abundant proteins have a much stronger attractive interaction with the surface than the smaller ones that predominate in the plasma bulk [60]. Albumin, fibrinogen, immunoglobulin G, fibronectin, high-molecular-weight kininogen and factor XII bind competitively and sequentially, whereby the highest mobility proteins adsorb first and are then displaced by less mobile proteins with higher affinity for the surface. In HD, this redistribution of proteins is further affected by blood flow and shear rates used for each treatment.

More hydrophobic membranes generally display reduced adsorption of proteins whereas others such as polymethylmethacrylate (PMMA) are recognized as protein-adsorbing membranes [61, 62]. The protein layer deposits ('pseudo membrane') not only affect the polymer surface but could seep into the pores as well, resulting in narrowing of the pores thereby lowering the sieving properties and hence reducing solute removal particularly for larger solutes [63, 64]. The effects are amplified with sub-optimal heparin levels that enhance blood coagulation and at higher ultrafiltration fractions when the phenomenon of polarization thickens the protein deposit on the membrane surface [65]. The performance characteristics of a membrane are thus highly dependent on the plasma protein adsorption phenomenon [56, 66]. Any significant removal of uraemic toxins through an adsorption mechanism is unlikely as the adsorption phenomenon is highly non-specific, poorly defined and extremely difficult to quantify reliably [67]. The 'secondary membrane' in HD is influenced by several factors related to blood composition, chemical properties of proteins, physicochemical membrane characteristics (surface roughness, thickness, porosity, composition, hydrophobicity and charge) and operating conditions within the dialyser (blood flow dynamics and temperature) [53, 63, 64, 68, 69]. The impairment of either diffusive and convective transport by secondary membrane formation increases the resistance to mass transfer; this is undesirable and contrary to the core prerequisite of biocompatibility, viz., the nature of blood–material interactions should be such as not to diminish or impair the functioning of the device in its intended use [70].

Activation of coagulation and platelets

Throughout the development of dialysis and all blood-contacting devices, prevention of blood clotting has been the major obstacle to the contend with until advancements in anticoagulation made dialysis possible [30, 71, 72]. The adsorption processes described above not only modulate the overall biocompatibility of a material or device but are fundamental to the triggering of the intrinsic (contact activation) pathway of coagulation (Figure 3). Binding of factor XII (contact activation factor/Hagemann factor), together with prekallikrein and high-molecular-weight kininogen, to negatively charged surfaces (e.g. glass) sets off the reaction cascade-activating factors X and II leading to thrombin generation which acts on fibrinogen to form an insoluble fibrin 'clot' or thrombus. Significantly, factor XII and high-molecular-weight kininogen are major proteins [together with albumin immunoglobulin G (IgG) and fibrinogen] of the adsorbed protein layer involved in the adsorption–desorption of the Vroman effect [49].

Platelet adhesion to surfaces is an intrinsic early-stage activation characteristic of platelets, like that which occurs *in vivo* when there is rapid plugging of the site of vascular injury (e.g. a lesion or cut) as part of the primary haemostasis that subsequently involves the coagulation cascade (secondary haemostasis) [73]. Adsorbed proteins such as fibrinogen and other adhesive proteins (e.g. fibronectin, vitronectin and collagen) promote platelet adhesion by binding to glycoprotein IIb/IIIa receptors on the platelet surface. The conformation, as well as the amount, of adsorbed proteins is influential for this process. Platelets begin to lose their shape and begin to spread and flatten out through the formation of pseudopodia. Simultaneously, procoagulant phospholipids (phosphatidylserine and -choline) from the internal plasma membrane leaflet are exposed to the outside (flip–flop mechanism) to bind plasma coagulation factors. The secretion of granular content (e.g. β-thromboglobulin, platelet factor 4 and prostaglandins) and the procoagulant activity leads rapidly to aggregation of platelets to form the platelet-fibrin mesh of the clot or thrombus. The procoagulant state of HD patients is amplified by dialysis membrane-related of complement activation: upregulation of complement receptor 3 (CR3) on neutrophils is also

