

# Hypersensitivity reactions to synthetic haemodialysis membranes

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## ABSTRACT

Undergoing a haemodialysis (HD) session poses a certain risk of hypersensitivity adverse reactions as large quantities of blood are in contact with various synthetic materials. Hypersensitivity reactions to ethylene oxide and non-biocompatible membranes, such as cuprophane, have been described in HD. Cases of hypersensitivity with biocompatible membranes, such as polysulfone, and even polysulfone-polyvinylpyrrolidone, have also been reported. In this article we describe six cases of mostly early-stage hypersensitivity reactions to HD occurring in our department, characterised by malaise, desaturation, bronchospasm and arterial hypotension, with good response to the session's temporary suspension and with reappearance in subsequent sessions that used a synthetic dialyser. No hypersensitivity reactions reappeared in successive observations when the sessions were carried out using a cellulose membrane.

**Keywords:** Haemodialysis. Allergy. Polysulfone. Hypersensitivity reaction. Anaphylaxis. Eosinophilia.

## Reacciones de hipersensibilidad a membranas sintéticas de hemodiálisis

### RESUMEN

La realización de una sesión de hemodiálisis (HD) supone un cierto riesgo de aparición de reacciones adversas de hipersensibilidad, al estar en contacto abundantes cantidades de sangre con diferentes materiales de origen sintético. En HD han sido descritas reacciones de hipersensibilidad al óxido de etileno y a membranas no biocompatibles como el cuproamónio. También se han comunicado casos de hipersensibilidad con membranas biocompatibles como la polisulfona, e incluso con polisulfona asociada a polivinilpirrolidona. En este artículo queremos describir seis casos acontecidos en nuestro servicio de reacciones de hipersensibilidad mayoritariamente temprana a la sesión de HD, caracterizados por mal estado general, desaturación, broncoespasmo e hipotensión arterial, con buena respuesta a la suspensión temporal de la sesión y con reaparición en sesiones posteriores siempre que se utilizase un dializador sintético. Todas tienen en común no haberse dado de nuevo en sucesivas observaciones cuando las sesiones fueron realizadas con una membrana de celulosa.

**Palabras clave:** Hemodiálisis. Alergia. Polisulfona. Reacción de hipersensibilidad. Anafilaxia. Eosinofilia.

## INTRODUCTION

Undergoing a haemodialysis (HD) session poses a certain risk of hypersensitivity adverse reactions as large quantities of blood are in contact with various synthetic materials. These hypersensitivity reactions associated with the HD technique have been traditionally categorised into

two types: type A or hypersensitivity reactions, which tend to occur immediately, and type B or non-specific reactions, which tend to start later<sup>1</sup>.

Hypersensitivity reactions to ethylene oxide and non-biocompatible membranes, such as cuprophane, have been described in HD<sup>2-4</sup>. Cases of hypersensitivity with biocompatible membranes, such as polysulfone, and even polysulfone-polyvinylpyrrolidone, a compound used to prevent possible adverse reactions produced by the interaction of the polysulfone membrane with platelets and plasma proteins, have also been reported<sup>5-7</sup>.

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In this article we would like to describe 6 cases of adverse reactions to synthetic HD membranes in our department since 2011, with particular intensity between May and July 2013.

## CLINICAL CASES

### Case 1

A 58-year-old male patient, positive for hepatitis C virus (HCV), with chronic renal failure (CRF) secondary to adult hepatorenal polycystic disease, on the HD programme from 1996 to 2000, the year in which he received a cadaveric-donor kidney transplant. Functioning transplant until May 2010, when he restarted HD due to stage 4-5T chronic allograft dysfunction secondary to chronic humoral rejection in the biopsy. The patient usually received high-flux polysulfone dialyser by predilution online (Helixone<sup>®</sup> FX-800, FMC). He had no known history of allergies. In July 2011, due to supply problems, the dialyser was changed to high-flux polyamide (Polyflux<sup>®</sup> 210H, Gambro). After being connected for 20 minutes, we noted oppressive chest pain accompanied by hypotension (blood pressure [BP] 80/40 mmHg) and 88% desaturation. Pulmonary auscultation did not reveal wheezing. After returning the circuit and prescribing high-flow oxygen, the patient improved spontaneously. After stabilising the vital signs (BP 130/70 and 94% baseline oxygen saturation), the session was restarted and ultrafiltration reduced, without further complications.

In the following HD session, after being connected for 20 minutes, he presented the same symptoms as in the previous session (chest pain with hypotension and 78% oxygen saturation). The patient was returned to and prescribed high flow oxygen and 1g intravenous (IV) paracetamol. He improved noticeably following this treatment and consequently the HD session was restarted, finishing without complications.

