CHAPTER 151

Biocompatibility of the Dialysis System

Giordano Fumagall and Vincenzo Panichi

OBJECTIVES

This chapter will:

1. Present the fundamentals of biocompatibility of membranes and other factors contributing to the biocompatibility of dialysis.
2. Discuss the findings of meta-analyses concerned with the effect of biocompatibility on treatment outcomes.

Biocompatibility may be defined as "the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient of that therapy, but generating the most appropriate beneficial response (…) and optimising the clinically relevant performance of that therapy"[1].

In patients with severe AKI, renal replacement therapy (RRT) encompasses several modalities, including continuous RRT, prolonged intermittent RRT and intermittent hemodialysis. All these treatments expose patients' blood to nonphysiological materials, which include: dialyzer membrane and housing, tubing sets, dialysate and infusate. Contact with these materials may activate a variety of biological responses, involving humoral and cellular pathways, with clinical sequelae. Initially, biocompatibility studies mainly focused on the interaction between blood and dialysis membranes. To date, the concept of biocompatibility has greatly evolved and it may be regarded as the sum of interactions and biological responses elicited with blood exposure to all components of the hemodialysis system. This definition also includes the effects induced by manufacturing processes, sterilization modes, contaminants, leachables and particles. In this chapter we discuss the available evidence on the main issues related to the biocompatibility of the dialysis system and its clinical implications in the therapy and outcomes of patients with AKI.

DIALYSIS MEMBRANES AND DETERMINANTS OF BIOCOMPATIBILITY

The dialysis membrane is the largest surface of contact between blood and a nonphysiological material, therefore it is the main device where several biological responses are elicited. From a clinical perspective, it is appropriate to classify dialysis membranes according to permeability and biocompatibility characteristics. On the basis of chemical composition, membranes are grouped in those made of unmodified cellulose (Cuprophan), those in which the cellulose structure is modified by replacing hydroxyl ions with hydrophobic substances and those based on synthetic polymers. Among cellulose membranes, only cellulose diacetate (CDA) and cellulose triacetate (CTA) are still commercially available. Except for those made of ethylene vinyl alcohol (EVAL), most of the synthetic membranes are based on hydrophobic polymers: polysulfone (PS), polyethersulfone (PES), polyester polymer alloy (PEPA) polyacrylonitrile (PAN) and polymethylmethacrylate (PMMA). Hydrophobic polymers require to be rendered hydrophilic for improving solute transport, either by blending with hydrophilic agents (e.g. polyvinylpyrrolidone in PS and PES membranes), or by being produced as copolymer with hydrophilic compounds (e.g. sodium methallyl sulfonate in the PAN membrane AN69)[2,3]. Nowadays, synthetic membranes are the most frequently used in RRT and are considered more biocompatible than those based on cellulose. However, reactivity to blood contact is exhibited by all membranes to some extent,

because a universal biocompatibility does not exist: the absence of response in a single biological pathway does not automatically avoid activation of others.

Protein Adsorption

Blood exposure to artificial surfaces, such as dialysis membranes, leads to the deposition of a plasma protein layer over the polymer and within the membrane pores. Protein adsorption is a complex phenomenon governed by hydrophobic and electrostatic interactions, hydrogen bonding and Van der Waals forces. Furthermore, it 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 dialyzer (blood flow dynamics and temperature). It has been proposed that adsorption occurs in two ways. The first, known as Vroman effect, is a competitive deposition onto membrane surface of high molecular weight proteins, in which albumin, immunoglobulins, fibrinogen, factor XII (Hageman factor) and high molecular weight kininogen (HMWK) are sequentially adsorbed onto the membrane surface, one displacing the other. The second is a dynamic adsorption of low and medium molecular weight proteins within the membrane, which is dependent upon membrane characteristics and limited by its permselectivity[4–6].

Adsorption of plasma proteins on dialysis membranes is of critical importance for their biocompatibility. Once adsorbed, proteins undergo conformational changes with possible autoactivation. Adsorbed proteins also modulate the membrane bio-reactivity, by triggering the humoral and cellular pathways. It has been shown indeed that protein layers with a low albumin/fibrinogen ratio may increase the thrombogenicity, by enhancing platelet adhesion to different membranes. Finally, protein adsorption may either modulate the biocompatibility of some synthetic membranes with great absorptive capability, by removing cytokines, anaphylatoxins and complement factor D, or impair both diffusive and convective transport, by forming a secondary resistance to mass transfer[5–8].

