



Hypersensitivity reactions in patients receiving hemodialysis

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ABSTRACT

Objective: To describe hypersensitivity reactions in patients receiving maintenance hemodialysis.

Data Sources: PubMed search of articles published during the past 30 years with an emphasis on publications in the past decade.

Study Selections: Case reports and review articles describing hypersensitivity reactions in the context of hemodialysis.

Results: Pharmacologic agents are the most common identifiable cause of hypersensitivity reactions in patients receiving hemodialysis. These include iron, erythropoietin, and heparin, which can cause anaphylactic or pseudoallergic reactions, and topical antibiotics and anesthetics, which lead to delayed-type hypersensitivity reactions. Many hypersensitivity reactions are triggered by complement activation and increased bradykinin resulting from contact system activation, especially in the context of angiotensin-converting enzyme inhibitor use. Several alternative pharmacologic preparations and dialyzer membranes are available, such that once an etiology for the reaction is established, recurrences can be prevented without affecting the quality of care provided to patients.

Conclusion: Although hypersensitivity reactions are uncommon in patients receiving hemodialysis, they can be life-threatening. Moreover, considering the large prevalence of the end-stage renal disease population, the implications of such reactions are enormous. Most reactions are pseudoallergic and not mediated by immunoglobulin E. The multiplicity of potential exposures and the complexity of the environment to which patients on dialysis are exposed make it challenging to identify the precise cause of these reactions. Great diligence is needed to investigate hypersensitivity reactions to avoid recurrence in this high-risk population.

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Introduction

Chronic kidney disease (CKD) remains prevalent at 14.8% in the US general population based on the most recent United States Renal Data System annual report. Within this broad category of patients, those with the most severe renal disease necessitating dialysis have increased in numbers in recent years. As of December 2014, there were 678,383 cases of end-stage renal disease (ESRD), the vast majority of whom were receiving hemodialysis¹; this number continues to increase by approximately 21,000 cases per year as a result of the ongoing shortage of organ donors for renal transplantation and the impact of diabetes and hypertension on renal survival. To decrease the morbidity and mortality experienced by patients with CKD resulting from the detrimental effects of the uremic environment, patients on hemodialysis typically receive a large number of medications; this polypharmacy exposure and a recurring in-center "clinic" environment with several possible

antigenic exposures and sustained contact with extracorporeal circuits can predispose patients to hypersensitivity reactions.

The increasing prevalence of patients on hemodialysis, the large number of possible causes of hypersensitivity reactions in these patients, and the possible perturbing effect of the uremic milieu on the immune system make it imperative for the allergist to know how to approach the evaluation and management of reactions in this high-risk population.

Categorization of Hypersensitivity Reactions Based on Type of Reaction

The types of reactions experienced by patients receiving hemodialysis can vary from mild (such as contact dermatitis and urticaria) to more serious (such as hypotension and angioedema). Most reactions reported in patients on dialysis are anaphylactic (and pseudoallergic) or delayed-type hypersensitivity (DTH) reactions; for several offending agents, precise mechanistic pathways leading to the reaction have not been clearly elucidated and for some more than one pathway could be in play, as discussed below and presented in Table 1. Although robust epidemiologic data on hypersensitivity reactions in patients on dialysis are lacking,

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Table 1
Causes and Management of Anaphylactic and Pseudoallergic Reactions Related to Hemodialysis