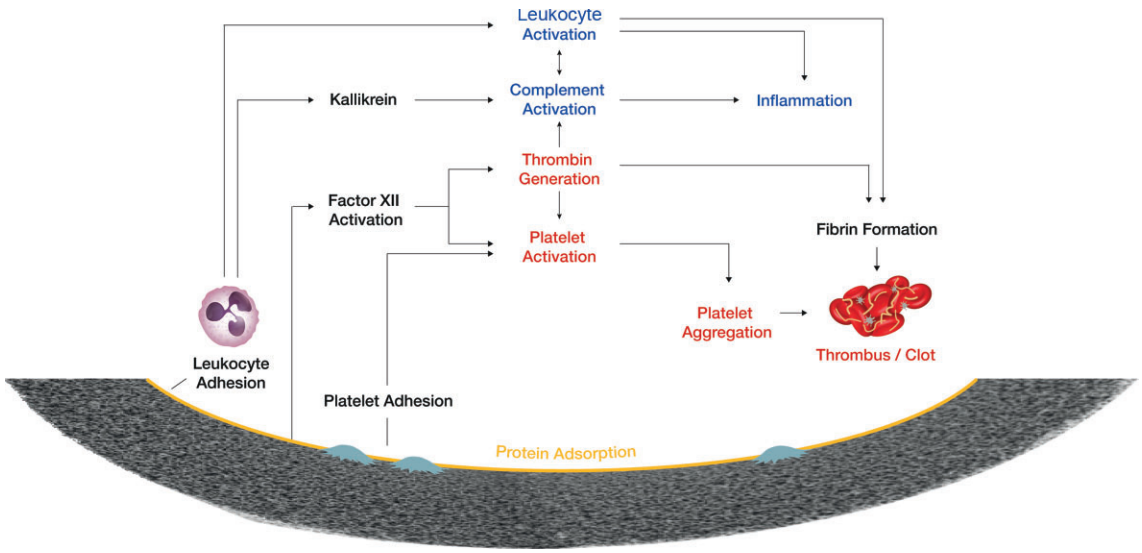

FIGURE 3: The various biochemical pathways that are activated during the interaction of blood components (plasmatic and cellular) with artificial surfaces. The protein adsorption-dependent activation involves activation and adhesion of both platelets and leukocytes. The figure emphasizes the interplay of the coagulation cascade and the complex complement pathways that collectively induce a local pro-inflammatory response. Modified from reference 125 (with permission of authors and publishers).

important for the formation of platelet–neutrophil complexes, which contributes to thrombotic processes, and C5a generation leads to the expression of tissue factor and granulocyte colony-stimulating factor in neutrophils [74].

During HD therapies, the entire sequence of reactions described is triggered by multiple stimuli, not just by the dialysis membrane [71]. The needle use for venipuncture (together with the trauma induced by the step) and contact of air are important initial stimuli that initiate chain of events [27]. Blood tubing, trauma caused by blood pumps of the ECC (haemolysis releases ADP that causes platelet aggregation), the header region of the dialyser (potting compound material used to ensure blood enters the lumen of the hollow fibres), as well as the bubble trap chamber (where frothing denatures proteins) all are sources of significant activation of both coagulation and platelets [28, 72]. It is important to emphasize that well before visible clots are apparent in any part of the ECC, coagulation pathway is almost always activated during each dialysis session. These 'preclotting' stages can be assessed by prothrombin fragments 1 + 2, thrombin antithrombin III (TAT) complex and soluble fibrin (D-dimer). Even more important, use of heparin either unfractionated or as low-molecular-weight heparin (LMWH) does not totally block the coagulation and platelet activation steps, unlike the more effective anticoagulants citrate and EDTA [73].

Activation of complement and leukocytes

The clinical actuality of complement activation and leukopenia induced by early dialysis membranes has had an unprecedented impact on not just the HD field but on all blood-contacting applications or medical devices [74]. The better understanding of the mechanisms of biomaterials–immune response activation pathways has led to the development of improved and safer dialysis membranes with less potential for undesired biological reactions [53]. The complement system-dependent incompatibility leads to inflammation and is associated with thrombosis and fibrosis. A comprehensive overview of the role, mechanisms and consequences of complement activation in dialysis has been described recently by Poppelaars *et al.* (Figure 4) [74]. Interventions targeting the complement system could improve biocompatibility, dialysis efficacy and long-term outcome.