Coagulation and Kallikrein-Kinin Systems

The coagulation system is activated during contact between blood and dialysis membrane. Coagulation is considered as a cascade of proteolytic reactions, ultimately resulting in fibrin clot and thrombus formation. Its triggering occurs either by surface mediated reactions (intrinsic pathway) or through expression of tissue factor (TF) by cells (extrinsic pathway). Thereafter, through activation of factor X, these systems converge on the common pathway to convert prothrombin to thrombin and produce insoluble fibrin[9,10]. The intrinsic pathway is thought to be prominently involved in triggering coagulation when blood is exposed to artificial surfaces, such as dialysis membranes. The contact phase proteins prekallikrein, HMWK, factor XI and factor XII are adsorbed onto biomaterial surfaces. Negatively charged surfaces easily trigger the intrinsic pathway: it depends on the conformational changes and self-activation of Hageman factor, induced by interactions with negative charges. However, the adsorbed protein layer may itself provide the required negative charges. Once activated, factor XII cleaves prekallikrein to kallikrein: this allows a reciprocal activation of kallikrein and Hageman factor as well as the triggering of coagulation, through the generation of activated factor XI. The procoagulatory activity varies among different membranes. The AN69 has been found to be the most thrombogenic membrane, because of a high surface electronegativity, resulting from its sulfonate groups. Nevertheless, activation of coagulation can occur during dialysis with all membranes, since it may be triggered independently of the contact phase through expression of TF by leukocytes, release of active compounds by activated platelets, air microbubbles and blood flow turbulences[9–11].

In the 1990s a new life threatening anaphylactoid reaction was described in patients dialyzed with the AN69 membrane, who were receiving angiotensin converting enzyme (ACE) inhibitors[12]. Negatively charged membranes also trigger the kallikrein-kinin system and activated kallikrein cleaves HMWK to release bradykinin. This vasoactive and pro-inflammatory peptide is rapidly metabolized by the ACE and other peptidases. With simultaneous administration of ACE inhibitors, bradykinin is not degraded and high concentrations can be reached in the systemic circulation within the first minutes of hemodialysis session. Less severe anaphylactoid reactions were also described with PMMA membranes in patients treated with ACE inhibitors. Similarly, activation of the kallikrein-kinin system using PMMA filters was found to be related to their surface electronegativity, which is intermediate between the AN69 and other cellulosic and synthetic membranes[13,14]. Neutralizing the electronegativity of AN69 membranes, by coating the surface with a polyethyleneimine layer (AN69 ST), has been demonstrated to dramatically reduce kinin formation[15].

Complement Activation

The complement system is a potent mechanism for the initiation and amplification of anaphylactic, oxidative and inflammatory responses. In the 1970s, Craddock and colleagues first proved that the transient leukopenia, observed with Cuprophan membranes, was due to pulmonary vascular leukostasis resulting from complement activation[16]. The complement cascade may be activated by three pathways: the classical pathway (CP), triggered by the C1q bond to antigen–antibody complexes; the mannan-binding lectin pathway (LP), triggered by the binding of lectin or ficolins to carbohydrates of pathogens; the alternative pathway (AP), directly triggered by foreign surfaces. The main event in complement activation is the cleavage of C3 into C3a and C3b, via two enzyme complexes, known as C3 convertases: in the CP and LP, C2 and C4 form the C4b2a complex; in the AP, C3b creates the C3bBb complex added by factors B and D. Thereafter, the system converges on a common pathway where C5 is cleaved into C5a and C5b, via the classical or alternative C5 convertase. Finally, C5b recruits other components to form the terminal complement complex C5b-9, which causes cellular lysis, once inserted in cell membranes. Complement activation also releases the anaphylatoxins C3a and C5a, which bind to specific receptors on leukocytes, mast cells and endothelial cells. Anaphylatoxins may induce vasodilation, chemotaxis, mast cell degranulation and leukocyte activation. C5a and soluble C5b-9 activate platelets and up-regulate the expression of adhesion molecules, thereby promoting interactions between leukocytes and endothelial cells[9,17]. Finally, animal models on the pathogenesis of acute lung injury have implicated the role of anaphylatoxins and soluble C5b-9[18,19].

