

## ALLERGIC REACTIONS TO POLYSULFONE DIALYSIS MEMBRANES – AN OLD PROBLEM TAKING A NEW DIMENSION?

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DEAR EDITOR,

Allergic reactions to polysulfone dialysis membranes are uncommon. According to data from a study conducted in 1993 in 1536 patients from 30 dialysis centers, the annual incidence was 4.2 *per* 1000 dialysis treatments<sup>1</sup>. Such allergic reactions may occur immediately after the first contact of the membrane with the patient's blood or after a number of treatments, making them more difficult to diagnose, particularly if the clinical presentation is atypical<sup>2-4</sup>. There are two types of reactions: type A ('hypersensitive') and type B ('non-specific'). Although the etiology remains largely unknown, the increased frequency of type A response was observed in patients with allergic diathesis, and type B is thought to be mediated by complement activation. Type A reactions are usually apparent immediately, at the very beginning of the dialysis process, whereas type B occurs during the first 15-30 minutes or later. Type A reactions present with itching, urticaria, angioedema and anaphylaxis, whereas the most common signs and symptoms of type B reactions are chest or back pain, dyspepsia, vomiting and hypotension. The use of angiotensin-converting enzyme (ACE) inhibitors increases the likelihood of allergic reactions to polysulfone dialysis membranes<sup>5</sup>. Allergic reactions may be mild to life-threatening (anaphylactoid reaction, angioedema, severe bronchospasm or refractory hypotension), or may occasionally exacerbate the symptoms of pre-existing diseases (asthma, susceptibility to intradia-

lytic hypotension)<sup>6</sup>. Mild symptoms usually subside towards the end of hemodialysis (HD), and therefore the procedure may not need to be stopped immediately. Once apparent, the symptoms occur during each next contact of patient's blood with a polysulfone dialysis membrane. Cross-reactivity between different types of synthetic dialysis membranes is also possible<sup>7</sup>. Upon entering the era of the highly prevalent use of synthetic dialysis membranes, as required by modern renal replacement procedures, many dialysis centers use this modern type of dialysis membranes exclusively. Along with the increasing use of synthetic membranes, we have noticed and recognized allergic reactions to dialysis membranes that had not previously been observed during HD procedures using triacetate membranes. In the last 10 years, allergic reactions to polysulfone membranes were identified in six patients at Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital Center in Zagreb. Retrograde analysis of the following data from dialysis protocols was performed: type of dialysis membrane, method of membrane sterilization, time of symptom onset in relation to HD initiation, number of HD procedures from first use of incriminated membrane until diagnosis, leading and accompanying symptoms, need of interruption of HD procedure or its continuation towards the end of the planned time, ACE inhibitor in chronic therapy, and efficacy of the replacement triacetate membrane on the absence of symptoms. Results are shown in Table 1.

Table 1.

*Patients with allergic reaction to synthetic dialyzer membrane in the last 10 years at Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital Center*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Membrane type and sterilization method	Elisio 17H (Nipro, Polynephron, gamma radiation)	Elisio 17H (Nipro, Polynephron, gamma radiation)	Elisio 17H (Nipro, Polynephron, gamma radiation)	Rexeed21L (Asahi Kasei, Polysulfone, gamma radiation)	Rexeed21L (Asahi Kasei, Polysulfone, gamma radiation)	Rexeed21L (Asahi Kasei, Polysulfone, gamma radiation)
Symptom onset	15-90 min since start of HD	15-30 min since start of HD	60-90 min since start of HD	1-5 min since start of 4 <sup>th</sup> HD	During the 1 <sup>st</sup> hour of HD	During the 1 <sup>st</sup> hour of HD
Recognition of allergic reaction	After 7 HD procedures	After 10 HD procedures	After 12 HD procedures	Immediately	During 2 <sup>nd</sup> HD procedure	During 2 <sup>nd</sup> HD procedure
Leading symptom	Worsening of dyspnea	Chest tightness	Colicky abdominal pain	Anaphylactoid reaction	Sharp back pain	Sharp back pain
Accompanying symptoms	Sweating, hypertension	Mild dyspnea, Occasional hypotension	Worsening of dyspnea	Bronchospasm, cyanosis, angioedema, hypotension	Hypotension, nausea, dyspnea	Hypotension, mild dyspnea
ACE inhibitor therapy	Yes	Yes	Yes	Yes	Yes	Yes
Termination of hemodialysis procedure	7 <sup>th</sup> HD	10 <sup>th</sup> HD	18 <sup>th</sup> HD	Immediately	2 <sup>nd</sup> HD	2 <sup>nd</sup> HD
Effect of membrane replacement (Nipro, Sureflux, cellulose triacetate)	Immediate	Immediate	Immediate	Immediate	Immediate	Immediate