Inciting agent	Timing in relation to administration	Type of reaction	Management
Ethylene oxide and formaldehyde	immediate	anaphylactic	thorough rinsing of dialyzers; use of other disinfecting strategies such as gamma radiation or steam
Dialyzer membranes	immediate to delayed	pseudoallergic	avoiding angiotensin-converting enzyme inhibitors when using AN69 membranes; using coated AN69 membranes; substituting synthetic membranes for alternatives that have no cross-reactivity; using ultrapure dialysis solutions with high-flux dialyzers
ESAs	immediate to delayed	anaphylactic (to ESA); anaphylactic (to gelatin); pseudoallergic to polysorbate	avoidance (rarely feasible); desensitization; use of preparations without gelatin/polysorbate
Intravenous iron	immediate	pseudoallergic (mast cell/basophil activation); type III (to iron dextran); complement activation	substitution with safer iron preparation especially iron sucrose
Heparin	immediate	pseudoallergic owing to over-sulfated chondroitin sulfate contamination (mediated by bradykinin) or from platelet and leukocyte activation (type II reaction from heparin-PF4 immune complexes)	use of low-molecular-weight heparin (use with great caution) or preferably alternative anticoagulants (such as citrate and non-heparin anticoagulants)
Bovine thrombin	immediate	anaphylactic	alternative hemostatic agents

Abbreviations: ESA, erythropoiesis-stimulating agent; PF4, platelet factor 4.

current evidence suggests that exposure to pharmacologic agents during dialysis is the leading cause of such reactions.^{2,3}

Anaphylactic and Pseudoallergic Reactions

Reactions attributed to dialysis membranes and solutions

Sterilizing agents. Ethylene oxide and formaldehyde, used historically as sterilizing and disinfecting agents for dialyzers during their manufacturing process, have been well studied and implicated as a cause of anaphylactic reactions.^{4–6} Although not currently in use in the United States, they do deserve mention and brief discussion because it is quite possible that their use continues in other geographic areas. Ethylene oxide is an alkylating agent with the capability of altering proteins, making them immunogenic. Immunoglobulin (Ig) E antibodies against human serum albumin altered by ethylene oxide have been noted in patients with anaphylactic reactions during hemodialysis. These reactions typically occur during the first use of the dialyzer because of the residual agent in the dialyzer and are more common when dialyzers are not rinsed thoroughly; reactions typically are noted within the first few minutes of the start of dialysis, although they can be delayed by up to 30 minutes. With the transition to alternative sterilization techniques, this has become rare. Formaldehyde is another disinfecting agent associated with contact dermatitis and with anaphylactic reactions related to the presence of IgE antibodies to the formaldehyde and human serum albumin conjugate.

Dialyzer membrane. Certain types of dialyzers have been associated with pseudoallergic reactions, without documented specific IgE antibodies. These reactions can occur soon after the start of dialysis or later in the course and are typically milder in symptomatology. Before the use of more biocompatible and synthetic membranes, such reactions were more common and were usually seen with the patient's first exposure to cuprophane membrane dialyzers, which were attributed to complement activation.⁷ More relevant in the current era are hypersensitivity reactions associated with the newer generation of biocompatible membranes. One such classic membrane-associated reaction is seen with the use of the high-flux polyacrylonitrile membrane AN69.⁸ Investigations have established that the negatively charged dialysis membrane leads to activation of factor XII, which then converts prekallikrein to kallikrein, increasing the production of bradykinin and activating complement factors C3 and C5. These mediate the pseudoallergic reaction. Although such reactions with AN69 can be seen without other predisposing factors, the use of

concomitant angiotensin-converting enzyme inhibitors increases the risk significantly by decreasing the degradation of bradykinin. Therefore, the use of angiotensin-converting enzyme inhibitors should be avoided at all costs in patients who are being dialyzed using this specific membrane. Moreover, using an AN69 dialyzer coated with a biocompatible polymer that can partially neutralize the negative charge of the membrane also can alleviate these reactions.⁹

Even with other biocompatible dialyzers, complement activation can be seen leading to pseudoallergic reactions. These reactions have been described with polysulfone and polyamide membranes with cross-reactivity to other similar membranes.¹⁰ More specifically, polysulfone dialyzers can activate glycoprotein IIb and IIIa platelet membrane receptors, causing platelet activation, and can adsorb proteins such as ficolin-2, which can cause activation of the lectin complement pathway.¹¹ As a result of the high solute permeability of many newer high-flux dialysis membranes, backfiltration of contaminants and bacterial products from the dialysate compartment into the blood can lead to pseudoallergic reactions. These reactions typically occur shortly after starting the treatment and can vary from mild to quite severe.¹² The inflammatory mediators for such reactions appear to be triggered by bacterial endotoxins. This indicates the importance of using sterile dialysis fluid and strict precautions to avoid bacterial contamination when high-flux membranes are used.