During hemodialysis, complement activation rapidly reaches its maximum within the first 30 minutes, thereafter it gradually returns to basal levels. The entity of activation closely depends upon the dialysis membrane type. Conventionally, it is believed that complement activation occurs via the AP, as a consequence of spontaneous

formation of C3b in the plasma and its deposition onto the membrane surface. Once adsorbed, C3 can act similarly to C3b, after undergoing conformational changes. Biomaterials with nucleophilic surface sites, such as Cuprophan membranes with hydroxyl groups, are much more prone to activate complement, since nucleophiles covalently bind C3b and favor its interaction with factors B and D to form C3 convertase. Substitution of hydroxyl groups decreases complement activation, because it renders modified cellulose membranes capable of binding factor H rather than factor B. This prevents the AP activation through C3b inactivation[9,17]. Synthetic membranes have the advantage of reducing complement activation, particularly those with adsorptive capability, such as PAN and PMMA. These membranes remove C3a and C5a to a greater extent and adsorb factor D, thereby reducing both exposure to anaphylatoxins and formation of C3 convertase[7,8]. Additionally, PEPA membranes manufactured without polyvinylpyrrolidone have shown to hardly activate complement[20]. Nevertheless, all membranes elicit complement activation to some extent, since both the classical and lectin pathways may be involved. The CP can be triggered either through the interaction between adsorbed immunoglobulins and C1q or through C1 activation by Hageman factor and kallikrein. The LP could be activated by certain PS membranes through their binding to ficolin 2, as suggested by recent proteomic investigations[6,9,17,21].

Activation of Blood Cells, Inflammation and Oxidative Stress

Interaction between blood and membrane influences leukocyte, platelet and endothelial cell functions, either through direct contact with the membrane or indirectly through mechanisms of cross-talk between humoral and cellular systems.

Several studies have shown a decrease in platelet count during the first 30 minutes of dialysis. Contact with membranes leads to platelet activation, degranulation, adhesion and aggregation. Both cellulosic and synthetic membranes elicit platelet activation to some extent, even though it seems to be reduced with synthetic ones. Additionally, the amount of polyvinylpyrrolidone alloyed onto PS membranes seems to reduce platelet activation[22,23]. These responses are also mediated by platelet binding to fibrinogen and von Willebrand factor, adsorbed on dialysis membranes, through specific receptors (GPIIb/IIIa and GPIb). Membrane hydrophobicity, roller pump action, air microbubbles, soluble C5b-9 and activation of coagulation may additionally stimulate platelet functions. Once activated, platelets release a number of compounds (e.g. platelet factor 4, adenosine diphosphate, thromboxane A2) and up-regulate their surface markers. Platelets may adhere and aggregate onto dialysis membrane or form circulating platelet-platelet and platelet-leukocyte aggregates, by the expression of P-selectin and other molecular mechanisms. Interaction between platelets and leukocytes leads to mutual activation, thereby promoting oxidative, inflammatory and thrombotic responses. Whether this cross-talk between platelets and leukocytes may have a role in the pathogenesis of cardiovascular disease in chronic hemodialysis patients remains to be elucidated[9,22,24,25].

As mentioned above, activated neutrophils migrate in pulmonary capillaries, leading to transient leukopenia. Lung vascular leukostasis has been regarded as a possible mechanism in the multifactorial pathogenesis of intradialytic hypoxemia. Indeed, a strong correlation between leukopenia and complement activation has been found. Besides, synthetic membranes elicit neutropenia and hypoxemia to a lower extent than Cuprophan ones. According to animal models, pulmonary leukostasis seems to be related to the expression of C5a receptors within the lungs. Both C5a and cellulosic membranes modulate the expression of several molecules (e.g. CD11b/CD18 and L-selectin) on leukocytes, thereby promoting their adhesion to endothelial cells. Similarly, reversal of leukopenia, observed towards the end of dialysis session, has been explained through a decrease in serum C5a levels and a reduced expression of its receptors on granulocytes[26–28].

Leukocyte activation also leads to degranulation and release of reactive oxygen species (ROS) by neutrophils and production of inflammatory cytokines, such as interleukin-1, tumor necrosis factor-α and interleukin-6, by monocytes. The role of cytokines in mediating acute hypotensive and febrile reactions as well as metabolic, immunological and inflammatory changes was first introduced by Henderson and colleagues as "the interleukin hypothesis"[29]. Several studies have shown the role of cellulose membranes in triggering both cytokine and ROS production through direct and complement-mediated activation of leukocytes[27,30]. As discussed below, with synthetic high-flux membranes, pro-inflammatory and pro-oxidative responses may occur because of blood exposure to microbial contaminants originating from dialysis fluids. The inflammatory cytokines stimulate liver to synthesize acute phase proteins, such as C-reactive protein, thereby promoting a state of chronic inflammation in hemodialysis patients. Inflammation and oxidative stress have a synergistic relationship in development and progression of vascular and tissue damage. Several authors have regarded inflammation as a general pathway associated with poor biocompatibility of hemodialysis system and patients' long-term complications, such as anemia, malnutrition, atherosclerosis and cardiovascular disease[27,31,32].