The mechanisms by which complement is activated, either direct or indirect, depends on the properties of the biomaterial used [20]. Indirect mechanisms complement activation are: (i) immunoglobulin G binding to the biomaterial initiating the classical pathway; (ii) lectin pathway activation by carbohydrate structures or acetylated compounds; or (iii) activation of the alternative pathway by altered surfaces, e.g. plasma protein-coated biomaterials. Direct activation entails binding of complement materials to the biomaterial. The result of the activation processes is always cleavage of C3 to form C3a and C3b, with the latter generating C5-convertase that cleaves C5 to C5a, a powerful anaphylatoxin (such as C3a), and C5b. Initially, upregulation of complement receptor 3 (CR3) by allows leukocytes to bind C3 fragments deposited on the membrane, leading to leukopenia. Finally, binding of C5b with C6-C-9 results in membrane attack complex (MAC-C5b-9) generation.

The complement activation–leukopenia characteristic of all cellulosic membranes was subsequently attributed to that the abundant hydroxyl (-OH) groups within the cellobiose structure [75]. By replacing a small proportion of the hydroxyl groups with other chemical entities, several alternative cellulose membranes were created with distinctly diminished complement-leukopenia responses [41,76]. However, none of these substituted cellulose membranes (as they came to be classified) matched the lower activation of synthetic membranes manufactured from man-made polymers such as polysulfone. The kinetics of complement-leukopenia activation revealed firstly that C3a or C5a generation and leukopenia peaked simultaneously; depending on the membrane type this was between about 10–30 min of initiation of dialysis, decreasing thereafter until the end of the dialysis session, i.e. anaphylatoxin formation during HD is a transient phenomenon.

Chronic kidney disease, like most chronic conditions, is an inflammatory condition; several sources, pathways and conditions that result from amplification of inflammatory

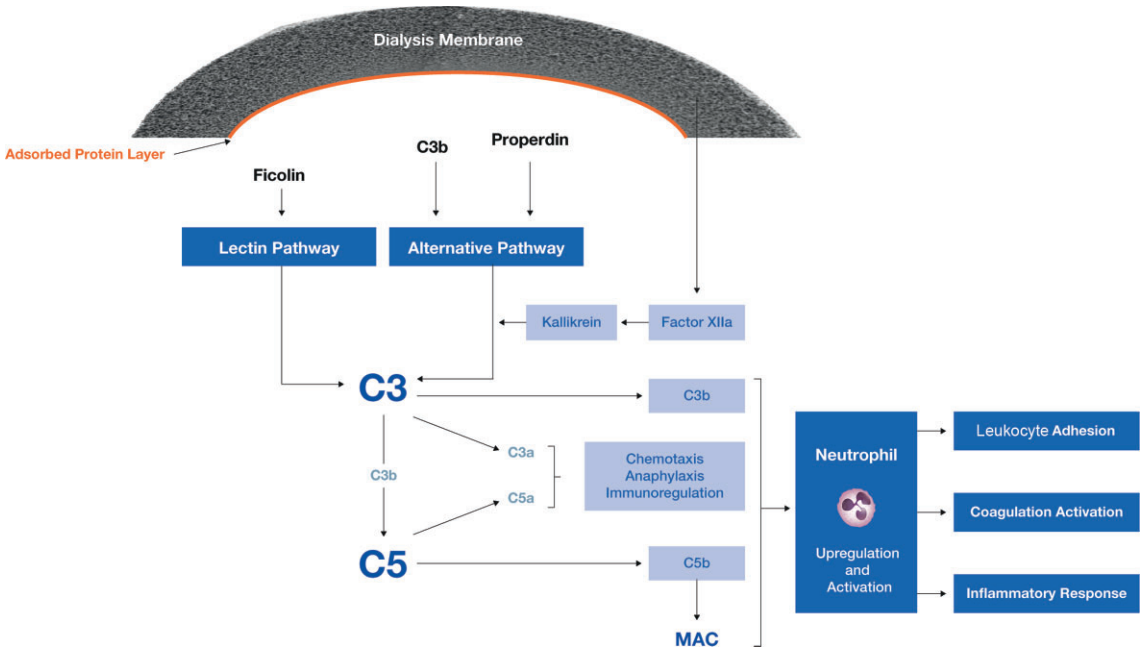

FIGURE 4: The complex dialysis membrane-dependent activation of complement and leukocytes culminating not only in triggering the inflammatory response but also in inducing the procoagulant state.

