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Review Article

Reactions to Synthetic Membranes Dialyzers: Is there an Increase in Incidence?

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Abstract
Background: Reactions to dialyzers used in dialysis have been reported more frequently in recent years. Evidence, however, shows that the reaction rate has remained stable for years. ***Summary:*** One explanation for the apparent increase in publication frequency could be the lack of knowledge that dialyzer reactions may well occur with biocompatible membranes. Studies showed that the cause of these reactions is very diverse and varied, involving multiple materials. However, polyvinylpyrrolidone continues to be the main suspect, but without conclusive results. There are no differences between the different fibers, and although polysulfone is the most described, it is also the most used. ***Key Messages:*** The change to cellulose triacetate continues to be the most appropriate form of treatment. The classification of these reactions into type A and B complicates the diagnosis, and its true usefulness is in doubt.

Introduction

During hemodialysis, human blood directly contacts different materials in an extracorporeal circuit. The large number of materials involved, both solid and fluid, justifies the existence of occasional clinical or subclinical reactions as evidence of bioincompatibility. Reactions related to dialysis membranes have been described from the outset of hemodialysis

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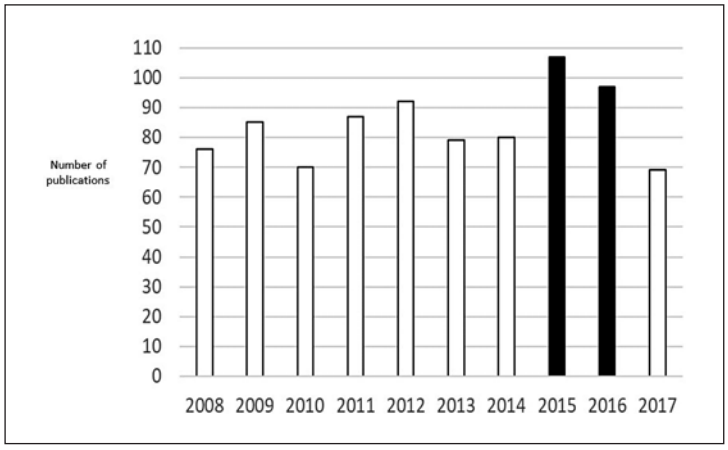

Fig. 1. Number of references in PubMed under the search "(hemodialysis OR dialyzer) AND reaction" performed on September 28, 2018.

programs [1–8]. Reactions were initially explained by bioincompatibility, which resulted in coagulation, complement and inflammatory cascade activation. Over the years, biocompatibility improved through modification of dialysis membrane materials (e.g., change from cellulose to synthetic membranes), sterilization methods, discarding ethylene oxide, which was responsible for the first reactions notified in 1975, and of additional complementary materials like needles, lines, binders, plastic and others [1]. During 2015 and 2016, an increase in the number of reports led to the speculation that manufacturers may have introduced changes that resulted in a higher incidence of dialyzer reactions (Fig. 1). However, the absence of comprehensive epidemiological studies has hindered the understanding of reactions to dialysis membranes. We now review the current evidence on the evolving epidemiology of these reactions.

Daugirdas and Ing [9] classified reactions into type A and B. Type A reactions begin within the first 30 min after the start of the hemodialysis session. They have variable symptoms (itching, burning in the vascular access, cough, runny nose, abdominal cramps, dyspnea, bronchospasm, and even cardiorespiratory arrest) that can be mediated by mechanisms dependent on immunoglobulin E (anaphylactic reactions) or not (anaphylactoid reactions). Some anaphylactic type A reactions were related to the use of ethylene oxide, which behaves as a hapten reacting with proteins, including albumin, promoting their denaturation, and potentially exposing neoantigens that may stimulate the immune response. Formaldehyde, latex, chlorhexidine, intravenous iron, erythropoiesis stimulating agents (this has been related to the use of bovine gelatin and polysorbate 80) and heparin could also act as haptens. Anaphylactoid type A reactions may be triggered by opiates, iodine contrasts, and the AN69 membrane in patients on angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. A reaction is considered type A if it meets the Daugirdas criteria [9] (Table 1).

Type B reactions are more common and have milder symptoms. They are considered to be secondary to the release of histamine, leukotrienes, and bradykinin. They have been reported more frequently in patients dialyzed to less biocompatible cellulose membranes. They generally occur later than 30 min after the start of the session. Symptoms are very variable and may include dyspnea, chest pain, headache, nausea, vomiting, and hypotension. Given the partial overlap in symptoms between type A and B reactions, the timing could not be the only differentiating feature.