A severe anaphylactoid reaction occurred in a single patient (Patient 4) after three HD procedures with the same dialyzer had already been performed without any symptoms. All other patients had milder forms of allergic reactions. Apart from the clinical picture, an important role in establishing the diagnosis lies in the patient's ability to associate the symptom onset with the initiation of HD. In one patient (Patient 3), due to advanced psychorganic syndrome and reduction of cognitive functions, verbalization of previously known polymorphic symptoms (chronic obstructive pulmonary disease, asthma, abdominal angina, intradialytic hypotension) was inadequate. Therefore, the correct diagnosis of allergic reaction to polysulfone membrane was made after 18 HD procedures had already been performed, each using a polysulfone membrane. In this patient, HD procedures were previously performed using triacetate dialysis membranes. It was only during close supervision of this patient in inpatient conditions that the absence of symptoms of asthma and abdominal pain was noted, except for the first hour of HD. Upon reinstating the triacetate dialysis membrane, the aforementioned symptoms became absent. After one month, HD was accidentally initiated with a polysulfone membrane, with the symptoms reappearing, thus confirming the diagnosis of an allergic reaction. This case of a patient with reduced cognitive functions imposes the question of recognizing allergic reactions to polysulfone membranes in unresponsive, critically ill patients on continuous renal replacement therapy

(CVVHD/HDF), using modern dialysis systems with only highly permeable, highly effective synthetic dialysis membranes. In such patients, it is almost impossible to discern whether worsening of the symptoms upon initiation of renal replacement therapy is the result of allergy to the dialysis membrane or of exacerbation of the pre-existing disease. Apart from carefully monitoring the patient's clinical condition, vital and hemodynamic parameters in critically ill patients in which renal replacement therapy has been initiated, timely recognition of deterioration of respiratory function with arterial hypotension refractory to standard treatment procedures, or possible dermatologic manifestations, there is no reliable, accurate or fast diagnostic tool for establishing the diagnosis of an allergic reaction to the synthetic dialysis membrane. In order to raise suspicion of an allergic reaction in such patients, substantial clinical experience of nephrology and intensive medical teams is necessary for the diagnosis to be quickly established only with replacement of the dialysis membrane by that made of semi-synthetic material, after which the symptoms would recede<sup>8</sup>. Since most modern continuous renal replacement therapy systems (CVVHD/HDF) have a factory-integrated synthetic membrane inseparable from the rest of the extracorporeal circuit system and therefore irreplaceable with a dialyzer of some other material, there is a clear limitation for dialysis treatment of such patients. By integrating the dialyzer into the extracorporeal circuit, manufacturers of such sophisticated devices (PRISMAflex®System Gambro) provide almost ideal

conditions of continuous renal replacement therapy, as well as ensure the sale of their original dialyzers. However, as such they are unusable for treatment of those critically ill and allergic to synthetic membranes. There are few machines for continuous renal replacement therapy that allow the use of different types of dialyzers, and those of different manufacturers, that can be linked to the original extracorporeal circuit system, dialysate circuit and replacement fluid circuit for the particular device (MultiFiltrate-Fresenius, Plasmauto Σ-Asahi Kasei, Diapact® CRRT system B. Braun). In order to conduct a method of continuous renal replacement therapy, primarily CVVHDF, high-flux dialysis membranes with ultrafiltration coefficient >20 mL/h/mm Hg are required.

Only a few non-synthetic, non-polysulfone membranes have such properties, such as cellulose triacetate membranes (Sureflux UX-Nipro, Tricea G-Baxter, ACE SY-MC Assomedica SRL) with UFC >35 mL/h/mm Hg. They are used almost exclusively for high-flux HD and hemodiafiltration (HDF). Although some studies have pointed to the triacetate high-flux membrane as a possible alternative to synthetic membranes for continuous renal replacement therapy, it has not been widely implemented<sup>9</sup>.

Despite good biocompatibility, high-flux and high-efficiency, triacetate membranes have no ability to adsorb the inflammatory mediators, have lower permeability for large molecules than modern synthetic membranes, and are not nearly as good as synthetic membranes in the treatment of patients with sepsis. That is why there are no studies of their effectiveness in the treatment of such patients. Although the era of mass use of triacetate membranes has passed, with superior polysulfone membranes widely available, triacetate membranes have gained value precisely in the treatment of polysulfone-hypersensitive patients. The critically ill with established allergy to synthetic membranes can therefore be treated only by intermittent HD/HDF or one of the hybrid methods, using high-permeability triacetate membranes (UFC >20 mL/h/mm Hg). The inability to perform bedside intermittent HD/HDF in intensive care units due to technical deficiencies (absence of central water supply system for dialysis or portable reverse osmosis)

complicates the work of medical staff and exposes the patient to the risk of transport to a dialysis center. Due to the unpredictability of sometimes life-threatening allergic reactions, possible cross-reactivity to different types of polysulfone membranes, each dialysis center should have at least two different types of dialysis membranes available at any time. The triacetate membrane serves both as a diagnostic tool and as the only option for dialysis treatment of patients allergic to polysulfone membranes.

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