AKI is known to be associated with inflammation. Regardless of the initial insult, intrarenal inflammation plays a major role in the pathogenesis of AKI and it exerts harmful effects on distant organs, by promoting a systemic inflammatory response[33]. Moreover, high levels of pro-inflammatory cytokines have been associated with increased mortality in AKI[34,35]. In the clinical setting, the nature and outcome of inflammatory responses in AKI may be reasonably influenced by the biocompatibility of hemodialysis system. As discussed below, studies on this topic are lacking and limited to the comparison of membranes.

Finally, immune dysfunctions have been linked to uremia per se, although limited evidence suggests a possible influence of membrane biocompatibility. Compared to synthetic membranes, cellulose ones have been found to suppress phagocyte function[36], to increase leukocyte susceptibility to apoptosis[37] and to induce premature senescence of monocytes, as demonstrated by a decrease in telomere length and an increase in pro-inflammatory cells CD14+/CD16+[38].

DIALYSATE AND INFUSATE

Dialysis fluid quality has a pivotal role in determining the biocompatibility of hemodialysis system, since contaminants may elicit acute reactions and contribute to long-term complications[39]. Although high-flux synthetic membranes may adsorb endotoxins, this capability is limited. Back-transport into blood of endotoxins and bacterial fragments from contaminated dialysate may occur, as a consequence of backfiltration and backdiffusion[40]. Replacement fluids are infused into the patient's circulation, thereby raising the

possibility of direct exposure to biological contaminants. The risk of microbial contamination of fluids and circuitry cannot be excluded even with use of sterile fluids during continuous RRT[41]. Consequently, any measures should be taken to avoid patients' exposure to impure dialysis fluids, particularly in vulnerable patients with AKI. The use of ultrapure dialysate, produced in accordance with latest standards, should be regarded as mandatory and a rigorous monitoring of microbiological quality is particularly needed with on-line production of replacement fluids[42].

THE HEMODIALYSIS CIRCUIT AS A POSSIBLE SOURCE OF TOXINS: LEACHABLES AND STERILIZATION PROCESS

Dialyzer housings and tubing sets contain several chemical compounds. Polyurethane is applied as a potting material to secure the hollow fibers at both dialyzer ends; silicone rings prevent fluid leakage; polycarbonate, polypropylene or polystyrene are used for casings. Polyvinyl chloride (PVC), as a biomaterial for tubing, needs plasticizers for its flexibility, such as diethylhexyl phthalate. All of these compounds may affect the biocompatibility[2].

Bisphenol A (BPA) has been found to leach into blood during hemodialysis and an increase in serum BPA levels may be detected after a single session. Polycarbonate dialyzer housings, PVC bloodlines and PS and PEPA membranes are potential sources of BPA[2,43,44]. BPA is an endocrine disruptor, which interferes with estrogen receptors. Several studies have shown an association between BPA exposure and development of obesity, metabolic syndrome, diabetes, hypertension, proteinuria and renovascular damage in humans[45]. In vitro studies have found a pro-inflammatory effect of BPA on cultured leukocytes and a potential cytotoxicity on monocytes[44,46]. To date, little information concerning BPA exposure from medical devices is available, especially in patients receiving RRT. However, the European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has recently recommended to evaluate the possibility of finding alternatives for BPA containing materials, especially for neonates in intensive care units, infants undergoing prolonged medical procedures and dialysis patients[47]. Similarly, diethylhexyl phthalate (DEHP), the most widely used plasticizer, is released into blood from bloodlines and other components made of PVC. In rodents, DEHP is an endocrine disruptor and a liver carcinogen; it exerts developmental effects and toxicity on the reproductive system and kidneys. Additionally, it has been classified as possibly carcinogenic to humans[48]. In vitro studies have found that DEHP-plasticized PVC increases platelet adhesion and aggregation, activates the complement and exerts a pro-inflammatory effect on human neutrophils[49–51]. Although available evidence on effects of DEHP exposure in humans is limited, several scientific and regulatory agencies have pointed out possible health risks for infants, children, pregnant women and adults receiving medical treatments with DEHP-plasticized PVC devices[48,52,53]. Hemodialysis patients may receive a relevant amount of DEHP, which may exceed the tolerable daily intake. Since induced effects of such exposure cannot be excluded, the Health Canada Expert Advisory Panel and the SCENIHR have suggested to consider the use of devices with low release potential or not containing DEHP. However, given the paucity of data on the effects of alternate materials and plasticizers in medical devices, they have underlined the need for further studies to develop alternatives with a favourable profile for efficiency and safety[48,53].