In 1982, Villarroel [2, 3] described an incidence of 3.5 reactions per 100,000 sessions in the United States, resulting in a mortality rate of 5 cases per year. Between 1986 and 1996,

Table 1. Daugirdas criteria for defining type A reactions (12)

Major criteria	
1	Reproducible episode in the consecutive session using the same type and dialyzer brand
2	Urticaria
3	Rhinorrhea tearing
4	Abdominal cramps
5	Itching
Minor criteria	
1	Developing within 20 min from the beginning of the hemodialysis session
2	Dyspnea
3	Burning/heat sensation on body and/or vascular access
4	Angioedema

A diagnosis of type A reaction is made when there are 3 major criteria or 2 major criteria and 1 minor criterion. A possible case is suspect in the presence of 2 major criteria; or 1 major criterion and 2 minor criteria; or 3 minor criteria.

Table 2. Incidence of hemodialysis membrane reactions in major studies

Year	Membranes	Country	Incidence per 1.000 patients/year	Incidence per 1.000 sessions/year	Incidence (% reactions)	Ref.
1980s						
1984	Cellulosic	USA	–	–	–	7
1984	–	USA	–	–	–	2
1985	Cuprammonium cellulose	USA	–	0.008	–	4
1985	–	USA	3.3 (Hollow fiber) 0.3 (flat plaque)	–	–	3
1987	–	UK	20.2	0.13	2–5	15
1990s						
1990	Cellulosic (Cupro-phan)	Germany	18.3	0.12	10.1	14
1996	Cellulosic Synthetic	France	21.5 (in 6 months)	0.17 (Cellulosic) 4.2 (Synthetic)	–	9
2000s						
2018	Synthetic	Spain			2.37	24

the number of reported cases increased [5, 7, 10–13]. In 1987, Nicholls [14] described a prevalence of 1 in 20–50 patients using a new dialyzer. In 1996, Simon [12] published 33 anaphylactoid reactions in 1,536 patients (2.1% of patients) from 30 dialysis centers in a study of 122,694 sessions. The annual incidence may vary according to the type of membrane, with reported figures of 0.17/1,000 sessions for cellulose membranes and 4.2/1,000 sessions for synthetic membranes (Table 2).

In recent years, an increased number of reports focused on polysulfone dialyzers [15–20]. In 2014, Sánchez-Villanueva et al. [15] published 6 simultaneous cases of hypersensitivity reactions during dialysis sessions, with homogeneous symptoms and associated to the use of polysulfone membranes. This and additional publications involving polysulfone

membranes have alerted the nephrological community to the possibility of recent changes in the manufacturing processes or additive composition of synthetic polysulfone membranes [21].

Recent Spanish Experience

We have recently collected the experience from several centers in Spain [22]. Hemodialysis hypersensitivity reactions were observed in 37 different patients from 9 centers within the period August 2015 to August 2017. A detailed description was available for 33 reactions. The most frequently described symptom was dyspnea (64%), and eosinophilia was quite common (74% of cases). The reactions were categorized by the attending physician into type A or B reactions (18 vs. 15 cases). However, no significant differences were found between the 2 types of reactions in terms of symptoms described, composition of the membrane involved, method of sterilization, season of the year or timing during the hemodialysis session. This suggests that in clinical practice, hemodialysis physicians are unable to recognize both types of reactions as separate clinical entities and questions the usefulness of the type A or B reaction categorization. A simpler approach, making a diagnosis of hemodialysis reaction and clarifying its severity may be more practical in terms of therapeutic decision-making, that is, changing the composition of the dialysis membrane. In this regard, in all cases, replacement of the dialysis membrane by a different one, usually cellulose triacetate, was associated with the disappearance of symptoms.

A majority of patients, 23 (62.2%) presented reactions associated with polysulfone membranes. Additional membranes involved were polynephron (21.6%), polyethersulfone (2.7%), and polyacrylonitrile (2.7%) [23]. This ranking essentially reproduced the frequency of use of different membranes in the participant centers, arguing against changes in the manufacturing process of a specific membrane as a driver of a clustering of cases. The overall incidence was 2.37% of patients [22], within the range reported >20 years ago. These results suggest that the use of more biocompatible synthetic membranes has not decreased the incidence of hypersensitivity reactions and that, within synthetic membranes, not just polysulfones are associated with this type of reaction.