Miscellaneous. As will be discussed in the subsequent section on DTH reaction, with latex exposures being common in the hemodialysis population, latex should always be investigated as a possible cause of anaphylactic reactions in patients receiving hemodialysis. However, as reviewed in greater detail below, latex sensitization is surprisingly not more common in patients receiving hemodialysis compared with the general population.

Reactions from medications used during dialysis procedure

Hypersensitivity reactions to medications must be considered, especially when such reactions occur during or shortly after drug administration. The 3 most common pharmacologic agents used on a consistent basis in patients on dialysis are iron, erythropoiesis-stimulating agents (ESAs), and heparin, which have been associated with hypersensitivity reactions.

Erythropoiesis-stimulating agents. The first report of an anaphylactic reaction to recombinant human erythropoietin was published in 1993, and since then several other reports have appeared

in the literature.¹³ Erythropoietin is a 166-amino acid glycoprotein hormone that plays a critical role in hematopoiesis and has revolutionized the care of patients with ESRD, because it allows avoidance of blood transfusions, which can be associated with iron overload and sensitization of patients, making future transplantation problematic. The first patient described presented with an anaphylactic reaction immediately after administration of intravenous erythropoietin with symptoms of angioedema, bronchospasm, and hypotension. Testing for specific IgE antibodies was positive by radioallergosorbent test; elimination of the medication resulted in cessation of further reactions.¹³ Subsequent reports have described patients who developed similar immediate reactions to ESAs containing additives such as bovine gelatin and polysorbate 80. The presence of IgE antibodies to bovine gelatin without the presence of anti-ESA antibodies confirmed the investigators' suspicion and allowed continuation of therapy with products that did not contain gelatin as a stabilizer, with no reactions.¹⁴ Such reactions have been reported from gelatin present in other pharmaceutical products such as vaccines. Two additional patients were reported to have possible anaphylactic reactions to ESA products that contained polysorbate 80 as the excipient.¹⁵ Although these patients had angioedema and skin rash, in one the reaction was delayed and developed 11 hours after administration of darbepoetin; intradermal test reaction was positive for polysorbate-containing products and negative for those ESA products that were free of polysorbate. However, no IgE testing was performed, which makes it unclear as to whether these were pseudoallergic or truly anaphylactic reactions. Polysorbates are mixtures of fatty acid esters of sorbitol-derived ethers and are known to be nonspecific mast cell activators, which likely contributed to many of the described symptoms. They are commonly used in different pharmaceuticals and were used as a substitute for human serum albumin, which was the excipient in earlier ESA preparations but was removed for concerns over its stability and possible biological hazard. As described earlier, reactions have been reported with different ESA preparations including epoetin- α , epoetin- β , and darbepoetin; the situation becomes even more complicated because of the different preservatives and excipients that are used in different commercial preparations and that vary based on whether single-dose or multidose formulations are being used.¹⁶ This highlights the importance of thorough investigation into the precise type of ESA used and should be considered when discussions of substituting one formulation for another are undertaken. In addition to switching to a different formulation, desensitization has been attempted and been successful in some instances.¹⁶

Iron. Intravenously administered iron has become the primary route of iron repletion in patients with CKD, especially those with ESRD on hemodialysis.¹⁷ This is because of its improved gastrointestinal tolerability and absorption and its greater efficacy compared with oral iron in adults with CKD.¹⁸ Different parenteral iron preparations are available, some of which have been associated with anaphylactic or pseudoallergic reactions leading to several deaths. By far the most common iron preparation linked to such reactions is iron dextran, with its clinical manifestations including urticaria and shock. A recent and very large retrospective cohort study, albeit in patients not on dialysis, compared the risk of anaphylaxis among the various intravenous iron preparations and found that the highest risk of reactions was with iron dextran and the lowest risk was with iron sucrose; iron gluconate and ferumoxytol were associated with an intermediate risk.¹⁹ In the dialysis population, iron dextran has been associated with pseudoallergic reactions with a frequency of approximately 1.8%, typically seen with the first dose exposure. It is estimated that the