The sterilization process may have a major impact on biocompatibility, since adverse reactions may result from leaching of residues or physicochemical polymer alterations and subsequent release of degradation products. The sterilizing agent ethylene oxide (ETO) is retained by polyurethane potting compounds and it can be released into patients' blood during hemodialysis treatment. ETO may form an allergenic albumin-ETO conjugate, which can trigger IgE-mediated reactions, encompassing itching, rhinitis, asthma, urticaria, angioedema or, rarely, anaphylactic shock[2,54]. Sterilization with ETO is now less common, having been widely replaced with other methods such as steam heat, γ rays or electron-beam irradiation. However, these methods have disadvantages too. Moist heat sterilization cannot be employed for heat sensitive polymers, such as PMMA, PAN and CTA. Irradiation with γ rays may induce formation or breaking of bonds and creation of free radicals within the polymer structure, thereby increasing patients' oxidative stress and cytotoxicity. Aromatic polyurethane may release the carcinogen 4,4'-methylenedianiline during sterilization with both γ irradiation and steam heat[2,55,56]. During the manufacturing process, infusion with perfluoroheptane can be used to detect and repair leaks in hollow fibers. Residuals from this compound can cause lethal complications through lung embolism and exposure to hydrogen fluoride, a highly toxic decomposition product that can be generated using either γ and β sterilization[57]. Finally, a retrospective cohort study by Kiaii and colleagues suggested that the sterilization of PS dialyzers with electron-beam irradiation is a possible cause of dialysis-induced thrombocytopenia[58]. However these findings were not confirmed by other studies and need to be further investigated[59,60].

THE EFFECT OF DIALYSIS MEMBRANES ON PATIENTS' OUTCOMES IN AKI

As discussed above, poor biocompatibility of Cuprophan membranes has been implicated in acute and long-term complications of chronic hemodialysis patients. It has been hypothesized that the inflammatory response and immune dysfunction induced by less biocompatible membranes may exacerbate the AKI and delay recovery of renal function. Three meta-analyses have reviewed the impact of dialysis membranes on AKI outcomes and their findings are conflicting. Subramanian and colleagues, analyzing 8 trials and 867 patients, reported a significant lower risk of death among patients treated with synthetic membranes compared to those dialyzed with cellulose membranes. However, after stratifying by cellulose membrane type (unsubstituted and substituted), the survival advantage for synthetic membranes remained limited to the comparison with Cuprophan ones[61]. Jaber and coworkers, analyzing 7 studies and a total of 722 patients, did not find any survival advantage conferred by the use of synthetic membranes versus cellulose ones[62]. Similarly, in the most recent meta-analysis of 10 trials in 1100 patients, Alonso and colleagues could not establish any advantage for synthetic membranes[63]. None of the mentioned meta-analyses demonstrated a relevant impact of dialysis membranes on recovery of renal function. Several limitations may have affected these meta-analyses: insufficient sample size of included studies, inclusion of non randomized controlled trials and heterogeneity in the study populations due to differences in age, comorbidities, etiology of AKI,

severity of acute illness and RRT modality. Moreover, these findings are likely to be biased by the inclusion of both modified cellulose and Cuprophan membranes in a single group, since the former are much more biocompatible than unsubstituted ones.

Thus, the issue of dialysis membrane biocompatibility in treatment of AKI is still unsolved. Nevertheless, given the strong association between AKI and mortality, particularly in critically ill patients requiring RRT[64,65], the use of membranes with a high profile of biocompatibility should be considered to minimize the activation of biological pathways and possible undesirable responses. Cuprophan membranes have been phased out over time, while cost differences between modified cellulose and synthetic membranes have been decreasing, therefore the use of less biocompatible dialysis membranes in AKI therapy has become anachronistic[2,66]. Nowadays, a relevant issue is which synthetic membranes may confer additional benefits. An interesting approach may be the use of membranes with great bulk adsorption capability (PMMA, AN69 ST and AN69 Oxiris) to increase removal of cytokines and endotoxins, particularly in septic patients. However, available evidence in this regard is limited and not conclusive[67].

Conclusion

Within the context of RRT, the concept of biocompatibility has greatly evolved. It has become apparent that not only the dialysis membrane but also the other system components and even the manufacturing process may determine the biocompatibility. Additionally, new findings have emerged, such as the role of dialysis fluid quality and of pro-inflammatory cytokines. In chronic hemodialysis patients, the system biocompatibility has been shown to be a determinant of long-term complications. In the setting of AKI, available evidence concerning the influence of the system biocompatibility on patients' outcomes is not conclusive. Further studies aimed at evaluating how the dialysis system may affect the biological processes associated with AKI, such as inflammation, are desirable.