Given a suspicion of adverse reaction to the dialyser, we decided to change it in the following session to a polyneuron membrane (Elisio<sup>™</sup>-21H, Nipro). When he had been connected for 35 minutes, he experienced central chest pain, holocranial headache and abdominal pain. Pulmonary auscultation did not reveal wheezing. BP was 80/50mmHG, for which reason we returned to the patient. High doses of oxygen and 1g IV paracetamol were prescribed, with which the patient improved and 30 minutes after presenting symptoms, the HD session was restarted, which was completed without complications.

Complementary tests (troponin I and electrocardiogram [ECG]) found no significant differences with respect to earlier tests. The analysis of the third session only showed leucopenia (2,300 leukocytes/ml) with normal formula, the

same magnitude of thrombocytopenia as previously (54,000 platelets/ml), slightly elevated C-reactive protein (CRP) (11.5mg/l) and increase of D-dimer (8,544ng/ml; 2,117ng/ml in June 2011). Therefore, a computed tomography angiogram of the pulmonary arteries was requested, which showed pulmonary thromboembolism.

Given a suspicion of possible allergy to synthetic membranes, we decided to perform the next HD session using cellulose triacetate (SureFlux<sup>®</sup>-21UX, Nipro). The patient did not present symptoms in either this session or in any subsequent session to date.

### Case 2

An 80-year-old female with CRF of multifactorial aetiology, on HD since May 2012. The patient had no known history of allergies. She regularly underwent HD using Helixone<sup>®</sup> FX-80 from the start.

On 14 September 2012, an hour and a half into dialysis, she experienced sweating, tachypnoea and dyspnoea; 78% oxygen saturation was observed, overcome using high-flow oxygen. Maintained BP. Pulmonary auscultation did not reveal wheezing. Analysis showed mild leukocytosis (12,500 leukocytes with normal formula), normal troponin I with CRP 8mg/l, with no other noteworthy findings. ECG was similar to previous tests. 20 minutes after presenting symptoms, spontaneous improvement of the patient was observed, finishing HD without complications. Post-HD thoracic radiography was performed, which did not show consolidations, effusion or vascular redistribution; it only showed the known increased cardiothoracic index.

After this incident, HD sessions ran without problems for a month, until 17 October 2012, when the patient experienced sweating and significant dyspnoea during HD, with 76% oxygen saturation. Pulmonary auscultation did not reveal wheezing. The patient was administered oxygen at 5bpm, 200mg of IV hydrocortisone and 2 salbutamol inhalations 15 minutes apart. BP: 115/55mmHg. ECG was performed with sinus rhythm 98bpm, with no changes from the previous ECG. Analysis showed 19,000 leukocytes/ml, 75% neutrophils (remainder of normal formula), CRP 18mg/l, negative troponin I, with no further alterations. On re-examining the patient, we examined the pruritus that had appeared on the lower limbs since the start of the session. Saturation improved to 98%, but the patient subsequently presented hypotension of 65/31mmHg, for which reason the circuit was returned and the session suspended. She was transferred to the Emergency department for observation, being discharged without symptoms the next day.

Given the patient's symptoms, we decided to change the filter to Poliflux<sup>®</sup> 210H for the next HD session.

## clinical case

Subsequent sessions ran without complications. On 24 October 2012 (third session with Poliflux), 1h from finishing HD, she experienced general discomfort, sweating, dyspnoea and hypotension (87/36mmHg). Pulmonary auscultation did not reveal wheezing. 200mg of hydrocortisone was administered, with complete disappearance of the symptoms. The filter was changed again to Elisio™-21H for subsequent HD sessions, which ran without complications. On 7 June 2013, eight months later, the patient presented dyspnoea and non-irradiated, oppressive central chest pain 30 minutes into dialysis. BP: 210/75mmHg. 90% oxygen saturation with oxygen nasal cannula. Physical examination revealed general hypoventilation, with wheezing in all lung fields. Despite administering 300mg of hydrocortisone, the patient persisted with general wheezing; therefore we decided to stop HD and disconnect the whole system. An additional 200mg of hydrocortisone, 40mg of IV methylprednisolone and ipratropium bromide inhalation were administered. The patient's clinical symptoms improved progressively, with respiratory symptoms disappearing. For this reason we decided to continue the HD session using SureFlux®-21UX; the patient remained asymptomatic. Only CRP 21.6mg/l and haemoglobin 8.6g/dl stood out in the analysis, for which reason 2 red blood cell concentrates were transfused. ECG did not show changes from previous tests.

SureFlux®-21UX dialyser was kept for subsequent HD sessions, with no complications to date.

### Case 3

A 75-year-old male with stage 4 CRF, admitted to cardiology due to complete auricular-ventricular block requiring implantation of a pacemaker, along with symptoms of decompensated heart failure and secondary reduced renal function. The patient had no known history of allergies.