processes have been extensively reviewed [77–87]. The proposed mechanism of membrane material-related complement activation is promoted by recruitment and activation of leukocytes resulting in oxidative burst and the release of pro-inflammatory cytokines and chemokines [74]; in addition, the activation of neutrophils by C5a leads to the release of granule enzymes, e.g. myeloperoxidase, that are characterized by powerful pro-oxidative and pro-inflammatory properties. Thus, a simple clinical observation led to the study of biochemical and cell activation pathways that revealed the deleterious effects of complement activation on a range of body functions both in the short and long term. As complement activation worsens underlying conditions such as inflammation and oxidative stress, promotes coagulation and cardiovascular calcifications contributing to cardiovascular events, inhibition of complement in dialysis is still a relevant safety target today [74, 88].

Adverse dialyser- and dialysis-related reactions

During HD, a category of undesirable reactions could occur that are not just a consequence of the direct interaction of blood with the membrane material described but are part of the overall biocompatibility equation. These pertain to, or are induced by, other constituents of the ECC or the mode of delivery of dialysis. The multiplicity of potential exposures and the complexity of the ECC environment to which large volumes of patients' blood is exposed to often make it challenging to identify the precise cause of these reactions [89]. Patients on dialysis suffer regularly from an array of intradialytic symptoms, some of which can be linked to components of the ECC; the large number of possible causes of hypersensitivity reactions in these patients often makes it difficult to attribute reactions to specific substances. Salem *et al*. published a list of caveats pertaining to dialyser reactions that need to be considered when examining and correlating a particular constellation of causal stimuli with clinical signs and symptoms [90].

As a detailed consideration of this category of biocompatibility on HD is beyond the scope of this article, some of the more established examples are discussed. Ethylene oxide (ETO) is an agent that was used as a sterilizing agent for dialysers and tubing was found to be the major cause of hypersensitivity reactions in the 1980s [91]. ETO is in the category of leachable substances that induce adverse effects and includes formaldehyde and glutaraldehyde, commonly used disinfectant during the practice of reuse of dialysers and associated with allergic reactions [90, 92, 93]. The membrane material itself may to contribute to such dialyser reactions via two different pathways. In the first, release of the potent anaphylatoxins C3a and C5a by complement-activating membranes may, by augmenting release of mediators such as histamine or thromboxane, amplify IgE-mediated anaphylactic reactions due primarily to ETO or another cause [90, 93, 94]. In the 1990s, a number of severe incidences of anaphylactic shock reactions were reported and related to the AN69 dialyser comprising the polymer polyacrylonitrile [6]. Subsequent analysis revealed that the reactions with AN69 dialysers appeared in patients receiving angiotensin-converting enzyme (ACE) inhibitor therapy. The AN69 membrane used at the time was highly negatively charged, activating the contact system coagulation pathway to increase factor XII levels, increasing kallikrein (from prekallikrein), which in turn increases formation of bradykinin (from kininogen) that is involved in anaphylaxis. Normally, ACE inactivates bradykinin, but in patients on ACE inhibitors, the half-life of generated bradykinin is prolonged, allowing it to pursue its physiological role in anaphylaxis. Confirmation of AN69-induced, ACE inhibitor-related bradykinin generation that caused the severe anaphylactic shock reactions observed in clinical situations was thereafter provided [95, 96].

The mechanisms, types of reactions, symptoms and incidence of dialyser-related hypersensitivity reactions have been reviewed by several authors [90, 97–100]. Type A (or type 1) reactions that are more severe than type B (type 2) occur within 20 min, usually within the first 5 min. The more severe type of reactions such as anaphylaxis can be life-threatening and

include responses such as hypotension, bronchospasm and upper airway angio-oedema, culminating in respiratory arrest and death [97, 101]. The immediate treatment involves cessation of HD without returning the blood in the circuit to the patient; epinephrine, antihistamines or steroids are other options to deal with severe cases that may require respiratory support [90]. The onset of milder type B reactions is later (~20–40 min after start of HD), abating after some time although severe cases of type B (e.g. chest discomfort) are difficult to distinguish from the severe type of reactions.