Drivers of Dialyzer Reactions

It is difficult to explain the pathophysiology of single reactions, since different molecules may underlie different reactions through recruitment of different mediators. In this regard, the timing of onset, symptoms, and severity are highly variable. The only common point is that symptoms disappear after replacing the synthetic membrane, in the vast majority by a cellulose membrane. However, there are also reports of symptoms disappearing following replacement by a different synthetic membrane without polyvinylpyrrolidone (PVP) or bisphenol A (BPA) or to similar membranes but produced through a different manufacturing process [24].

Different types of PVP are added to polysulfone dialyzers and other synthetic membranes as a hydrophilic pore-forming agent to improve permeability. PVP is attached to the dialyzer membrane by strong cross-linked bonds, but not in all cases. Thus, both the previous washing with saline and the stress of shearing the blood on contact with the membrane can release PVP molecules that pass into the patient's blood. The subsequent elimination of this compound and, above all, of its soluble derivatives, is not very clear [25, 26]. Some studies [24] seem to show that PVP is not responsible for these reactions, as there is no correlation with the prick test on skin. However, it could happen that some PVP-derived soluble compound detached from the dialyzer membrane may be a causal agent in these reactions, since the most modern PVP-free membranes do not generally cause hypersensitivity reactions. New membranes without PVP or with structural modifications that decrease platelet aggregation and subsequent inflammation are presented as a promising alternative in the near future [27, 28].

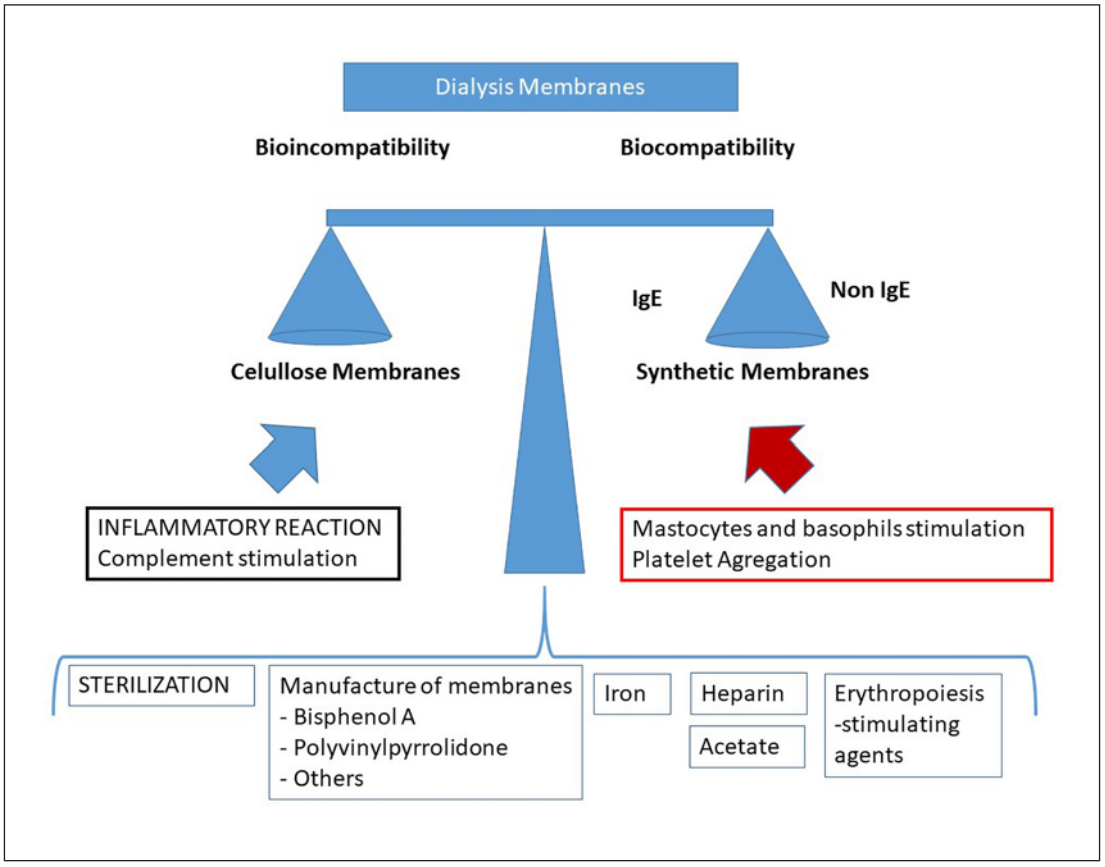

Fig. 2. Diagram showing the main causes and mechanisms of bioincompatibility of dialysis membranes. IgE, immunoglobulin E.