On 28 May 2013, we opted for the patient's acute HD treatment. Conventional HD using Helixone® FX-100 Classix was prescribed. 15 minutes into the session, the patient suddenly experienced dyspnoea, 72% oxygen saturation and clinical signs of severe bronchospasm. The blood pump was stopped and 300mg of hydrocortisone and high-flow oxygen were administered. We decided to interrupt the HD session and, given the suspicion of adverse reaction to the dialyser, the blood was removed from the circuit. After 15 minutes the patient was asymptomatic. HD was not required until 16 June 2013, when a session was carried out using FX-100. After 15 minutes the patient experienced the same symptoms as previously and oxygen saturation reduced to 80%. The blood

pump was stopped and 300mg of hydrocortisone, 40mg of methylprednisolone and high-flow oxygen were administered. It was decided not to return the circuit's blood, changing the dialyser to SureFlux®-21UX. The patient slowly started to improve until symptoms completely disappeared, finishing the session with the new dialyser, and with no further complications to date.

### Case 4

A 48-year-old male, positive for human immunodeficiency virus and HCV, diagnosed with CRF of multifactorial origin, with no known history of allergies, who had stopped follow-up consultations and was admitted due to worsening renal function (Cr 15mg/dl), secondary to chronic diarrhoea of 6 months progression and sustained hypotension (70/40mmHg). During admission, the right jugular vein was channelled and one HD session was carried out on 16 July 2013. The Helixone® FX-100 Classix dialyser was used. Two hours into treatment he experienced sudden dyspnoea, with 78%-80% oxygen saturation, presenting general hypoventilation with bibasal crackles and wheezing in both hemithorax in pulmonary auscultation. We decided to interrupt treatment and not return the system. Saturation rose to 98% following administration of high-flow oxygen and 100mg IV hydrocortisone, with pulmonary auscultation without pathological sounds and improvement of respiratory dynamic. The patient was transferred from the department, for which reason we lost the follow-up.

### Case 5

A 70-year-old male, solitary right kidney, with history of stage 5 CRF secondary to nephrosclerosis, with no known allergies, was admitted in June 2013 as scheduled for myocardial revascularisation due to chronic ischaemic heart disease expressed as lesion of the left coronary trunk and three vessels. During admission he presented multiple post-operative complications, requiring continuous techniques of kidney replacement therapy during his stay in the resuscitation unit using a polysulfone dialyser (Aquamax® HF-12, Baxter). After his transfer to the medical ward, periodic HD sessions with Helixone® FX 100 Classix were prescribed. 20 minutes into the first session, the patient experienced hypotension (80/40mmHg), dyspnoea and bronchospasm symptoms. After stopping the blood pump and returning the system, 200mg of hydrocortisone and high-flow oxygen were administered; the patient improved progressively. 20 minutes into the next HD session using the same filter, the clinical symptoms repeated. For this reason we decided to carry out subsequent HD sessions using cellulose triacetate (SureFlux®-21UX), with no complications to date.

## Case 6

An 83-year-old female patient, diagnosed with stage 5 CRF secondary to chronic pyelonephritis, admitted due to worsening renal function in the context of diarrhoea. The patient had no known history of allergies. Given the lack of improvement of the renal function, we decided to begin HD on 11 July 2013 using Helixone® FX-100 Classix. After 30 minutes of conventional HD, the patient presented symptoms of arterial hypotension, dyspnoea and 60-80% oxygen desaturation, accompanied by poor peripheral perfusion. High doses of oxygen and fluid therapy were administered, with improvement of BP, but not the clinical situation; therefore we decided to stop the HD session. After suspending dialysis, saturation returned to baseline values and the patient improved clinically. In subsequent sessions, the filter was replaced by SureFlux®-21UX, with no new complications to date.

## DISCUSSION

We present a six-case series of mostly early-stage hypersensitivity reactions to an HD session, characterised by general malaise, desaturation, bronchospasm when determined, and arterial hypotension. There was good response to the session's temporary suspension and reappearance of reactions in subsequent sessions which used a synthetic dialyser. No hypersensitivity reactions reappeared in successive observations of sessions using a cellulose membrane. No patients had a history of allergies and no causal relationship with the administered medication was found.

As a peculiarity in the first two cases, there was the apparent saturation of the hypersensitivity mechanism for the dialyser that caused the reaction; that is, the reaction only occurred in the first moments and it was possible to resume HD using the previous dialyser, without complications. The remaining cases showed greater reaction severity and there was no other choice but suspension of HD. These cases were a learning curve for professionals in recognising the situation. The genesis of apparent universal hypersensitivity to synthetic membranes was also common among those patients in which a different membrane from the same group was tried. This procedure was not performed in some patients given the severity of their previous symptoms. After presenting symptoms, all patients were submitted to one or several HD sessions using a cellulose dialyser with no similar complications, centring the hypersensitivity process on the dialyser.