minimum case fatality rate for such reactions is as high as 15.8%.²⁰ Very limited data are available exploring the precise mechanism underlying these reactions. Nevertheless, they do not appear to be mediated by IgE, to the best of our knowledge. Possible mechanisms for reactions with iron dextran include an IgG-mediated immune complex type III hypersensitivity reaction²¹ and a direct effect on mast cells and basophils leading to histamine release²²; in vitro complement activation also has been reported with iron dextran and ferric carboxy maltose and could be another contributor.²³ The preponderance of reactions to iron dextran are not surprising because high-molecular-weight dextran complexes have been known to be immunogenic and associated with reactions.

Heparin. With rare exceptions, heparin is universally used for maintenance hemodialysis to anticoagulate the extracorporeal circuit. Much has been published about heparin-associated reactions, because it is a very commonly used anticoagulant with widespread use in many other clinical settings. The reader is referred to a recent review that exhaustively covers the subject for greater details.²⁴ Suffice it to say that heparin-induced reactions are typically pseudoallergic without documented clear evidence of IgE-mediated reactions. Although heparin use also has been conclusively linked to DTH reactions manifesting as skin necrosis, such reactions are encountered when heparin is used subcutaneously, which is not applicable to patients receiving maintenance hemodialysis and therefore will not be discussed further.²⁵ The most common type of heparin-induced reaction occurs in the context of heparin-induced thrombocytopenia, a classic type II hypersensitivity reaction. Patients clinically present with life-threatening reactions immediately after heparin re-exposure, although hypertension as opposed to hypotension is classically seen; at laboratory testing, a significant decrease in platelet count is noted. Concomitant venous or arterial thromboses also are commonly seen in this setting.²⁴ The pathogenesis of the reactions is unclear, although it seems to be related to in vivo platelet and leukocyte activation leading to the release of inflammatory mediators. Heparin-induced thrombocytopenia is most commonly seen with unfractionated heparin, especially when used in lower doses, because that possibly creates optimal conditions for the formation of immune complexes. The target antigens in heparin-induced thrombocytopenia are created when the negatively charged glycosaminoglycans in heparin bind to positively charged platelet factor 4 and neutralize its positive charge. This leads to the synthesis of IgG antibodies against the complex; these heparin-platelet factor 4 immune complexes bind to platelet Fc γ receptors leading to platelet activation and creating a procoagulant environment. Cross-reactivity to low-molecular-weight heparin preparations can be encountered in patients who have heparin-induced thrombocytopenia; therefore, these agents should be used with great caution in this setting. A second type of heparin-induced reaction, which is much less common, clinically presents with hypotension and angioedema immediately after intravenous heparin administration. An epidemic of such reactions was noted starting in 2007 in the United States, prompting extensive investigations. Ultimately it was determined that these pseudoallergic reactions were due to a contaminant in heparin called over-sulfated chondroitin sulfate. Over-sulfated chondroitin sulfate and heparin contaminated by over-sulfated chondroitin sulfate act as strong contact activators by facilitating autocatalysis of factor XII, which then activates plasma prekallikrein to kallikrein. This converts high-molecular-weight kininogen to bradykinin and activates complement factors C3 and C5 to their anaphylatoxins, leading to hypersensitivity reactions. Some investigators have proposed a contributory role for angiotensin-converting enzyme inhibitors in promoting such reactions.²⁶