The latter case points to the involvement of molecules used during membrane sterilization.

Components potentially involved in dialysis reactions include PVP, BPA, parabens, carbamates, thiurams, formaldehyde, rubber materials, plastics, epoxy resins, polyurethanes, and glues among others, that could be present in dialyzers, lines, needle, cannula or other components of the hemodialysis equipment (11, 16, 17, 20, 23). Given the lack of information in the dialyzer datasheets, it is difficult for the clinician to link reactions to specific dialyzer components. But we do know that polynephron does not contain BPA, and yet there are polynephron-associated cases arguing against the role or single role of BPA (Fig. 2). PVP and BPA are not exclusive to either polysulfone or a single manufacturer.

Arenas et al. [29] published a case report of the most frequent type of secondary reaction with a synthetic membrane that disappears when cellulose triacetate membranes are used. For polysulfone, Butani found activation in platelet receptor GPIIB/IIIA, causing platelet activation, and can adsorb proteins such as ficolin-2, which can cause activation of the lectin complement pathway [7]. Rodríguez Sanz observed the activation of basophils, T cells, and complement factors C3 and C4, which was ascribed to the adsorption of dialyzer molecules. This would justify an improvement of clinical symptoms by increasing the volume of the dialyzer wash before connection. However, this procedure does not always achieve good results [17]. Even brand models of the same membrane may or may not cause hypersensitivity reactions depending on the way they are manufactured [18].

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Table 3. Potential causes of hypersensitivity reactions during hemodialysis

Sterilization methods	
ETO	Epoxy and polycarbonate resins
Manufacture of membranes, catheters and grafts	Formaldehyde PVP
BPA	Binders
Glue (epoxy resins)	Natural rubber latex
Other plastics	Carbamates
Silicones	Polyurethanes
Thiurams	Polypropylene
Dialyzer membranes	
Synthetic membranes (AN-69, polynephron, PES, polysulfones, PMMA)	
Cellulose membranes	
Others	
Acetate in the bicarbonate dialysate	
Metals (beryllium, nickel)	
Topic antiseptics (chlorhexidine, povidone iodine)	
Native proteins denatured	
Medications	
Eritropoiesis stimulating agents and excipients (bovine gelatin, polysorbate-80)	
Heparin and excipients (parabens: paraoxybenzoic esters)	
Iron	
Opioids	
NSAIDs	
Iodine contrast	
ACEI	
Topical antibiotics	
Topical anesthetics (Lidocaine)	

ETO, ethylene oxide; BPA, bisphenol A; PVP, polyvinylpyrrolidone; AN-69, Polyacrylonitrile; PES, polyethersulfone; PMMA, polymethylmethacrylate; NSAID, non-steroidal inflammatory drugs; ACEI, angiotensin converting enzymes inhibitors.

Finally, the individual background may also impact the occurrence of dialyzer reactions. Thus, we are likely not dealing with a single responsible material (Table 3), and additionally, the individual predisposition may differ for each patient. This complexity may be addressed by innovative approaches. As an example, an emphasis on individualized prevention may involve the development of chips representing all materials and molecules used in dialyzer manufacturing and processing that are allowed to react with the patient blood in vitro or in vivo using methods similar to prick tests.

Conclusion

In conclusion, hypersensitivity reactions to synthetic membranes continue to be observed and disappear following a change of membrane, usually to cellulose triacetate. The cause of these reactions remains obscure, and both the nature of the membrane and the changes in native proteins denatured after contact with dialysis-related molecules have been proposed

[15]. The recent increase in notifications does not appear to reflect a real increase in these reactions, but an increase in awareness and hypersensitivity diagnosis. No differences are encountered among synthetic membranes, as higher incidence associate with a higher market share. We propose that the classification into type A or B reactions be dropped and replaced by a classification based on the severity of reactions that provides relevant information regarding the need to take action.

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Disclosure Statement

There is no conflict of interest in the information contained in the manuscript.

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