Key Points

1. In addition to dialysis membranes, all elements of the circuit and the manufacturing process combine to determine the system biocompatibility.
2. In the setting of AKI, biological mechanisms and consequences related to the biocompatibility of dialysis system are not fully elucidated

Key References

2. Vienken J, Gottschalk O. Polymers in Nephrology. In: Puoci F, ed. *Advanced Polymers in Medicine*. Springer International Publishing; 2015:371-400.
17. Nilsson B, Ekdahl KN, Mollnes TE, et al. The role of complement in biomaterial-induced inflammation. *Mol Immunol*. 2007;44:82-94.
41. Luo Y, Kanagasundaram NS. Microbial control in renal support for acute kidney injury. *Semin Dial*. 2011;24:203-207.
63. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure. *Cochrane Database Syst Rev*. 2008;(1):CD005283.
67. Honore PM, Jacobs R, Joannes-Boyau O, et al. Newly designed CRRT membranes for sepsis and SIRS – a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. *ASAIO J*. 2013;59:99-106.

A complete reference list can be found online at ExpertConsult.com.

References

1. Williams DF. On the mechanisms of biocompatibility. *Biomaterials*. 2008;29:2941-2953.
2. Vienken J, Gottschalk O. Polymers in Nephrology. In: Puoci F, ed. *Advanced Polymers in Medicine*. Springer International Publishing; 2015:371-400.
3. Krieter DH, Wanner C. Membranes for Dialysis and Hemofiltration. In: Jörres A, Ronco C, Kellum AJ, eds. *Management of Acute Kidney Problems*. Heidelberg: Springer-Verlag Berlin; 2010:491-505.
4. Chanard J, Lavaud S, Randoux C, et al. New insights in dialysis membrane biocompatibility: relevance of adsorption properties and heparin binding. *Nephrol Dial Transplant*. 2003;18: 252-257.
5. Huang Z, Gao D, Letteri JJ, et al. Blood-membrane interactions during dialysis. *Semin Dial*. 2009;22:623-628.
6. Pieroni L, Levi Mortera S, Greco V, et al. Biocompatibility assessment of haemodialysis membrane materials by proteomic investigations. *Mol Biosyst*. 2015;11:1633-1643.
7. Perego AF. Adsorption techniques: dialysis sorbents and membranes. *Blood Purif*. 2013;35(suppl 2):48-51.
8. Thomas M, Moriyama K, Ledebo I. AN69: Evolution of the world's first high permeability membrane. *Contrib Nephrol*. 2011;173:119-129.
9. Gorbet MB, Sefton MV. Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes. *Biomaterials*. 2004;25:5681-5703.
10. Fischer K-G. Essentials of anticoagulation in hemodialysis. *Hemodial Int*. 2007;11:178-189.
11. Frank RD, Weber J, Dresbach H, et al. Role of contact system activation in hemodialyzer-induced thrombogenicity. *Kidney Int*. 2001;60:1972-1981.
12. Tielemans C, Madhoun P, Lenaers M, et al. Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. *Kidney Int*. 1990;38:982-984.
13. Schwarzbeck A, Wittenmeier KW, Hällfritzsch U. Anaphylactoid reactions, angiotensin-converting enzyme inhibitors and extracorporeal hemotherapy. *Nephron*. 1993;65:499-500.
14. Renaux JL, Thomas M, Crost T, et al. Activation of the kallikrein-kinin system in hemodialysis: role of membrane electronegativity, blood dilution, and pH. *Kidney Int*. 1999;55: 1097-1103.
15. Désormeaux A, Moreau ME, Lepage Y, et al. The effect of electronegativity and angiotensin-converting enzyme inhibition on the kinin-forming capacity of polyacrylonitrile dialysis membranes. *Biomaterials*. 2008;29:1139-1146.
16. Craddock PR, Fehr J, Dalmasso AP, et al. Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. *J Clin Invest*. 1977;59:879-888.
17. Nilsson B, Ekdahl KN, Mollnes TE, et al. The role of complement in biomaterial-induced inflammation. *Mol Immunol*. 2007;44:82-94.
18. Bosmann M, Ward PA. Role of C3, C5 and anaphylatoxin receptors in acute lung injury and in sepsis. *Adv Exp Med Biol*. 2012;946:147-159.
19. Liu K, Mao Y-F, Zheng J, et al. SC5b-9-induced pulmonary microvascular endothelial hyperpermeability participates in ventilator-induced lung injury. *Cell Biochem Biophys*. 2013;67: 1421-1431.
20. Igoshi T, Tomisawa N, Hori Y, et al. Polyester polymer alloy as a high-performance membrane. *Contrib Nephrol*. 2011;173: 148-155.
21. Mares J, Thongboonkerd V, Tuma Z, et al. Specific adsorption of some complement activation proteins to polysulfone dialysis membranes during hemodialysis. *Kidney Int*. 2009;76:404-413.
22. Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. *Kidney Int*. 2012;82:147-157.
23. Hayama M, Yamamoto K, Kohori F, et al. How polysulfone dialysis membranes containing polyvinylpyrrolidone achieve excellent biocompatibility? *J Memb Sci*. 2004;234:41-49.
24. Sirolli V, Amoroso L, Pietropaolo M, et al. Platelet-leukocyte interactions in hemodialysis patients: culprit or bystander? *Int J Immunopathol Pharmacol*. 2006;19:461-470.
25. Kobayashi S, Miyamoto M, Kurumatani H, et al. Increased leukocyte aggregates are associated with atherosclerosis in patients with hemodialysis. *Hemodial Int*. 2009;13:286-292.
26. Munger MA, Ateshkadi A, Cheung AK, et al. Cardiopulmonary events during hemodialysis: effects of dialysis membranes and dialysate buffers. *Am J Kidney Dis*. 2000;36:130-139.
27. Hörl WH. Hemodialysis membranes: interleukins, biocompatibility, and middle molecules. *J Am Soc Nephrol*. 2002;13(suppl 1):S62-S71.
28. Van Teijlingen ME, Nubé MJ, Ter Wee PM, et al. Haemodialysis-induced pulmonary granulocyte sequestration in rabbits is organ specific. *Nephrol Dial Transplant*. 2003;18:2589-2595.
29. Henderson LW, Koch KM, Dinarello CA, et al. Hemodialysis Hypotension: The Interleukin Hypothesis. *Blood Purif*. 1983;1:3-8.
30. Hernández MR, Galán AM, Cases A, et al. Biocompatibility of cellulosic and synthetic membranes assessed by leukocyte activation. *Am J Nephrol*. 2004;24:235-241.
31. Panichi V, Tetta C. On-line hemodiafiltration in the large RISCAVID study. *Contrib Nephrol*. 2011;175:117-128.
32. Libetta C, Sepe V, Esposito P, et al. Oxidative stress and inflammation: Implications in uremia and hemodialysis. *Clin Biochem*. 2011;44:1189-1198.
33. Rabb H, Griffin MD, McKay DB, et al. Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps. *J Am Soc Nephrol*. 2016;27:371-379.
34. Jaber BL, Rao M, Guo D, et al. Cytokine gene promoter polymorphisms and mortality in acute renal failure. *Cytokine*. 2004;25:212-219.
35. Simmons EM, Himmelfarb J, Sezer MT, et al. Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int*. 2004;65:1357-1365.
36. Banche G, Allizond V, Giacchino F, et al. Effect of dialysis membrane biocompatibility on polymorphonuclear granulocyte activity in dialysis patients. *Nephrol Dial Transplant*. 2006;21:3532-3538.
37. Martín-Malo A, Carracedo J, Ramírez R, et al. Effect of uremia and dialysis modality on mononuclear cell apoptosis. *J Am Soc Nephrol*. 2000;11:936-942.
38. Carracedo J, Ramirez R, Soriano S, et al. Monocytes from dialysis patients exhibit characteristics of senescent cells: does it really mean inflammation? *Contrib Nephrol*. 2005;149:208-218.
39. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. *Nephrol Dial Transplant*. 2013;28:438-446.
40. Schiffl H. High-flux dialyzers, backfiltration, and dialysis fluid quality. *Semin Dial*. 2011;24:1-4.
41. Luo Y, Kanagasundaram NS. Microbial control in renal support for acute kidney injury. *Semin Dial*. 2011;24:203-207.
42. Upadhyay A, Jaber BL. We Use Impure Water to Make Dialysate for Hemodialysis. *Semin Dial*. 2016 (epub ahead of print). doi:10.1111/sdi.12493.
43. Murakami K, Ohashi A, Hori H, et al. Accumulation of bisphenol A in hemodialysis patients. *Blood Purif*. 2007;25:290-294.
44. Bosch-Panadero E, Mas S, Sanchez-Ospina D, et al. The Choice of Hemodialysis Membrane Affects Bisphenol A Levels in Blood. *J Am Soc Nephrol*. 2016;27:1566-1574.
45. Bosch RJ, Quiroga B, Muñoz-Moreno C, et al. Bisphenol A: An environmental factor implicated in renal vascular damage. *Nefrologia*. 2016;36:5-9.
46. Neri M, Virzì GM, Brocca A, et al. In vitro Cytotoxicity of Bisphenol A in Monocytes Cell Line. *Blood Purif*. 2015;40:180-186.
47. European Scientific Committee on Emerging and Newly Identified Health Risks. Safety of the use of bisphenol A in medical devices; 2015. Available at: http://ec.europa.eu/health/scientific_committees/emerging/opinions/index_en.htm.
48. European Scientific Committee on Emerging and Newly Identified Health Risks. The safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk (update); 2015. Available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf.
49. Kim SW, Petersen RV, Lee ES. Effect of phthalate plasticizer on blood compatibility of polyvinyl chloride. *J Pharm Sci*. 1976;65:670-673.