The hospital's allergologists admitted, after evaluating the cases, that they could be classified as serious hypersensitivity reactions to the polysulfone dialyser.

We also attributed a certain epidemic character to the entire episode, due to the study being concentrated in two years, July 2011-July 2013, especially between May and July 2013. After this date, despite using the membrane in 90 % of our population, there was no reoccurrence of a similar case. The cases were notified to the Spanish Agency of Medicines as adverse reactions and they informed us that they had not received any similar correspondence. There are still yet to be further notifications on this matter.

Traditionally hypersensitivity reactions to a dialyser have been considered as rare events (4 out of every 100,000 sessions); however, at the end of the 1980s, Nicholls et al. carried out a study in the United Kingdom and highlighted that the problem could be of greater significance<sup>8</sup>. Type A hypersensitivity reactions regularly occurred in the first minutes of the HD session after blood came into contact with components of the extracorporeal circuit. These processes are mediated by preformed antibodies and, in the most serious cases, can cause dyspnoea, hypertension, unconsciousness, cardiac arrest and death. Given the suspicion of this adverse reaction, immediate action consists of stopping the blood pump, disconnecting the entire extracorporeal circuit, and administering high-flow oxygen, as well as short-acting antihistamines and corticosteroids, hydrocortisone and starting assisted respiration where necessary. Type B hypersensitivity reactions, much less frequent, usually occur after the first 30 minutes of the HD session. Clinical signs are less specific, such as chest and back pain, and do not require the HD session to be interrupted.

Bigazzi et al. described how, in the presence of contaminated fluid and through high-flux membranes, there could be back-filtration of pyrogens into the blood compartment. This causes hypersensitivity reactions at the start of the session in patients dialysed using these membrane types<sup>9</sup>. In the case of our patients, all were dialysed using highly permeable membranes and ultrapure water in accordance with European Pharmacopoeia standards<sup>10</sup>. Complying with these regulations, with periodic monthly checks, and the absence of reactions in sessions immediately performed using another highly permeable, non-synthetic dialyser, make it very unlikely that it is the triggering mechanism of a hypersensitivity reaction.

The majority of adverse reactions occurred between May and July 2013 in the patients' first HD session using modified polysulfone dialysers. Cases of severe reactions to polysulfone have been described<sup>5,6</sup>, as well as hypersensitivity crossed to other types of membrane such as polycarbonate and polymethyl methacrylate<sup>11</sup>. These reactions to polysulfone could be different depending on its manufacturer. Therefore, HD sessions using other synthetic dialysers were attempted in cases 1 and 2 without success.

## clinical case

Another point of interest is the different sterilisation method of the dialysers. Müller et al. reported that vapour-sterilisation could increase the dialyser's biocompatibility in comparison to sterilisation using ethylene oxide<sup>12</sup>. Golli-Bennour et al. affirmed that the membranes sterilised using vapour increased the viability of the endothelial cells compared to sterilisation methods using radiation or ethylene oxide<sup>13</sup>. In addition, they showed that, according to the sterilisation method, the concentration of serum malondialdehyde, used as a marker for lipid peroxidation, increased substantially with respect to healthy patients when the dialyser's sterilisation was by gamma radiation or ethylene oxide. However, other authors have reported that vapour sterilisation does not seem to have an effect on the freeing of pro-inflammatory cytokines, such as interleukin-1. In our patients, membrane sterilisation was heterogeneous; FX and Poliflux dialysers are sterilised using vapour, while cellulose triacetate and Eliseo dialysers are sterilised using gamma rays, making it difficult to establish a causal relationship.

A key finding in the cases in our department is that all hypersensitivity reactions disappeared after changing the dialyser to cellulose triacetate. Urbani et al. showed differences between the helixone and cellulose triacetate dialysers when they were studied through proteomics<sup>14</sup>. Abundant proteins involved in the blood-dialyser interaction were found on the helixone membrane, such as ficolin-2 and fibrinogen fragments. Other authors had already demonstrated the absorption of ficolin-2 in polysulfone dialysers, which could contribute to the complement's activation, leukocyte adhesion and, at worst, blood coagulation<sup>15,16</sup>. In addition, it was published that cellulose triacetate induces less hypersensitivity reactions, probably due to less activation of the platelet membrane (GpIIb/IIIa), producing less aggregation disease<sup>17</sup>. The mechanisms making our patients sensitive to the described synthetic dialysers and not to the cellulose triacetate dialyser are not clear. Therefore we are designing specific *ex vivo* response studies on immunocompetent cells for those patients who showed allergic reaction to synthetic dialysers, as well as cross-sectional response studies on hypersensitivity with various HD membranes.

Adverse reactions to dialysers are a severe complication intrinsic to the therapy itself. The nephrologists should be alert to this possibility, acting immediately faced with mere clinical suspicion and referring the patient to the allergy department to complete the study as soon as possible.

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### Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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