Topical bovine thrombin. Topical bovine thrombin has been used as a hemostatic agent to decrease bleeding intraoperatively, postoperatively, and after cannulation and decannulation of arteriovenous fistulae used for hemodialysis access. The literature describes a patient who developed an anaphylactic reaction characterized by hypotension, dyspnea, and urticaria after administration of topical bovine thrombin. Skin prick test reaction was positive as were specific serum IgE and IgG antibodies to bovine thrombin.²⁷ Symptoms resolved with the elimination of this exposure. Then, the investigators measured bovine thrombin specific IgE and IgG antibodies in 65 patients on hemodialysis who had been exposed to this agent and compared them with 14 patients on hemodialysis without topical bovine thrombin exposure and with 32 age- and sex-matched controls. In this study, specific bovine thrombin antibodies were more frequent in the exposed patients on hemodialysis (28% for IgE and 26% for IgG) compared with controls (4% for IgE and 9% for IgG). Based on a survey, the investigators also determined that clinical allergic symptoms such as rhinoconjunctivitis were more common in the patients on hemodialysis who had positive IgG antibodies to topical bovine thrombin, although the frequency of other allergic symptoms was not any different.

DTH Reactions

Some patients develop a DTH reaction, typically appearing within 48 hours of a dialysis session. Clinically these present as allergic contact dermatitis (ACD), which can be localized (eg, at the dialysis access site) or, more rarely, generalized. ACD in patients on dialysis has been attributed to chemical materials to which patients are exposed during the dialysis session or to pharmacologic agents.

ACD to dialysis unit-related chemical exposures

Because the hemodialysis apparatus contains several rubber-containing components, it has been suggested these rubber materials might serve as sources of various rubber derivatives or plasticizers. In 1984, Buxton et al²⁸ described a 40-year-old man who developed an eczematous dermatitis affecting his hands, face, arms, and above the left forearm where his dialysis fistula was situated. Patch test reactions were strongly positive to thiurams and weakly to carbamates, another rubber accelerator. Moreover, a few years earlier, this same patient had shown sensitization to formaldehyde with a similar eczematous rash, which disappeared when a disposable artificial kidney sterilized with ethylene oxide was used in place of formalin. Kruis-de Vries et al²⁹ reported on 6 patients with subacute dermatitis in the area around the forearm fistula. All patients had positive patch test reactions to thiuram; 4 showed sensitization to a carbamate mix, but only 1 patient reacted to the rubber in the dialysis equipment and the other 5 reacted mainly to components in gloves. After these early studies, several other cases of ACD to dialysis components were reported in the literature related to epoxy resin present in the glue of hemodialysis needles or cannulae.^{30–32} Epoxy resin usually causes an eczematous dermatitis at the site of needle insertion or around the dialysis shunt, but sometimes a widespread eczematous rash can occur³¹ and can be accompanied by eosinophilia.³²

Several investigators have explored latex sensitization in patients receiving maintenance dialysis because this patient population is exposed on a recurring basis to latex present in gloves and other equipment. In 2001, Nettis et al³³ performed a series of tests (skin prick tests, patch tests, glove user test) to latex, gloves, and rubber extracts and measured total and serum specific IgE to latex in 154 patients on hemodialysis. Only 1 patient who had no history of atopy had latex allergy clinically (urticaria at site of contact with latex) and on testing. Sixteen of the 83 patients (19%) who underwent patch testing had positive results to rubber antigens (most

commonly to thiurams); 9 of them had clinical symptoms of contact dermatitis when exposed to rubber. However, the investigators could not establish whether rubber sensitization was induced by hemodialysis or existed before the initiation of dialysis. A more recent study of 205 patients on hemodialysis confirmed a very low prevalence of positive allergy testing reactions to latex (2.4% with latex-IgE positivity and 1% with positive latex skin prick test reactions); none of these patients had any clinical symptoms of latex sensitivity.³⁴ The unexpectedly low prevalence of latex sensitivity in a population that is so frequently and repeatedly exposed to latex could stem from the immune dysregulation seen in the setting of CKD, as will be discussed later.