Severe adverse reactions also occur from medications used for or during the HD procedure. Anticoagulation is mandatory in most HD patients, with heparin being the universal anticoagulant of choice [89, 102]. While in Europe usage of LMWHs is widespread for ECC therapies such as HD, unfractionated heparins are predominantly used in the USA. Although metabolized differently, both are effective anticoagulants in HD and addressed as equally safe [103]. Heparin-induced anaphylactoid reactions are typically pseudo allergic without documented evidence of IgE-mediated reactions, e.g. attributed to over-sulphated chondroitin sulphate contamination (mediated by bradykinin). Alternatively, during platelet activation negatively charged heparin binds to positively charged platelet factor 4 (PF4) to form heparin–PF4 immune complexes to cause heparin-induced thrombocytopenia (HIT) [89, 104]. Immune-mediated HIT, characterized by thrombocytopenia and paradoxical hypercoagulability, is a rare but severe adverse reaction to heparins, particularly to unfractionated heparin, being around 1–3% for unfractionated heparin and below 1% with LMWH [103, 105–107].

MITIGATING THE EFFECTS OF HAEMOINCOMPATIBILITY IN HAEMODIALYSIS

There are two main approaches to mitigate the unavoidable consequences of the interactions that occur at the blood–material interface, based on the knowledge acquired laboratory studies as well as clinical observations. Although correlation of the findings from the two modes of investigation has been difficult there is reasonable consensus as to what needs to be achieved.

Appropriate selection of materials and production processes for membrane manufacture

Achieving an acceptable haemocompatibility profile for HD membranes (a balance between the hydrophobic and hydrophilic properties) needs to be balanced with its functionality features. The primary goal of every manufacturer is to achieve a membrane structure that allows the efficient removal of a broad spectrum of uraemic toxins. To achieve this, the core polymer and the copolymer must be selected such that they comply with the complex set of thermodynamic principles involved in creation of porous structures by phase separation principles (described in this supplement). Membrane spinning processes necessitate usage of solvents and other chemicals for the structure-forming steps of the membrane formation process. In addition to the target of achieving membrane structures that are optimal for transport of uraemic toxins across the membrane wall, the following factors need to be considered for the selection of materials for manufacturing processes to ensure that the final membrane has a favourable haemocompatibility profile [108]:

(i) Highly hydrophilic surfaces result in elevated complement, leukocyte activation/leukopenia.
(ii) Highly hydrophobic surfaces cause thrombocytopenia and platelet activation.
(iii) Highly negative charged surfaces are undesirable as they activate factor XII-dependent pathways resulting in extreme cases anaphylactic shock reactions (together with ACE inhibitors). In addition, being a highly negatively charged polysaccharide, heparin easily binds on to the cationic surfaces via ionic interactions resulting in diminished or negligible anticoagulant activity compared to free plasma heparin [73].

Clearly, achieving the desired balance from such a diverse set of requirements is challenging, but additional factors can impact haemocompatibility further and need to be considered. The most important of these are product sterilization mode and the ability of membranes to adsorb any endotoxins that may arise and enter the bloodstream from dialysis fluids (by the mechanism of backtransport) contaminated with Gram-negative strains of bacteria [109–111]. The inflammatory response triggered by endotoxins in HD has been well documented and adds to the inflammation load associated with chronic kidney disease [112, 113]. The optimal biocompatibility profile of membranes is essentially achieved by a trial-and-error approach that is both costly and time-consuming, with the added dilemma of having to take care not to contravene intellectual property rights.