50. Lamba NM, Courtney JM, Gaylor JD, et al. In vitro investigation of the blood response to medical grade PVC and the effect of heparin on the blood response. *Biomaterials*. 2000;21:89-96.
51. Gourlay T, Samartzis I, Stefanou D, et al. Inflammatory Response of Rat and Human Neutrophils Exposed to Di-(2-ethylhexyl)-phthalate-Plasticized Polyvinyl Chloride. *Artif Organs*. 2003;27:256-260.
52. U.S. Food and Drug Administration, Center for Devices and Radiological Health. Safety assessment of di(2-ethylhexyl) phthalate (DEHP) released from PVC medical devices; 2002. Available at: http://www.fda.gov/downloads/MedicalDevices/…/UCM080457.pdf.
53. Health Canada Medical Devices Bureau, Therapeutic Products Directorate, Health Products and Foods Branch. Health Canada Expert Advisory Panel on DEHP in Medical Devices: Final Report; 2002. Available at: http://www.hc-sc.gc.ca/dhp-mps/md-im/activit/sci-consult/sab_ces_pan_gr_list-eng.php.
54. Purello D'Ambrosio F, Savica V, Gangemi S, et al. Ethylene oxide allergy in dialysis patients. *Nephrol Dial Transplant*. 1997;12:1461-1463.
55. Golli-Bennour EE, Kouidhi B, Dey M, et al. Cytotoxic effects exerted by polyarylsulfone dialyser membranes depend on different sterilization processes. *Int Urol Nephrol*. 2011;43:483-490.
56. Allard B, Begri R, Potier J, et al. Dialyzers biocompatibility and efficiency determinants of sterilization method choice. *Le Pharm Hosp Clin*. 2013;48:e15-e21.
57. Zündorf J, Kremer S, Grüger T. Formation of hydrogen fluoride by gamma and beta sterilisation in medical devices containing perfluoroheptane. *Toxicology*. 2008;243:284-293.
58. Kiaii M, Djurdjev O, Farah M, et al. Use of electron-beam sterilized hemodialysis membranes and risk of thrombocytopenia. *JAMA*. 2011;306:1679-1687.
59. Filiopoulos V, Manolios N, Vlassopoulos D. Use of electron-beam sterilized hemodialysis membranes is not associated with significant and persistent thrombocytopenia. *Int J Artif Organs*. 2013;36:217-219.
60. De Prada L, Lee J, Gillespie A, et al. Thrombocytopenia associated with one type of polysulfone hemodialysis membrane: a report of 5 cases. *Am J Kidney Dis*. 2013;61:131-133.
61. Subramanian S, Venkataraman R, Kellum JA. Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. *Kidney Int*. 2002;62:1819-1823.
62. Jaber BL, Lau J, Schmid CH, et al. Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: a meta-analysis. *Clin Nephrol*. 2002;57:274-282.
63. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure. *Cochrane Database Syst Rev*. 2008;(1):CD005283.
64. Hoste EAJ, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? *Crit Care Med*. 2008;36:S146-S151.
65. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care*. 2010;14:R221.
66. Davenport A, Bouman C, Kirpalani A, et al. Delivery of renal replacement therapy in acute kidney injury: what are the key issues? *Clin J Am Soc Nephrol*. 2008;3:869-875.
67. Honore PM, Jacobs R, Joannes-Boyau O, et al. Newly designed CRRT membranes for sepsis and SIRS–a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. *ASAIO J*. 2013;59:99-106.