Another component of hemodialysis catheters and grafts that can cause ACD is polyurethane, as described in 2 case reports. These patients developed widespread dermatitis of the trunk within a few weeks of catheter placement.^{35,36} Patch tests were carried out with different components of similar catheters and in the 2 cases a positive patch test reaction was noted and persisted for 108 hours. Polyurethanes are derived from isocyanates, which are strong sensitizers, and probably, for that reason, such haptens induce a contact allergy a few weeks after catheter insertion with a long-lasting positivity to patch tests.³⁵ However, patients reporting an ACD induced by polyurethane often show a negative patch test reaction to isocyanates, which could be due to differences in the composition and concentration of the antigen in commercially available patch test preparations.³⁵ One of the described patients also exhibited a positive patch test reaction to 1% beryllium chloride in petrolatum, but the investigators did not investigate or speculate about the possibility of a clinically relevant hypersensitivity to that metal in the patient.³⁵ Metals should be considered another potential cause of contact allergy in patients on dialysis; only a single case of nickel dermatitis has been reported,³⁷ although contact dermatitis from nickel released by needles or infusion pumps has been described in the literature.^{38,39} In the patient with nickel ACD from hemodialysis, systemic nickel exposure occurred because of contamination of the dialysate from a stainless steel metal fitting; this resulted in an extensive papulovesicular reaction.

ACD from medications used during the dialysis session

Various topical disinfectants and drugs used to sterilize the hemodialysis access site and topical anesthetics have been linked to ACD.^{40,41} In 2 epidemiologic studies of patients on hemodialysis who underwent standardized patch testing using commercially available panels, a significant percentage were noted to have positive test reactions for povidone-iodine (approximately 4%)^{3,42} and lidocaine (10%).³ In all, approximately 17% to 25% of patients had positive skin test reactions and in most the antigen that tested positive could be linked to dialysis. However, not all patients who had a positive test reaction had clinical manifestations of ACD. Povidone-iodine and lidocaine are known to be irritants and sensitizers and therefore are plausibly linked to allergic reactions in such patients.

Conclusion

As has been outlined above, the complexity of care received by patients on hemodialysis and the multiple possible antigenic exposures in these patients make the recognition and management of hypersensitivity reactions challenging yet imperative. Clearly, a thorough history for timing of the reaction and a detailed investigation of all possible exposures, using a multidisciplinary approach, are critical to determine the precise etiology and management of such reactions. As a general measure, for severe reactions occurring during hemodialysis, dialysis should be immediately terminated and the blood within the dialyzer should not be returned to the patient because of the concern of worsening an anaphylactic or

pseudoallergic reaction by acutely increasing exposure of the patient to the immunologically active mediators; it stands to reason that other standard therapeutic measures, such as the use of epinephrine, and supportive interventions, such as antihistamines and corticosteroids, should be instituted as needed.

Although the approach to allergy testing remains essentially the same as in other patients (measurement of quantitative antigen specific IgE level in serum, skin prick test, and patch test), there are some unique considerations that must be given to those receiving hemodialysis. Because of the immune dysregulation in patients with ESRD, testing results might not be as straightforward to interpret and often clinical judgment will be needed to identify putative causal agents so they can be systematically eliminated. This could be due in part to the immunologic abnormalities seen in the setting of uremia. Several studies have described different immunologic abnormalities in patients with ESRD, including cutaneous anergy and decreased production of T-helper type 2 cytokines by T cells, an inhibition that could decrease specific IgE synthesis.^{43,44} At the same time, patients on hemodialysis have high in vitro spontaneous histamine release and abnormal levels of complement activation, which could lead to reactions that mimic anaphylactic reactions but are independent of IgE and T cells.^{45,46} Basophil activation, as determined by higher expression of CD63, after a dialysis session could be of use in exploring which dialysis membranes are less biocompatible and therefore have a greater propensity to cause pseudoallergic reactions.⁴⁷ Sometimes, despite all investigative efforts, the inciting agent cannot be identified even with systematic elimination of exposures; in such instances, steroid therapy can ameliorate symptoms and allow continuation of dialysis safely, if no other options are available.⁴⁸

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