Surface modifications of polymers and biomaterials

Other than modulating surface topography and structure, three general approaches are taken to improve the physicochemical properties of polymer surfaces to improve the biocompatibility profiles of devices in HD [70, 114, 115] (Figure 5). Both, passive and active approaches are available to modulate blood–material interactions [116–118]. Direct modifications of the surface chemistry of the biomaterial to reduce or change its reactivity for certain biochemical pathways are the most common option used. Reverting to the example of cellulosic HDs membranes, their complement- and leukocyte-activating characteristics were attributed to the large number of hydroxyl groups within the structure of the natural biopolymer. Chemical substitution of the -OH groups with chemical groups such as DEAE (diethylamino-ethylene) or acetate resulted in a dramatic reduction in both complement activation and leukopenia [119]. Varying haemocompatibility profiles were achievable, depending on the degree of substitution of the native cellulose structure, although the changes disturbed the biocompatibility profile with respect to other biochemical pathways [119, 120]. Another approach to mitigate unfavourable biocompatibility profiles of dialysis membranes is illustrated by the example of the AN69 membrane, whose hypersensitivity reactions were due to the high negative charges on its surface [121]. Modification of the surface with polycationic polyethyleneimine reduced the electronegativity that prevented contact phase activation and bradykinin generation that caused the anaphylactic shock reactions in conjunction with use of ACE inhibitors [122].

Attachment or coating of surfaces with biofunctional entities has been attempted over several decades to improve of biocompatibility profiles of a variety of surfaces devices in different applications [118, 123]. Most of these approaches are targeted towards the prevention of clotting in implants such as vascular grafts, stents and heart valves, and used in conjunction with

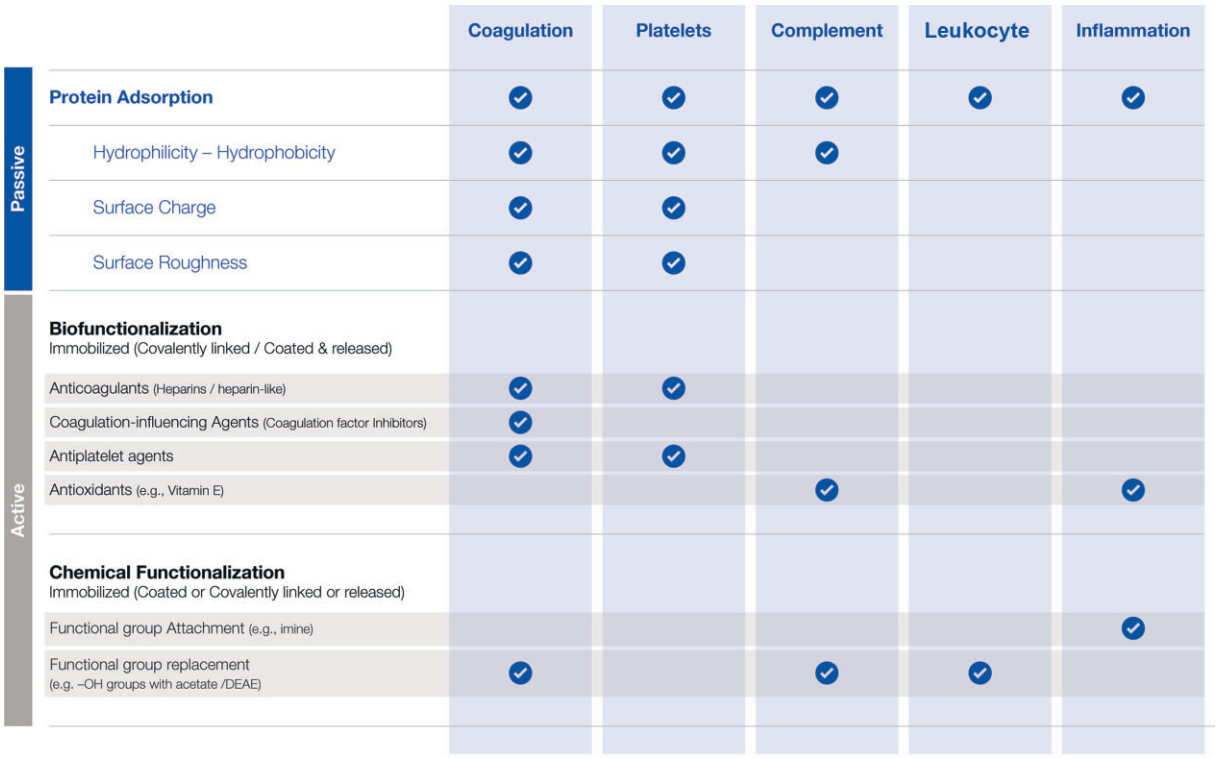

FIGURE 5: Some strategies to mitigate the effects of blood-incompatibility in HD. Dialyser membranes (and other components of the ECC) need to have an optimal balance between different parameters that induce minimal activation of various plasmatic biological pathways and of platelets and leukocytes. Although several novel surface modification techniques have been attempted for blood-contacting biomaterials, few can be extrapolated to the HD field because of the amount (surface areas) that need to be passivated due to the associated effort and related costs.

different anticoagulant strategies [124, 125]. These applications differ vastly from the situation in HD where blood is exposed simultaneously to large surface areas of several different materials and geometries extracorporeally without the protective effects of the endothelium and at unphysiological blood flow conditions [126]. Covalent attachment of anticoagulants or known pharmaceutical agents during membrane or dialyser production is inconceivable; manufacturing procedures for both are complex, requiring harsh conditions that would inactivate the agents that would be incorporated in an uncontrolled manner at huge costs. Several attempts to graft heparin or heparin–antithrombin II complexes directly or with spacers on to surfaces have been attempted but to date have not been used for HD [120, 125]. Passive coating of heparin (e.g. in the pre-rinsing steps prior to start of dialysis) helps in diminishing the initial activation, but as the need for systemic anticoagulation is not eliminated, the practice is not widespread particularly when cost-reduction is a consideration. Instead, improved haemocompatibility of dialysers may be achieved by novel surface modifying macromolecules leading potentially to reduced amounts of systemic heparin required during HD [124].

CONCLUSIONS

Haemo-incompatibility is an inevitability of all blood-contacting device applications and therapies, including HD [127]. Once blood leaves the environment of blood vessels it undergoes alterations that even anticoagulants cannot totally suppress. Inside the vessels, blood is protected by the endothelium, the ultimate non-thrombogenic surface that keeps it fluid and helps mitigate the effects of any foreign compounds that enter the circulation [8]. In the ECC of HD, blood encounters stimuli from multiple materials and rheological derangements as it is forced through conduits of different geometries and diameters by pumps that induce physical trauma to plasma and cellular components of blood. The blood compatibility equation thus involves the overall system, not just the biochemical activation or alteration of biological or cell pathways [26, 37].

Historically, haemo-incompatibility issues have centred around prevention of clotting within the circuit using anticoagulants without increasing the risk of bleeding in certain patients [102, 125, 127, 128]. Later the focus turned to the phenomenon of complement activation and associated leukopenia and hypersensitivity reactions [39, 74, 88, 94]. While the clinical relevance of the latter has still to be demonstrated convincingly, current evidence and opinion so far points towards the undesirable nature of these events and the need to suppress them [48, 54, 74]. Coagulation-related problems are easier to discern as the effects of sub-optimal anticoagulation are apparent during the treatment procedure, either visibly or by alarm signals of the machine [31]. It is important to consider that activation of coagulation is not just a risk factor in terms of clot formation, but low levels of activation could lead to increased adsorption of plasma proteins that block the pores of the membrane. This additional barrier impairs the transport of solutes across the membrane wall to decrease their clearance and hence negatively impacts the dose of dialysis a patient receives [56]. In this paper we have outlined multiple factors that need to be considered to

negate or minimize the unwanted blood-incompatibility events that accompany the toxin elimination function of HD. The measures begin during the research and development phase and extend to the manufacturing processes of product manufacture. Thereafter, certain steps can also be taken to mitigate haemoincompatibility during the treatment procedure itself such as optimization of anticoagulation regimens according to each patient's condition, or, avoiding damage to blood elements due to trauma induced by pumps the air–blood interface in the bubble trap chamber [72]. Most importantly, biocompatibility aspects also include mechanisms that increase the susceptibility to infection and lead to increased inflammation and oxidative stress [129]. Strategies that curtail inflammation induced by membranes (e.g. complement), dialysis fluid contamination or in the delivery of HD (dialysis-induced systemic stress) would contribute towards improving the outcomes of dialysis patients [5, 130].

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CONFLICT OF INTEREST STATEMENT

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